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Special Edition

Tracking the influenza H1N1
2009 pandemic
May – October 2009



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WHY ARE MEXICAN DATA IMPORTANT?

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This issue of Eurosurveillance contains an article by a French team on the transmission of the new influenza A(H1N1) in Mexico, which uses published figures from the outbreak to estimate important parameters for transmission, among them the reproduction rate, R [1]. Such studies may have important implications for public health action in Europe.

What is R?

The growth rate of an epidemic is determined by two factors: the number of new persons infected by each case and the time from start of infectiousness in one case to start of infectiousness in the secondary cases caused by him/her. The first factor is called 'reproduction rate' and is usually denoted R. If the disease is spreading in a population that is totally susceptible the term 'basic reproduction rate' (Ro) is used. R is the product of four terms: the risk of transmission in one single contact between an infectious and a susceptible person, the frequency of such contacts in the population, the duration of infectivity of a case, and the proportion of susceptibles in the population. If $R > 1$ this means that each case infects more than one new person, and the outbreak is likely to continue. If $R < 1$ the outbreak will eventually die out, even if there may be a number of cases before that. The time from infectiousness in one case to infectiousness in his/her secondary cases is called 'generation time' (Tg) and is basically a biological constant, even if its exact value depends on how it is estimated.

Values for the factors that determine R can be calculated on the basis of scientific knowledge of the disease, its context of transmission, and the immunity status of the population. However, during an epidemic an R value usually has to be derived from the analysis of the epidemic curve or by the study of transmission chains.

Several studies have now tried to estimate R (or Ro) and Tg for the new influenza A(H1N1) virus from Mexican data. In the one published in this issue of Eurosurveillance [1], the authors use one exponential fitting and one real-time estimation model to arrive at an estimate of R between 2.2 and 3.1. This is higher than the value found in an article in Science [2], which estimated Ro to be 1.4-1.6 using three models: one exponential fitting, one genetic analysis, and two standard SIR models for a confined outbreak in

La Gloria. Another analysis of the minor genetic changes in the virus over time arrived at a Ro estimate of 1.16 [3].

The growth rate of an epidemic is determined by two factors: the number of new persons infected by each case and the time from start of infectiousness in one case to start of infectiousness in the secondary cases caused by him/her.

Why is Ro important in public health?

The reproduction rate reflects effectiveness of transmission, and therefore has important implications for the efforts that public health authorities would have to make in implementing health measures aiming at containing or mitigating the outbreak.

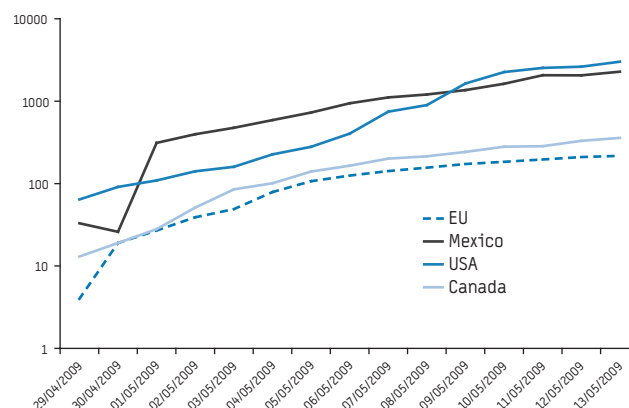
For example, with a Ro of 1.16, preventing 14% of cases will result in eventually interrupting transmission, while with a Ro of 3.1, preventing 68% cases would be needed – assuming a total random mixing of contacts in the population.

Why are Ro estimates so different for influenza?

A few studies have tried to measure Ro for seasonal influenza [4], and found it to be in the order of 1.2 to 1.4. However, for most of the seasonal strains, there is already some immunity in the population from past seasons, which lowers the reproduction rate

FIGURE

Daily reported cumulative number of cases in Mexico, Canada, USA, and EU/EFTA countries, outbreak of new influenza A(H1N1), April-May 2009



(and it should thus really not be called R_0 in this situation). For any epidemic of a disease that leads to immunity after infection the initial R_0 will also be higher than the actual R at any later stage, since the proportion still susceptible in the population will decrease. It should also be realised that delayed reporting of cases will affect an estimate of R ; a problem that adheres to the study in this issue and the others cited above.

What influences R_0 ?

The risk of transmission in a contact when an infective meets a susceptible is basically a biological constant (even if it varies over the time course of the infection), as is the duration of infectiveness. However, frequency of contacts varies considerably between populations and population groups. For example, among children in schools or day care, the contact frequency is higher than among adults [5], and it also varies by culture, by family size in a society, by types of social interaction, etc.

Why is the R_0 from Mexico important?

One could question why there is so much interest around studies of R and R_0 based on Mexican data. Would they apply to Europe? One could guess that contact density might be higher in a Mexican setting, but on the other hand, since the epidemic has already run its course for some time there, the proportion of non-susceptibles would be higher in Mexico and the European situation would more approach a 'true' (higher) R_0 , with a totally susceptible population.

In the graph, we have just compared the daily reported cumulative number of cases in Mexico, Canada, United States, and European Union and European Free Trade Association (EU/EFTA) countries. On a semi-logarithmic scale it is evident that the slope for Europe is very much the same as for Mexico. It is difficult to estimate the time lag for Europe, but it seems that we are some 1-2 months behind. If the generation times are the same for both epidemics – which seems highly plausible – then an estimate of R_0 for Mexico would apply also to Europe. A R_0 just above 1 could mean that a containment strategy might be successful.

The European Centre for Disease Prevention and Control (ECDC) is continuously monitoring the situation and with more data being available every day in Europe we will obviously be able to have a better picture here soon as well. Nevertheless, the similarities of the shapes of the epidemics indicate that lessons from Mexico could apply also to Europe.

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TO BAPTISE A VIRUS AND ITS DISEASE

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The currently circulating new novel Mexican North American Californian swine-like influenza A(H1N1) virus of swine origin has been named and renamed more than once since its recognition a month ago [1]. It is time to agree on names for the virus, and for the disease it causes.

When it comes to individual isolates, the issue seems to be straightforward. According to established convention, an A(H1N1) isolate obtained from a patient in California in 2009 could be called influenza A/California/4/2009(H1N1) swl. This name indicates the species (influenza virus), the type (A) and the subtype (H1N1), and details the origin of the isolate in question, in the case of our example, an isolate with laboratory number 4, obtained from a patient in California in 2009. The abbreviation swl, for swine influenza-like, also referred to as swine lineage, is added to the name to indicate that parts of this virus are genetically related to influenza A(H1N1) viruses circulating in pigs [2].

When it comes to a more general naming of the virus and the disease it causes, however, a consensus is harder to reach. The virus and disease have been called “swine flu”, a name that worried the pig farming industry, and “Mexican flu”, a name that threatened the Mexican tourism industry and “new” or “novel influenza A(H1N1)”, a name not chosen to last. Most simply, but unspecifically it is called, “influenza A(H1N1)” which is what currently appears on WHO’s website.

The name of the virus will have to become more specific quite quickly as there are already the circulating A(H1N1) seasonal viruses which are quite different from the new virus [3]. With the Southern Hemisphere influenza season nearly upon us there will be two “A(H1N1)” viruses co-circulating. Different names will be essential in this respect.

Among the later suggestions for the name of the virus are “influenza A(H1N1)swl” and “A(H1N1)-SL” – both stand for swine-like, as well as “A(H1N1)-SOIV” – for swine origin influenza virus and “A(H1N1)-SO” – swine origin [2,4]. On balance the term SL or swl seems more neutral and simply descriptive. It might be debatable how appropriate the denomination “swine-like” is, as the virus also contains genes from human and bird as well as from swine influenza viruses. However, this denomination is already widely used in the isolate names [2].

Also the question how to call the disease this virus causes is not an easy one. The term “swine flu” has been used so extensively in the media that it will be difficult to get rid of it. Swine flu however, is not desirable, neither medically or scientifically as this is now a human influenza, transmitting efficiently from one person to another. The vast majority of those infected will receive it from other humans not from pigs. Even if the disease pattern

currently mirrors seasonal influenza simply calling it “influenza” is also not optimal, as there are emerging indications that are distinct. Furthermore, there are implications that health professionals and the general public need to understand, when a human is infected with new influenza A(H1N1) rather than the

seasonal influenza A(H1N1) [5-7]. Even if the virus fits the three criteria of a pandemic strain: infecting humans, making them ill and transmitting efficiently from human to human, a pandemic remains yet to be declared so we cannot call it 2009 pandemic influenza.

Most simply, but unspecifically it is called,

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INFLUENZA A(H1N1)v IN THE SOUTHERN HEMISPHERE - LESSONS TO LEARN FOR EUROPE?

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Outside the tropics, influenza infections show seasonal patterns which depend on the latitude but appear not to be influenced by longitude. The factors influencing this seasonality are not yet fully understood, but indoor crowding, lower temperatures, decreased humidity and reduced levels of sunlight are believed to influence both transmission and host susceptibility [1]. Seasonal influenza typically occurs between November and March in the northern hemisphere, and between April and September in the southern hemisphere. However, a temporal overlap of influenza activity between both hemispheres has been described [2]. In tropical regions influenza occurs year-round; it remains unclear whether tropical regions serve as reservoir for the epidemics in both hemispheres.

During seasonal epidemics, dominant strains of influenza virus are described, that may vary within a hemisphere, and in their impact on morbidity. During the 2007-08 influenza season for example, the dominant strain circulating in Europe was seasonal influenza A(H1N1), whereas in the Americas influenza A(H3N2) was dominant [3,4].

Although they occur in distinct periods of the year, influenza strains circulating in the two hemispheres are not independent of each other. This is one of the reasons why the production of the seasonal influenza includes virological information from the circulating strains in both hemispheres. The recommendations for the composition of seasonal influenza vaccines are published twice annually by the World Health Organization before the start of the season in the respective hemispheres, usually in February and September [5].

Considering the interaction of seasonal influenza activity between the northern and southern hemisphere, we can expect the virus to behave similarly in terms of attack rates, clinical spectrum of illness and risk factors for severity. This gives an opportunity to countries in the northern hemisphere to learn from experiences in the southern hemisphere and prepare accordingly.

Current influenza situation in Chile and Australia

Large parts of Chile and Australia are located in the temperate area of the southern hemisphere, with a defined influenza season and the majority of cases occurring between May to September. Both countries have an established seasonal influenza surveillance

system [6,7]. Chile documents significant levels of influenza activity every two to four years, while Australia has reported a general increase in both influenza-like illness and influenza laboratory notifications in recent years.

In the past weeks, corresponding with the start of the influenza season in the southern hemisphere, both countries experienced a steep increase in reported cases of influenza A(H1N1)v. Chile reported its first cases in mid-May: small clusters (consisting of between two and six cases) in different schools as well as three cases having travelled back from the Dominican Republic. By the end of May, 11 of the 15 administrative regions in the country had reported cases [8]. On 12 June the total number of cases

was 2,335, including two deaths; the majority (66%) of infections occurred in persons 5-19 years of age, and 2% were considered severe, requiring hospitalisation [9]. In Australia, the first case of A(H1N1)v was confirmed on 8 May, three weeks later all eight jurisdictions of Australia reported laboratory confirmed cases. By 16 June, Australia reported 1,965 cases country-wide, of which 62% were from Victoria [10].

Chile and Australia responded to the first cases of influenza A(H1N1)v by implementing a 'containment' strategy. Following the rapidly evolving epidemiological situation, Chile changed to a 'mitigation' strategy by the end of May (two weeks after the first case report). Australia changed its strategy initially in the most affected state of Victoria, where a modified 'sustain' phase was implemented [11,12]. On 17 June, the country started moving into a new 'protect' phase, taking into account the less severe clinical characteristics of the current pandemic [13]. This change in strategy impacted among others the laboratory testing strategies, focusing mainly on the early detection and adequate treatment of (potentially) severe cases.

What lessons can we learn from the present situation in Chile and Australia?

As with seasonal influenza in the past years, the influenza A(H1N1)v situation in the winter period in the southern hemisphere is likely to reveal what can be expected in the winter in the northern hemisphere. Even if the season in the southern hemisphere has only started and there are only limited data on the influenza A(H1N1)v situation available, some early conclusions can be drawn already.

Seasonal influenza typically occurs between November and March in the northern hemisphere, and between April and September in the southern hemisphere.

However, it will be even more important for the northern hemisphere countries, including those in Europe, to continue monitoring the situation in the coming weeks closely, to gain further knowledge on populations most affected, risk factors for developing severe illness, changes in the virus' virulence, transmissibility, and susceptibility to anti-viral drugs, as well as the impact of pharmaceutical and non-pharmaceutical public health measures.

The current trend in the number of cases reported in Australia and Chile, which are rapidly increasing and coinciding with the influenza season, is different from what is being observed in Europe, where progression still seems to be slower and/or delayed. In Europe, influenza activity can be expected to remain on a low level during the northern summer months, whereas a steep increase, as seen currently in Australia and Chile, might be observed at the start of the influenza season in Europe around September. Both Chile and Australia rapidly moved from containment to mitigation or sustaining strategies.

The approach of the European Member States over the past few weeks has been to implement intense containment measures, including active case finding and tracing of contacts, isolation of cases and contacts, and antiviral treatment and prophylaxis. These measures were pertinent in reaction to the first appearance of the new virus in Europe. However, it is unclear if these efforts will still be sustainable in the coming winter season when the virus is likely to be widely circulating on the continent. It can be expected that countries will implement different measures depending on the national epidemiological and virological situation.

What additional information is needed to be able to respond adequately?

Studies on the effectiveness of non-pharmaceutical public health measures from the southern hemisphere will be important, even though caution is recommended when comparing to countries with different healthcare systems, population density and social structures. In addition, the behaviour of other seasonal influenza viruses in terms of co-circulation and predominance of one strain versus the other will be closely monitored. In Chile, in week 21, 90% of the circulating influenza virus detected was due to influenza A(H1N1)v and in week 22 in the United States, the proportion was 89% [14,15]. The predominance of the pandemic strain over other influenza strains is a phenomenon that has been observed in previous pandemics [16]. If this will also become true for other southern countries, the same can be expected in the northern hemisphere and public health measures, including vaccination and treatment, will need to be adapted accordingly.

Since its detection in April this year, a lot of information on the epidemiology and virology of the new influenza A(H1N1)v virus has become available, mainly from Mexico and the United States. However, this information reflected the initial spread of the virus, which may not be representative for the coming winter season. Hence, monitoring the situation in the southern winter period will help to better anticipate, and therefore prepare, for the northern winter and its influenza season. However, some of the findings might need careful interpretation and cannot necessarily be generalised for Europe. International efforts should aim at supporting countries in the southern hemisphere in their response to the pandemic, resulting in a mutual benefit: additional resources for the south, allowing in-depth and targeted investigations, and increased epidemiological understanding for the north, allowing better preparedness for the expected winter peak.

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THE ORIGIN OF THE RECENT SWINE INFLUENZA A(H1N1) VIRUS INFECTING HUMANS

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Preliminary analysis of the genome of the new H1N1 influenza A virus responsible for the current pandemic indicates that all genetic segments are related closest to those of common swine influenza viruses.

A new H1N1 influenza A virus has been identified in Mexico, and has spread rapidly to other regions around the world. The World Health Organization in collaboration with many other national and international agencies is working efficiently to evaluate, diagnose and implement measures to contain the spread of this virus. Among the many efforts is the timely release of the genomic sequences from different viral isolates [1]. This is allowing thousands of scientists to participate in the endeavour.

There have been some questions raised about the origin of the new strain. Influenza A is a single stranded RNA virus with eight different segments. When two viruses co-infect the same cell, new viruses can be produced that contain segments from both parental strains.

By using sequences collected in public databases, we can identify the closest relatives of the new strain found in Mexico, and construct clusters and phylogenetic trees. Sequence alignment and similarity, cluster analyses by principal component analysis and phylogenetic tree all point to similar results.

Our preliminary analyses show that the closest relatives to this new strain are found in swine, and occasionally in turkeys. Six segments of the virus are related to swine viruses from North America and the other two (NA and M) from swine viruses isolated in Europe/Asia. The closest clusters (for the HA segment) in the NCBI data base are North America swine influenza A(H1N2) and H3N2s. The closest relatives of the neuraminidase (NA) gene of the new virus, are influenza A isolates from 1992. As more data becomes accessible, the evolution of this gene could be clarified.

The North American ancestors are related to the multiple reassortants, H1N2 and H3N2 swine viruses isolated in North America since 1998 [2,3]. In particular, the swine H3N2 isolates from 1998 were a triple reassortment of human, swine and avian origin.

Therefore, this preliminary analysis suggests at least two swine ancestors to the current H1N1, one of them related to the triple reassortant viruses isolated in North America in 1998. So far, the new strain has not been reported in pigs. It is not clear if this is due to insufficient surveillance of the swine population, or if this virus has been generated in a very recent reassortment event.

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Rapid communications

FIRST SEQUENCE-CONFIRMED CASE OF INFECTION WITH THE NEW INFLUENZA A(H1N1) STRAIN IN GERMANY

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Here, we report on the first sequence-confirmed case of infection with the new influenza A(H1N1) virus in Germany. Two direct contacts of the patient were laboratory-confirmed as cases and demonstrate a chain of direct human-to-human transmission.

A patient in his 30s was admitted to the department of internal medicine of a district hospital in southern Germany, on 24 April 2009 with influenza symptoms. Two days earlier, he had returned from a vacation in Mexico. He presented with fever up to 40° C, cough and dyspnoea. Headache and myalgia were not present. In addition, this patient had an unrelated, previously undiagnosed chronic disease. He was isolated on the morning of 27 April, and fever and dyspnoea resolved during that day. Since the evening of that day, he has been treated with oseltamivir. Because of his underlying medical condition he was transferred to the University Medical Centre on 28 April, where he has been in stable condition until present, with no further clinical signs of influenza.

Laboratory analysis

On 27 April 2009, the Laboratory of Medical Microbiology and Hygiene at the University of Regensburg Medical Center received a nose and throat swab of the patient for influenza PCR, because an infection with the new influenza A(H1N1) strain was suspected [1,2].

TaqMan-PCR for an 86 bp fragment of the M1 matrix protein gene was performed on the same day and was negative for influenza B, but weakly positive for influenza A (10²-10³ copies from 1 ml of swab extraction buffer). The two involved hospitals and health authorities were informed immediately. The primers used (set A, see Table) were part of an in house TaqMan-PCR system designed for conventional influenza A strains.

Sequencing of this PCR product on 28 April showed that 45 bp excluding the primers were identical to the California 04/2009 H1N1 isolate from the current outbreak (GenBank entry

TABLE

Oligonucleotide primers used for amplification and sequencing

A	Influenza A-specific TaqMan PCR system	forward primer (InflA-MA2-1b) 5'-GYT CTC ATG GAR TGG CTA AAG ACA-3'	backward primer (InflA-MA2-2) 5'-GGC ACG GTG AGC GTG AA-3'	TaqMan probe (InflA-MA-So-2b) FAM-5'-ACC AAT CCT GTC ACC TCT GAC TAA GGG GA-3'-TAMRA	
B	Primers targeting M1 gene sequence	outer forward primer (MA-c_1) 5'-ACC GAG GTC GAA ACG TA-3'	outer backward primer (MA-c_2) 5'-CGA TCA AGA ATC CAC AAT ATC-3'	inner forward primer (MA-c_3) 5'-CAG AGA CTT GAA GAT GTC TTT G-3'	inner backward primer (MA-c_4) 5'-TTC TGR TAG GYC TGC AAA TT-3'
C	Primers targeting HA gene sequencing	outer forward primer (H1N1_HA_F1) 5'-CCG CAA ATG CAG ACA CAT TA-3'	outer backward primer (H1N1_HA_R1) 5'-CCC ATT AGA GCA CAT CCA GAA-3'	inner forward primer (H1N1_HA_F2) 5'-TGC GAA CAA TTC AAC AGA CA-3'	inner backward primer (H1N1_HA_R2) 5'-CCC AGG GAG ACT ACC AGT ACC-3'
D	Novel Influenza A(H1N1)-specific TaqMan PCR system [3]	forward primer (H1SW5) 5'-CAT TTG AAA GGT TTG AGA TAT TCC C-3'	backward primer (H1SWAs1) 5'-GGA CAT GCT GCC GTT ACA CC-3'	TaqMan probe (H1SWP) FAM-5'-ACA AGT TCA TGG CCC AAT CAT GAC TCG-3'-BBQ	

TaqMan PCR system A had been designed for conventional influenza A strains. Due to the two distinct nucleotides in the probe region, this assay may slightly underestimate the viral load of the novel influenza A(H1N1) strain. Primer system B had been designed for conventional influenza A strains. It does not exactly fit the novel influenza A(H1N1) strain in several positions, but worked well for sequencing the first German isolate.

FJ966085.1). The 45 bp sequence differed in three nucleotide positions from conventional human influenza A strains, two of them within the TaqMan probe region. This was considered a strong indication for infection with the new virus.

A larger 600 bp PCR fragment of the matrix protein gene was sequenced on the same evening, using primer set B (see Table). In a BLAST search it was 100% identical over a stretch of 597 nucleotides with the above mentioned California isolate, but differed in at least 5% from annotated human influenza A(H1N1) strains. Conventional porcine influenza H3N2, but also H1N1 strains, were generally more closely related to our sequence than human strains.

Therefore, we considered this isolate as the first proven case of the new influenza A(H1N1) in Germany. Health authorities and physicians were immediately informed. The 597 nucleotide sequence was submitted to GenBank on the same day (FJ970928*).

In parallel, a 1,446 bp fragment of the haemagglutinin gene was amplified and sequenced using primer set C (see Table), and submitted to GenBank (FJ974021) on 30 April. This sequence was identical to two California strains (GenBank FJ969511 and FJ966952) isolated in the current worldwide outbreak, with the exception of only one nucleotide mismatch. In addition a 1,109 bp sequence of the neuraminidase gene of our first isolate has meanwhile been deposited in GenBank (FJ984953) and in the database of the Global Initiative on Sharing Avian Influenza Data (GISAID). It had 100% similarity with the Texas/04 and Texas/05 isolates (FJ981614 and FJ966969).

Contact testing

In the presumed incubation time, the index patient had several contacts of varying closeness and duration before his admission to hospital. Contact tracing and testing through the public health authorities was started immediately. Detailed data on the contacts of the index patient before entering the hospital will be reported by the public health authorities.

Before the patient was isolated on the morning of 27 April under suspicion of new influenza, he had an estimated 19 close contacts among staff at the district hospital and one patient who stayed in the same twin room as the index case in the district hospital.

One of the nurses who had close contact with him has so far tested positive for the new influenza A (H1N1), and had influenza symptoms for a period of two days on 26-27 April. This case received oseltamivir treatment and stayed isolated at home until 5 May when she had tested negative for the new influenza A(H1N1) strain.

All other contacts among the district hospital staff and additional hospital staff who had not had contact with the index patient (a total of 32 people) were tested one or two times and have remained PCR-negative and healthy as of 7 May.

All 32 were tested and offered oseltamivir prophylaxis, but only a minority accepted the treatment. Contacts among the staff at the University Medical Centre remained healthy and were not tested, because the isolation care of the patient was continued without interruption from the beginning.

A sputum sample of the patient sharing the room with the index case was found positive on 29 April in an influenza A-specific TaqMan-PCR assay (set A, see Table). A second TaqMan-PCR assay, specific for the new influenza A(H1N1) strain (primer set

D, see Table), was found positive on the same day. The patient was isolated and treated with oseltamivir in the afternoon of 29 April, and health authorities were informed. He suffered only minor influenza-like symptoms.

Both this and the index patient have since tested negative for the new influenza A(H1N1) strain three times and have been released from isolation. Due to additional chronic diseases unrelated to influenza, however, they have not been released from the hospital yet.

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*Authors' correction:

On 8 May 2009, the following changes were made in this article: B Kochanowski was added to the author list. B Biermaier from the Straubing public health authorities was added to the Acknowledgements section. The GenBank entry "JF970928" was corrected to read "FJ970928" at the end of the fifth paragraph.

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INITIAL EPIDEMIOLOGICAL FINDINGS IN THE EUROPEAN UNION FOLLOWING THE DECLARATION OF PANDEMIC ALERT LEVEL 5 DUE TO INFLUENZA A (H1N1)

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The recent detection of a novel influenza A(H1N1) virus has led to the first WHO declaration of a Public Health Event of International Concern under the International Health Regulations (IHR 2005). Here we review the early epidemiological findings of confirmed cases in Mexico, the United States, Canada and EU/EFTA countries. Strengthened surveillance and continued, transparent communication across public health agencies globally will be necessary in coming months.

Background

Infections with swine influenza virus have been detected occasionally in humans since the 1950s and the resulting human disease is usually similar to human influenza viral infections [1-6]. Complications, including pneumonia and death, have been reported in the literature in adults without underlying disease [7]. Chains of human-to-human transmission had not previously been observed apart from an outbreak among young adult military recruits in New Jersey in 1976, causing 230 infections, 13 of whom were severe with one death [8].

On 21 April, the European Centre for Disease Prevention and Control (ECDC) was alerted of the existence of cases of respiratory illness in the United States (US) caused by a novel influenza virus [9]. On 23 April 2009, cases from Mexico were confirmed to be caused by influenza A(H1N1) virus. Initial cases in the US demonstrated no exposure to pigs, and some were clustered. In Mexico, the outbreak caused cases of severe respiratory illness and suspected deaths [9,10].

Preliminary investigations showed that six genomic segments of the virus were related to swine viruses from North America and the remaining two were from swine viruses isolated in Europe and Asia [11]. The virus was resistant to adamantanes, but susceptible to neuraminidase inhibitors [9,12].

On 25 April, the World Health Organization (WHO) declared this event a 'Public Health Event of International Concern' under the framework of the International Health Regulations (IHR 2005). On 26 April, New Zealand, Spain and the United Kingdom (UK) started investigating persons returning from Mexico with influenza-like symptoms. On 27 April, the first confirmed cases of the new influenza A(H1N1) were reported from Spain (n=1) and the UK

(n=3) in travellers returning from Mexico, and 10 additional European Union (EU) countries reported investigating cases.

On 27 and 29 April, WHO raised the pandemic alert phases to 4 and 5, respectively. Governments were requested to strengthen surveillance, to detect and treat cases early and implement infection control in all health facilities.

In the EU, the European Commission recommended that countries extend their routine seasonal influenza surveillance beyond week 20. Additionally, on 30 April 2009, an EU case definition for the novel influenza A(H1N1) virus was agreed upon by EU Member States [13].

A timeline of the events is shown in the Figure.

This article aims to review the preliminary epidemiological findings in the EU following the identification of influenza A (H1N1) in Mexico and the US.

Current global epidemiological situation

As of 7 May, 2,217 confirmed cases of influenza A(H1N1) have been confirmed worldwide, from 24 countries located in three WHO regions [14].

Countries not in the EU and European Free Trade Association (EFTA) (Non-EU/EFTA countries)

In Mexico, the epidemiological profile of 866 out of a total of 1,112 confirmed cases shows that the majority of cases occurred in the area around Mexico City (n=496, 53.8%) [15]. Forty-two deaths have been confirmed [14]. Fifty percent of cases are female and 49% of confirmed cases are under the age of 19 years [15].

In the US, 41 out of 50 states have reported 745 confirmed cases of the new influenza A(H1N1) [14]. Two deaths and 35 hospitalisations were reported. The median age of confirmed cases is 16 years, and 62% are under the age of 18 years [16].

Canada reported 201 confirmed cases of the new influenza A(H1N1) with one hospitalisation of a young girl [17]. Eight of 10 provinces and none of the territories have reported confirmed cases, with the majority reported from British Columbia (n=54), Nova Scotia (n=53) and Ontario (n=49) [18].

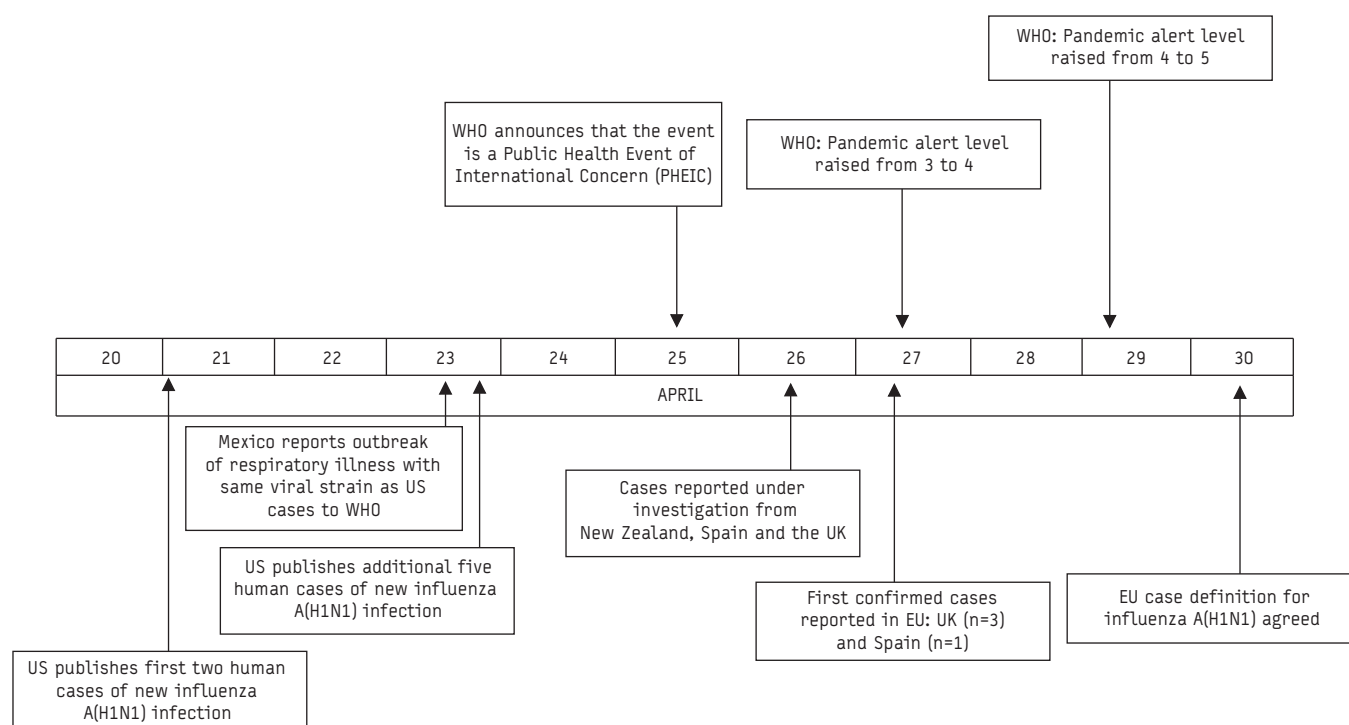
Sporadic cases have been reported from New Zealand, the Republic of Korea, Hong Kong, Israel, Costa Rica, Guatemala, Colombia and El Salvador.

EU and EFTA countries

Thirteen EU/EFTA countries have confirmed 142 cases since 27 April (Table 1). The majority of confirmed cases are from Spain

FIGURE

Timeline of major events: new influenza A(H1N1) outbreak, April 2009



EU: European Union; UK: United Kingdom; US: United States; WHO: World Health Organization.

TABLE 1

Reported current number of probable cases, cumulative number of confirmed cases and cumulative number of in-country transmission, influenza A(H1N1) outbreak 2009*

Country	Current number of probable cases	Cumulative number of confirmed cases	Cumulative number of in-country transmission
Austria	-	1	-
Denmark	0	1	-
France	3	7	-
Germany	0	9	2
Ireland	0	1	-
Italy	-	5	-
Netherlands	-	1	-
Poland	-	1	-
Portugal	0	1	-
Spain	-	81	5
Sweden	0	1	-
Switzerland	-	1	-
United Kingdom	1	32	10
Total	4	142	17

Data as of 7 May 2009, 8:00 hours (CEST) in European Union (EU) and European Free Trade Association (EFTA) countries [14].

Note: cases reported in the EU and EFTA countries correspond to the EWRS notifications by Member States or Ministry of Health websites.

(n=81) and the UK (n=32). Age and gender data are available for 35 confirmed cases (Table 2). The male-female sex ratio is 1.5, the median age is 23 years (range 3-50 years), and 49% of cases are between 20 and 29 years of age.

Seventeen confirmed cases (16%) acquired the infection through transmission within the EU. In Germany, a nosocomial cluster occurred in a nurse and patient who were exposed to a hospitalised confirmed case. Spain reported five autochthonous transmissions and the UK reported 10, including a cluster of five school children exposed to a confirmed schoolmate with travel history to the US. There is no indication of transmission occurring in the EU outside of close contacts of known cases.

Countries within the European Union have coordinated their public health measures on the basis of EU communicable disease legislation. The measures taken include: information to the public and travellers, raising awareness amongst healthcare workers and enhancing surveillance for influenza-like illness. On the basis of a risk assessment provided by the European Centre for Disease Prevention and Control (ECDC), the European Commission collaborates closely with the Member States, international organisations and third countries to ensure a coordinated response to this event on the EU level.

Discussion

Three out of six WHO regions have confirmed cases. However, community transmission, defined as transmission chains spreading beyond close contacts into the community, has to date only occurred in Mexico and in the US. EU/EFTA countries are still experiencing limited chains of transmission to close contacts of returning travellers from Mexico and the US.

Based on the experience from Mexico and the US, it appears that seeding events established by travellers from affected areas are occurring in closed community settings such as schools. The spread of the virus within these settings causes an amplification of the viral reservoir in the communities ultimately leading to community spread. In the EU, some confirmed cases have already been reported in children of school age and in close school contacts and monitoring of these events should continue to be done carefully.

TABLE 2
Gender and age distribution of confirmed cases in EU and EFTA countries, influenza A(H1N1) outbreak 2009 (n=35)

Age group (years)	Female	Male	Total
0-9	1	0	1
10-19	2	1	3
20-29	7	10	17
30-39	1	3	4
40-49	1	2	3
50-59	0	1	1
>59	0	0	0
Unknown	2	4	6
Total	14 (40%)	21 (60%)	35

EFTA: European Free Trade Association (EFTA); EU: European Union.

Half of the confirmed cases observed in the EU are between 20 and 29 years of age. This finding is influenced by the age structure of returning travellers among which most of the testing is carried out in EU/EFTA countries. It therefore does not indicate that this age group is at higher risk of disease. Most cases in the EU/EFTA countries are mild. However, more severe clinical presentation may be expected when the infection will spread in the general population.

Most of the efforts in the EU/EFTA countries are currently directed at detecting returning travellers from areas with community outbreaks, namely Mexico and the US. However, considering how the outbreak is progressing, the focus of surveillance is now shifting to the timely detection of community transmission. EU Member States are currently continuing their surveillance of seasonal influenza. As the national influenza centres are now all equipped with reagents to identify the novel influenza A(H1N1) strain, it is likely that cases that may occur in the community in the EU will be detected by virological surveillance.

Conclusion

It is still too early to predict how the outbreaks of influenza A (H1N1) will evolve in the EU/EFTA countries. Data from Mexico and the US suggest that this novel virus spreads rapidly in the communities once introduced from an affected area.

Continued strengthened surveillance efforts, coordination and information sharing amongst countries on a global level will support the EU and other affected countries in their preparedness and response for the potential spread of this novel influenza virus in the weeks and months to come.

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EARLY ESTIMATES OF THE EXCESS MORTALITY ASSOCIATED WITH THE 2008-9 INFLUENZA SEASON IN PORTUGAL

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The aim of this study was to estimate the excess mortality associated with the influenza activity registered in Portugal between week 49 of 2008 and week 5 of 2009. For this purpose available mortality data from the Portuguese Daily Mortality Monitoring (VDM) System were used. Several estimates of excess deaths associated with the recent recorded influenza activity were determined through statistical modelling (cyclic regression) for the total population and disaggregated by gender and age group. The results show that the impact of the 2008-9 influenza season was 1,961 excess deaths, with approximately 82% of these occurring in the age group of 75 years and older.

Background

At the end of 2008, Portugal was one of the first countries in Europe to experience an intense influenza activity that lasted a few weeks into 2009 [1]. High influenza incidence rate estimates were observed although the epidemic peak was below the previously observed maximum values. It was expected that this influenza activity should have an impact on mortality, as shown by other studies [2-3]. Available data from the Portuguese Daily Mortality Monitoring (VDM) System were used to quantify the impact. Since mid-2007, this system has been receiving information on daily mortality registered in all Portuguese Civil Register Offices from centralised databases hosted by the Institute of Information Technology in Justice at the Ministry of Justice. This study sought to give evidence of the impact of influenza activity on mortality by calculating estimates of excess deaths associated with influenza, and to test the VDM System.

Methods

Influenza activity

The information on influenza activity consisted of weekly estimates of influenza-like illness (ILI) incidence rates obtained by the Portuguese general practitioners (GP) sentinel network (Rede Médicos-Sentinela) [4] from week 41 of 2006 to week 7 of 2009 (up to 15 February 2009, inclusive). This period comprises the seasons 2006-7, 2007-8 and part of 2008-9.

Mortality

Weekly aggregated mortality data from week 1 of 2007 to week 7 of 2009 (up to 15 February 2009, inclusive) generated by the Daily Mortality Monitoring (VDM) System were used. Data were disaggregated by gender and age group (65-74 and ≥ 75 years).

Methods for calculating the estimated number of excess deaths

Statistical modelling was used to calculate the estimated number of excess deaths associated with the 2008-9 influenza epidemics.

First, all types of events potentially associated with excess mortality in the period from week 1 of 2007 to week 7 of 2009 (up to 15 February 2009, inclusive), were identified (Table 1). The periods of influenza epidemic were defined as the set of consecutive weeks with influenza virus detected and ILI incidence rate above the upper 95% confidence limit of the ILI incidence rate baseline. The heatwave period was defined as the weeks in which high temperatures were registered (two or more consecutive days with temperatures above 32°C). In both kinds of events an additional week was added to account for eventual delay of impact.

A cyclical regression model was fitted to the mortality time series after excluding the event periods (Table 1). This type of model is a multiple linear regression model whose independent variables are functions of the time sequence to adjust for the existence of long term trends and the seasonal annual pattern of mortality.

The weekly mortality predicted by the model was considered as the baseline mortality in the absence of the events potentially associated with excess mortality.

The period of excess mortality attributed to the 2008-9 influenza epidemic was defined as the set of consecutive weeks that began with two values of the observed number of deaths above the upper 95% confidence limit of the baseline and ended with two consecutive mortality values below the same limit.

TABLE 1

Events potentially associated with excess mortality observed in the period from week 1 of 2007 to week 7 of 2009 in Portugal

Event	Period (week/year)	Number of weeks
2006-7 influenza epidemic	3/2007 to 9/2007	7
July 2007 heatwave	30/2007 to 32/2007	3
2007-8 influenza epidemic	3/2008 to 7/2008	5
2008-9 influenza epidemic	49/2008 to 6/2009	10

The Figure represents a series of data, identifying the influenza epidemics and heatwave events and the baseline obtained by cyclical regression. The estimated excess deaths attributed to the 2008-9 influenza epidemic was obtained by summing the differences between the observed and the baseline mortality during the period of excess deaths, represented by dark blue bars in the Figure.

The excess deaths associated with the 2008-9 influenza season were computed by gender and age groups. Confidence intervals of the excess death estimates at 95% level were calculated by approximation to the normal distribution, using as standard error the product of the square root of the number of weeks with excess mortality by the standard deviation of the model residual. Excess mortality rates per 100,000 inhabitants were produced using the estimates of the Portuguese population at the end of 2007 [5].

FIGURE
Observed and expected weekly total mortality, weekly influenza incidence rates and potentially associated events; Portugal, January 2007 to February 2009

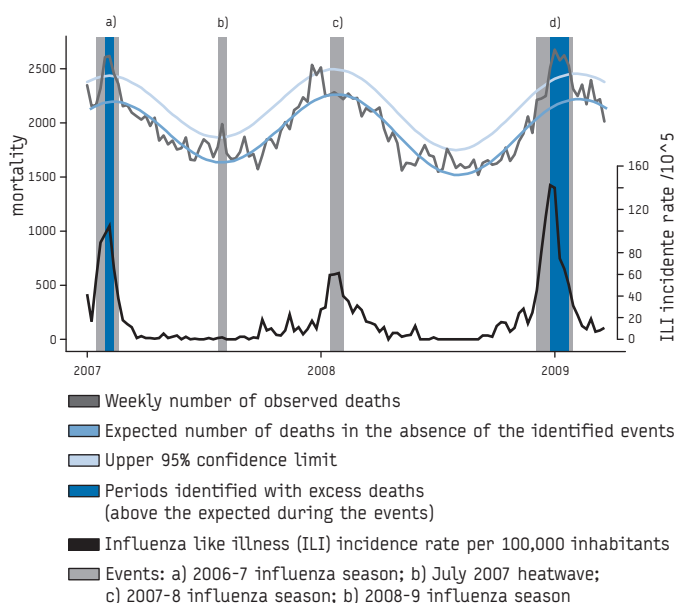


TABLE 2
Estimates of crude number of excess deaths and excess death rates, associated with 2008-9 influenza season in Portugal, in total, by sex and by age groups

	Excess deaths (95% CI)	Excess death rate/100,000 inhabitants
Total	1,961 (1,567-2,355)	18
Sex		
Men	703 (526-880)	14
Women	1161 (936-1,386)	21
Age group		
65-74	119 (75-163)	12
>=75	1,615 (1,317-1,913)	191

Statistical analysis was performed using R (www.r-project.org) package Flubase [6].

Results

The last influenza season (2008-9) was marked by more intense activity and earlier onset than the two previous seasons, with a medium to high activity between weeks 49 of 2008 and 5 of 2009, reaching a maximum value at the turn of the calendar year (Figure).

The main results indicate that although the epidemic lasted for nine weeks (from week 49 of 2008 to week 6 of 2009) excess mortality was observed only during five weeks (from week 52 of 2008 to week 4 of 2009). The overall impact was estimated to have resulted in 1,961 excess deaths, corresponding to an excess death rate of 18 per 100,000 inhabitants). The results also indicate that the impact was higher in women than in men and that 82% of the total estimated number of excess deaths occurred in individuals aged 75 years and older (Table 2).

Discussion and conclusions

The overall estimated number of excess deaths for the 2008-9 influenza season is within expected values. Past experience has shown that influenza activity and intensity can vary widely as does the respective attributable mortality. For Portugal, previous studies estimated an average of 1,773 and 2,475 deaths per epidemic period [2, 7-8].

Our results demonstrate that the currently existing tool for rapid mortality surveillance (VDM) can be used to promptly identify and estimate the impact of such public health events. A more accurate estimate could only be obtained if official routine mortality data were available.

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Rapid communications

NEW INFLUENZA A(H1N1) VIRUS INFECTIONS IN SPAIN, APRIL-MAY 2009

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An outbreak of infections with a new influenza A(H1N1) virus that was first detected in the United States and Mexico is currently ongoing worldwide. This report describes the initial epidemiological actions and outbreak investigation of the first 98 laboratory confirmed cases of infection with this new virus in Spain.

Background

On 25 April 2009, the World Health Organization (WHO) declared the outbreak of swine-origin influenza A(H1N1) virus infections, first reported by the United States (US) [1] and Mexico [2], as a 'Public Health Event of International Concern' (PHEIC) under the International Health Regulations (2005) [3]. The pandemic alert level was raised from level 3 to level 4 on 27 April, and to level 5 on 29 April, after verification of sustained community-level outbreaks in at least two countries from the same WHO region.

On 26 April, epidemiological and laboratory investigations on three persons returning from Mexico were initiated in Spain. On 27 April, Spain reported the first laboratory-confirmed case of the new influenza A(H1N1) virus infection in Europe, in a traveller returning from Mexico. Since then, the number of confirmed cases in Spain has risen continuously and reached a total of 98 as of 11 May 2009.

Enhanced surveillance

On 24 April, in response to alarming reports from the US of swine-origin influenza A(H1N1) virus infection in several patients [1,4] and media news of a possibly related outbreak of severe respiratory illness in Mexico, the Coordinating Centre for Health Alerts and Emergencies (CCAES) at the Spanish Ministry of Health and Social Policy, issued a national epidemiologic alert. The alert asked public health authorities at national and regional level to enhance surveillance and to report urgently any case of fever and severe respiratory illness among people with history of travel to Mexico or history of previous contact with a confirmed case of influenza virus A(H1N1) infection (Table 1).

On 25 April, following WHO's declaration of a PHEIC, the National Pandemic Influenza Preparedness and Response Plan was activated. A case definition as well as protocols for case and contact management and for infection control were developed and distributed to the National Health Service through regional health authorities and other involved institutions (Table 2).

No increase in seasonal influenza activity has been reported so far. Routine seasonal influenza surveillance will continue beyond week 20. Data analysis of mortality for all causes since 1 May has not shown an increase or change of patterns in mortality.

Since 24 April, the outbreak of new influenza A(H1N1) has been monitored by the Ministry of Health and Social Policy (Centro de Coordinación de Alertas y Emergencias Sanitarias, CCAES) jointly with the National Centre for Epidemiology (Instituto de Salud Carlos

TABLE 1

Timeline of key events in detection and response to the new influenza A(H1N1) virus outbreak, Spain, 24 April-11 May 2009

Date	Event
24 April	Alert issued to enhance surveillance at the public health services and national health system
24 April	Information for the public and recommendations for travellers going to and returning from Mexico published on the website of the Spanish Ministry of Health and Social Policy
25 April	National pandemic influenza preparedness and response plan activated.
25 April	Case definition, case and contact management, and infection control protocols distributed
26 April	Notification of the first three cases under investigation
27 April	First laboratory-confirmed case of new influenza A(H1N1) virus infection reported.
27 April	Ministry of Health recommends avoiding non-essential travel to Mexico
27 April	World Health Organization raises pandemic alert to phase 4
29 April	World Health Organization raises pandemic alert to phase 5
29 April	First secondary case of new influenza A(H1N1) virus reported
1 May	Regional influenza laboratories to start initial testing; National reference laboratory to confirm
7 May	New case definition approved, including the United States as an affected area, reducing incubation period (seven days) and establishing fever cut off at 38°C
11 May	First laboratory-confirmed tertiary case
11 May	Status: 98 laboratory confirmed cases of new Influenza virus A(H1N1) infection

III) and in coordination with all the Regional Surveillance and Alert Teams from the Autonomous Communities in Spain. This new influenza A(H1N1) investigation and control group also discusses and recommends prevention and control measures.

TABLE 2
Case definition and case classification, new influenza A(H1N1) infection, Spain, 25 April-7 May, 2009

Incubation period 10 days	
Clinical criteria	Any person with ONE of the following: <ul style="list-style-type: none"> Fever ($\geq 37.5^{\circ}\text{C}$)* AND signs or symptoms of acute respiratory infection Pneumonia Death from an unexplained acute respiratory illness
Epidemiological criteria	At least ONE of the following in the 10 days* prior to disease onset: <ul style="list-style-type: none"> Travel to an area where there are confirmed cases of new influenza A(H1N1) (Mexico*) Close contact to a confirmed case of new influenza A(H1N1) virus infection Recent history of contact with an animal with confirmed or suspected swine influenza A(H1N1) virus infection (This criterion was substituted on 27 April for: "A person employed at a laboratory and manipulating potentially contaminated samples").
Laboratory criteria	At least ONE of the following tests: <ul style="list-style-type: none"> RT-PCR Four-fold rise in new influenza A(H1N1) virus-specific neutralizing antibodies (implies the need for paired sera, at least from acute phase illness and then at convalescent stage 10-14 days later) Viral culture
Case classification	A. Case under investigation Any person meeting clinical AND epidemiological criteria B. Probable case Any person meeting clinical AND epidemiological criteria AND with a positive influenza A infection of an unsubtypable type C. Confirmed case Any person with laboratory confirmation*

* Differences to proposed case from the European Centre for Disease Prevention and Control.

FIGURE 1
Geographical distribution of cases of laboratory-confirmed new influenza virus A(H1N1) infection, Spain, as of 11 May 2009



Confirmed cases of new influenza virus A(H1N1)

As of 11 May, 98 laboratory-confirmed cases of infection with the new influenza virus A(H1N1) have been reported in Spain out of 640 possible cases investigated. The geographical distribution of reported cases by region is shown in Figure 1.

Seventy-six confirmed cases (78%) acquired the infection abroad; all these cases had a history of travel to Mexico. Of the 45 cases for whom this information was available, 16 (36%) were symptomatic during the inbound flight from Mexico. Dates of return from affected areas were available for 70 confirmed cases and ranged from 20 to 29 April (Figure 2).

Information on disease onset was available for 93 cases. The first of the 93 cases reported onset of illness (any symptom) on 19 April, and the most recent case reported onset on 4 May (Figure 3).

More than 2,000 contacts have been traced and followed. Of these, 39% were household members of cases and 45% friends of cases. Twenty-one confirmed secondary cases and one tertiary case have been reported. Secondary cases were family or close contacts of cases with history of travel to Mexico. Five secondary cases were infected by primary cases that did not meet clinical criteria. The

FIGURE 2
Cases of laboratory-confirmed new influenza virus A(H1N1) infection, by date of travel return to Spain, as of 11 May, 2009 (n=70)

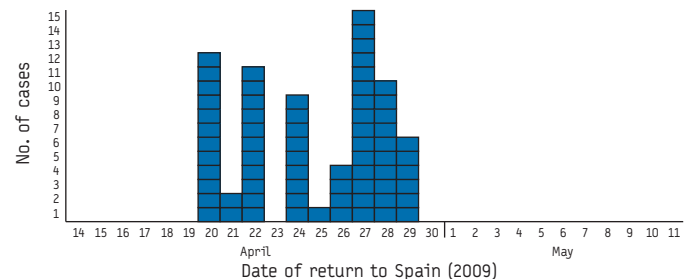
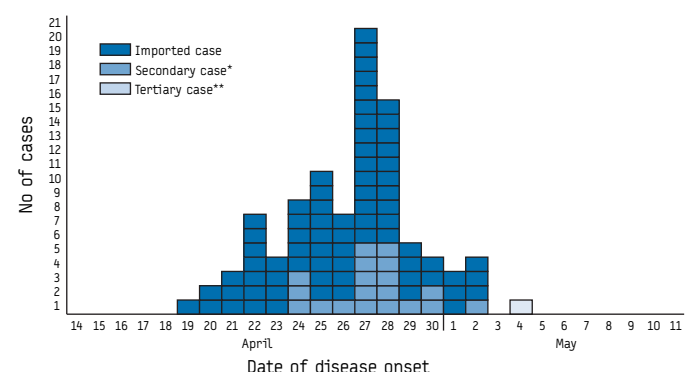


FIGURE 3
Cases of laboratory-confirmed new Influenza virus A(H1N1) infection, by date of disease onset, Spain, as of 11 May 2009 (n=93)



* contact of a confirmed imported case
** contact of a confirmed secondary case

tertiary case was a family contact of a secondary case. Analysis of secondary transmission is ongoing.

Four secondary cases had received prophylaxis with oseltamivir before being diagnosed as cases.

From the analysis of disease onset for primary and secondary cases, the median of the serial interval was estimated to be 3.5 days, ranging from one to six days. The estimation for the maximum incubation period ranged from one to seven days, with a median of three days.

Demographic and clinical features

Cases ranged in age from 14 to 55 years, with an average of 24 years (standard deviation (SD) 6.3) and a median of 22; 50 (51%) cases were male.

The most frequently reported symptoms were fever (96%) and cough (95%). Four cases did not have fever. Among 41 cases for whom this information was available, 17 (41%) reported diarrhoea (Table 3).

No deaths have been reported. Disease presentation has been described as a mild influenza-like illness with full recovery in all cases. Some cases were hospitalised at the beginning of the outbreak for respiratory isolation following the national pandemic preparedness plan, this procedure having no association with illness severity.

No differences in disease presentation have been described for secondary cases. No pregnancies among confirmed cases have been reported.

Information on seasonal influenza 2008-9 vaccine status is available for 52 cases (53%); of these, only five cases had history of vaccination.

Laboratory confirmation

Nose and throat swabs from cases who met clinical and epidemiological criteria were taken and referred to the national influenza reference laboratory (WHO National Influenza Centre) at the Instituto de Salud Carlos III for confirmation. Two independent

assays have been used for diagnosis; a reverse transcription (RT)-nested PCR designed for typing the nucleoprotein gene and another one for subtyping the haemagglutinin gene. An alternative RT-PCR was done in case the first two PCR gave contradictory results. Amplified products were sequenced and a phylogenetic analysis was done to identify the new A (H1N1) virus. The strain identified in all cases was confirmed as genetically similar to viruses previously isolated from cases in California (A/California/04/2009).

Detailed information on co-infection with other respiratory viruses is pending. Virological studies on antiviral sensitivity and on molecular-level indicators of severity are ongoing.

Discussion

Spain was the first country in Europe to report a laboratory-confirmed case of new influenza A(H1N1) virus infection. Several factors may have contributed: intense air traffic and contacts with Mexico [5] but also a timely alert with high media coverage that raised early awareness among public health and healthcare professionals, as well as among the public.

An extremely efficient surveillance system and a sensitive case definition that was distributed early in the event made it possible to detect cases at the very beginning of the outbreak and to trace more than 2,000 close contacts. Secondary cases have been identified among close contacts of the first reported cases. However, they are still only a minor percentage of all reported cases and further spread of this new influenza virus into the community has not been documented. The last imported case had disease onset on 2 May, but the change in the case definition on 7 May including the US as an affected area may lead to notification of new imported cases.

The preliminary findings from the analysis of the first 98 laboratory-confirmed cases of the new influenza A(H1N1) virus infection in Spain indicate that symptoms in these cases appear to be similar to those of seasonal influenza. Cases observed are mainly distributed among young adults, reflecting the age structure of returning travellers from Mexico. This group has no risk factors for influenza complications and is difficult at this stage to assess the potential severity of this virus. For the time being, the impact of this outbreak on the healthcare services has been negligible.

Conclusion

The evolution of this outbreak of influenza A(H1N1) in Spain is difficult to predict. Though notification of new confirmed cases has decreased and the disease seems mild, we will continue monitoring changes in the epidemiology and/or clinical severity of new influenza A(H1N1) virus infections in Spain in order to implement appropriate prevention and control measures.

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TABLE 3

Clinical features of confirmed cases for new influenza virus A(H1N1) infection, Spain, as of 11 May 2009

Symptom	Cases with symptom/ cases for whom information is available	Percentage
Fever (≥ 37.5 °C)	87 / 91	96%
Cough	83 / 87	95%
Headache	27 / 44	61%
Coryza	24 / 41	59%
Sore throat	29 / 48	60%
Myalgia	29 / 49	59%
Shortness of breath	18 / 70	26%
Malaise	23 / 38	61%
Diarrhoea	17 / 41	41%
Vomiting	4 / 32	13%

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EPIDEMIOLOGY OF NEW INFLUENZA A(H1N1) IN THE UNITED KINGDOM, APRIL – MAY 2009

Health Protection Agency and Health Protection Scotland new influenza A(H1N1) investigation teams*^{1,2}

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Following importations of cases from Mexico and the United States, by 11 May, United Kingdom surveillance activities had detected a total of 65 individuals with confirmed infections caused by the new influenza A(H1N1) virus. The infections were mainly in young people and younger adults and they spread within households and within schools. The illness in the United Kingdom is similar in severity to seasonal influenza and to date, besides one case of bacterial pneumonia, no clinically serious cases have occurred.

On 23 April, several cases of severe respiratory illness were confirmed as a new swine-lineage influenza A(H1N1) virus infection in the United States [1]. Genetic analysis of these viruses indicated that they were novel viruses, not detected previously in either the swine or human population in North America [2]. Coincidentally, in March and April 2009, Mexico experienced outbreaks of respiratory illness in several parts of the country. Analysis of viral isolates from affected cases in Mexico indicated that illness was associated with a novel then called “swine virus” similar to that identified in sporadic cases in the US [3]. This novel virus has since been identified in humans in Canada, Europe and elsewhere [4].

On 27 April, the first two confirmed United Kingdom cases of new influenza A(H1N1) virus infection were reported in Scotland, in a couple returning from travel to Mexico.

In response to the detection of confirmed cases of new influenza A(H1N1) in the United Kingdom, the Health Protection Agency (HPA) and the Devolved Administrations strengthened national surveillance of respiratory illness amongst travellers returning from affected areas. As part of case finding, a possible case was defined as any person with a history of acute respiratory illness and recent travel to an affected area or contact with a confirmed or probable case; a probable case was defined as a person who was a possible case and had tested positive for influenza A which was non-subtypeable and a confirmed case was an individual that tested positive for the new influenza A(H1N1) virus by specific-RT-PCR confirmed by sequence analysis.

During the period 27 April to 11 May, a total of 65 confirmed cases were detected. From the first reported cases on 27 April, initial cases were amongst travellers returning from Mexico, and then the United States, with a peak on 1 May. The first indigenously acquired infections in the United Kingdom were reported on 1 May and the proportion and number that are indigenously acquired has been reasonably stable since May 7

Cases of new influenza A(H1N1) have been identified in England (60) and Scotland (5). Of the English cases, 34 have been identified in London; six in North West and South East England; five in East of England; three in each of South West and West Midlands; two in East of Midlands and one each in North East and South East.

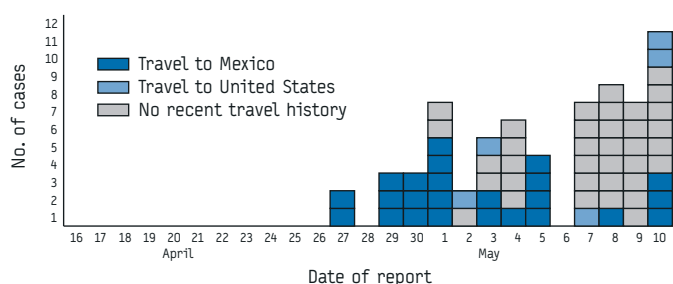
Of the 65 confirmed cases, 29 (45%) are female (Figure 2). Cases range in age from 5 to 73 years – with 58% of patients falling into the age range 10-29 years (Figure 2). The age distribution of indigenous cases is predominately in the 10-19 year age group (Figure 2b).

Travel history

Of the 65 cases, twenty-four reported a history of recent travel from Mexico and five from the US (one from each of California, Florida, Texas and two from New York).

The remaining 36 (56%) cases report no recent overseas travel and acquired their infection through secondary transmission in the United Kingdom. All but one of these can be linked to cases who travelled from affected areas. These indigenous cases are mainly affecting 10-19 year olds at present (Figure 2b). Of these cases, a number of secondary cases are linked to transmission in different household/close contact settings. Transmission has also occurred in two school settings in London. An in-depth field epidemiology investigation of the school cluster is presently underway.

FIGURE 1
Cases of laboratory confirmed new influenza A(H1N1) by day of report and travel history, United Kingdom, 10 May 2009* (n=65)



Clinical picture

The First Few Hundred (FF100 project) aims to collect information about a limited number of the earliest laboratory confirmed cases of new influenza A(H1N1) and their close contacts [5]. This is to gain an early understanding of some of the key clinical, epidemiological, and virological parameters of the new influenza A(H1N1) virus and to facilitate real-time modelling efforts to make predictions of the future course of the United Kingdom epidemic. By 11 May, of the total of 65 confirmed cases, 53 had been reported and entered into the First Few-100 database. Cases generally presented with the most common symptoms typical of influenza – with fever (94%), sore throat (82%), headache (81%), chills (80%) and malaise (80%). Diarrhoea (28%) and arthralgia (56%) were moderately frequently reported. Five cases reported epistaxis and one a seizure. Children were more likely to have dry cough (83% vs. 55% OR = 5.7 95% CI: 0.97-34.2), malaise (89% vs. 69% OR = 8.1 95% CI 0.78-85.0) and epistaxis (24% vs. 6% OR = 4.9 95% CI: 0.46-52.4) than adults. Females were more likely to vomit than males (40% vs. 11%, OR=6.7; 95% CI: 1.1-41.1) and have diarrhoea (39% vs. 14%, OR = 4.0 95% CI: 0.8-19.8).

No case in the United Kingdom, to date has died. Amongst those patients with detailed information, three have been hospitalised – one with secondary pneumonia and two for clinical investigation. None of the cases were reported to have underlying risk factors for severe influenza or to have been vaccinated with either seasonal influenza or pneumococcal vaccine.

All of the cases except one had been treated with oseltamivir once diagnosed. Contacts are currently being actively followed up to provide information to enable estimations of epidemiological parameters such as secondary attack rate, serial interval and reproductive rate.

Conclusions

In summary, the United Kingdom continues to observe sporadic importations of new influenza A(H1N1) virus from affected areas predominately Mexico, but also now from the United States. As sustained transmission becomes established in other countries,

importations from other parts of the globe to the United Kingdom will be observed. At this stage, healthy young adults and children are being proportionately more affected than other parts of the population. Based on the limited United Kingdom case series to date; the clinical presentation of cases continues to be relatively mild. Further work is on-going to describe more fully the emerging epidemiological, virological and clinical characteristics of this new influenza A(H1N1).

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*Authors' correction

In Figure 1 the date was corrected from 11 to 10 May. In the contributors' list the name of B. Carmen was added. These corrections were made upon the request of the authors on 18 May

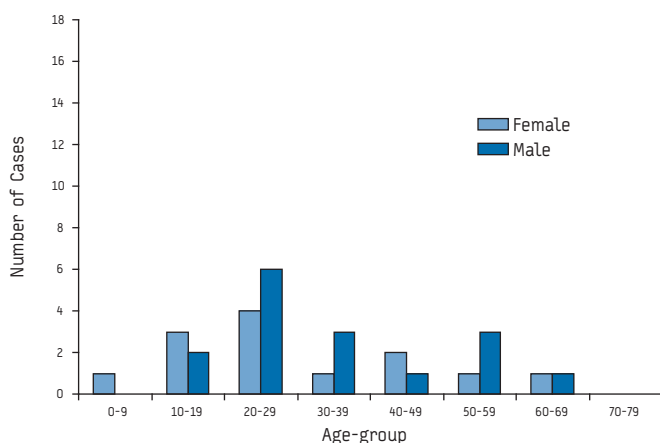
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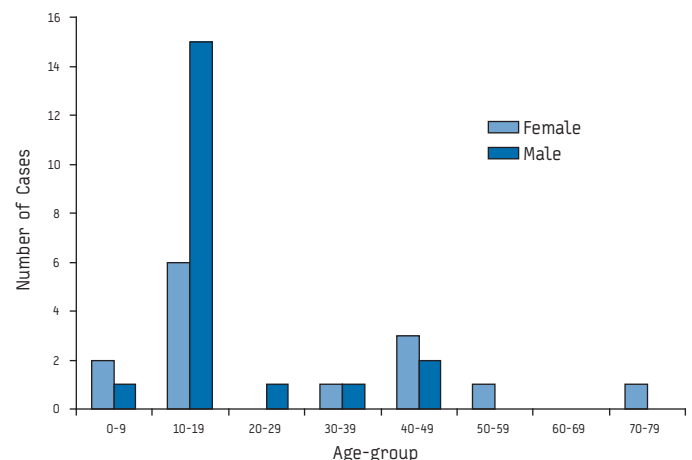
FIGURE 2

Cases of laboratory confirmed new influenza A(H1N1) by age-group and sex, United Kingdom, 11 May 2009 (n=65)

2a. Imported cases (n=29)



2b. Indigenous cases (n=36)



A PRELIMINARY ESTIMATION OF THE REPRODUCTION RATIO FOR NEW INFLUENZA A(H1N1) FROM THE OUTBREAK IN MEXICO, MARCH-APRIL 2009

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As of 12 May 2009, 5,251 cases of the new influenza A(H1N1) have been officially reported to the World Health Organization (WHO) from 30 countries, with most of the identified cases exported from Mexico where a local epidemic has been going on for the last two months. Sustained human-to-human transmission is necessary to trigger influenza pandemic and estimating the reproduction ratio (average number of secondary cases per primary case) is necessary for forecasting the spread of infection. We use two methods to estimate the reproduction ratio from the epidemic curve in Mexico using three plausible generation intervals (the time between primary and secondary case infection). As expected, the reproduction ratio estimates were highly sensitive to assumptions regarding the generation interval, which remains to be estimated for the current epidemic. Here, we suggest that the reproduction ratio was less than 2.2 – 3.1 in Mexico, depending on the generation interval. Monitoring and updating the reproduction ratio estimate as the epidemic spreads outside Mexico into different settings should remain a priority for assessing the situation and helping to plan public health interventions.

Introduction

As of 12 May 2009, 5,251 cases of the new influenza A(H1N1) have been officially reported to the World Health Organization (WHO) from 30 countries [1,2]. Two parameters must be estimated for this new virus using mathematical and computational models: the reproduction ratio (R), which measures the average number of secondary cases per primary case; and the generation interval, which measures the average time between infection in a primary case and its secondary cases. The larger the reproduction ratio, the higher the required efficacy of public health interventions [3]. Here we use two different methods to provide preliminary estimates of R for the outbreak in Mexico.

Methods

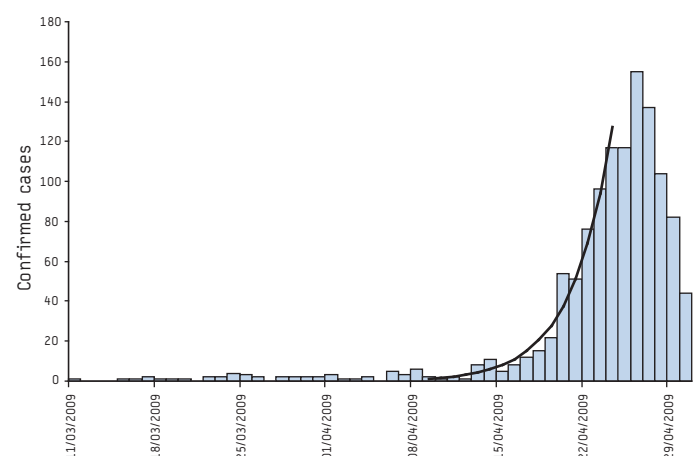
We used the daily incidence data from 11 March to 2 May 2009 as reported by the Mexican health authorities [4] (http://portal.salud.gob.mx/descargas/pdf/influenza/situacion_actual_de_la_epidemia_080509.pdf). The data consisted in 1,364 confirmed cases given as daily counts.

Two different approaches were used to estimate R:

- M1 - intrinsic growth rate [5]: the growth rate of the epidemic is estimated by Poisson regression over a given time interval and transformed to R using Laplace transform of the generation interval distribution. The assumptions are the exponential growth of the epidemic and known generation interval. After visual inspection of the epidemic curve, all periods starting before 20 April and ending after this date, more than five days long, were explored. Goodness of fit of the exponential model was judged by the deviance R-squared measure.
- M2 - real time estimation [6]: a daily reproduction ratio R(t) is determined by averaging the number of secondary cases over all possible chains of transmissions compatible with the epidemic curve. This approach assumes no imported cases, equiprobability of all chains of transmission compatible with the data and known generation interval.

FIGURE 1

Epidemic curve of the outbreak of new influenza A(H1N1) in Mexico and fitted exponential growth over the period 9 to 24 April 2009

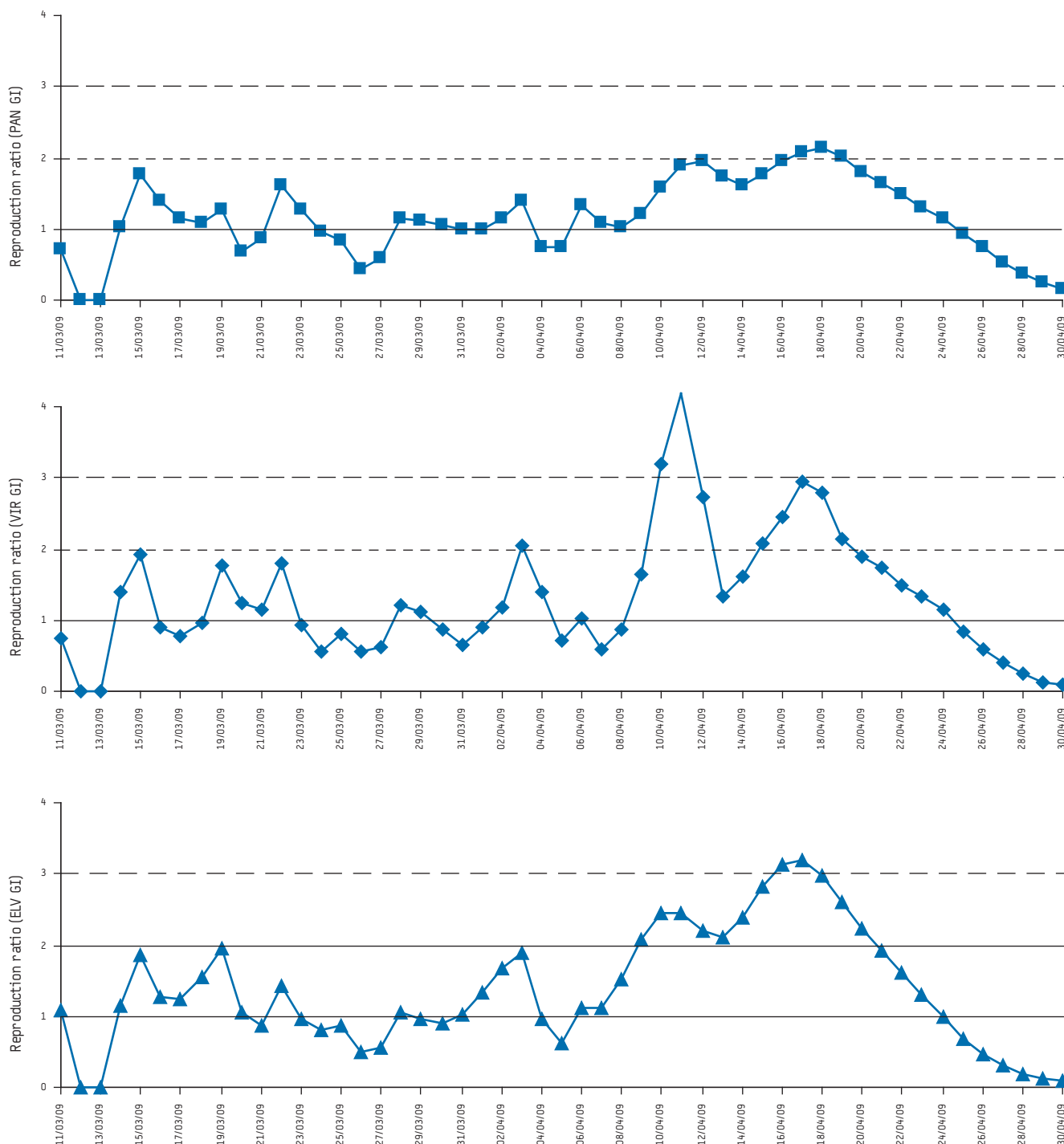


The two methods require full specification of the generation interval distribution. As no information regarding the actual generation interval in Mexico is available, we used three plausible candidate values of the generation interval (denoted GI) derived

from different approaches: one (denoted as PAN) obtained from household studies from the 1957 and 1968 pandemics [7], one derived from viral excretion in experimental influenza infection (denoted as VIR) [8], and a hypothetical distribution introduced

FIGURE 2

Estimates of the daily reproduction ratio $R(t)$ in the outbreak of new influenza A(H1N1) in Mexico, calculated with method M2 (see Methods) using three generation interval values: PAN GI (top), VIR GI (middle) and ELV GI (bottom)



in Elveback (denoted ELV) [9]. Their values with mean standard deviation (SD) were the following: PAN = 3.1 +/- 1.9 days; VIR = 2.6 +/- 1 day; ELV = 4.6 +/- 1.5 days.

Results

When using M1, the period starting on 9 April and ending on 24 April yielded the best fit for exponential growth, with daily rate $r = 0.30$ [CI95% 0.28-0.34] (Figure 1). The corresponding R was 2.2 [2.1, 2.4] for the PAN GI; 2.6 [2.4, 2.8] for the VIR GI; and 3.1 [2.9, 3.5] for the ELV GI. Overall, the differences in goodness of fit were small. The reproduction ratio decreased as the duration of the period used to estimate the growth rate increased: for the PAN GI, the maximum was 2.7 (8 days) and the minimum 2.0 (17 days).

With method M2, all three generation intervals led to similar profiles of $R(t)$ with time: $R(t)$ was around 1 up to 8 April then increased rapidly during the two following weeks (Figure 2). The magnitude of R depended on the generation interval: the maximum value was 2.1 (18 April) for the PAN GI; 4.0 (11 April) for the VIR GI; and 3.2 (17 April) for the ELV GI.

Discussion

Obtaining timely estimates of the reproduction ratio is crucial for deciding on public health interventions in case of a pandemic. In this respect, our analysis suggests that the maximum reproduction ratio was < 2.2 (for PAN GI); < 2.6 (for VIR GI) and < 3.1 (for ELV GI) during the outbreak in Mexico, subject to the following limitations.

Firstly, the epidemic curve was obtained by retrospective testing of samples, so that new cases may still be added. Indeed, for the same period (11 March to 26 April), there were 97 confirmed cases in the report published on 1 May, 682 in the 5 May report, and 803 in the 8 May report. With each new version of the epidemic curve,

the reproduction ratio estimates grew smaller. The increase in the epidemic curve coincided with the setup of enhanced surveillance (starting from 16 April), suggesting improved case-finding with time. This notification/surveillance bias leads to overestimation of the reproduction ratio, as a larger number of late cases would be attributed to fewer earlier cases; on the other hand, however, the effect of public health interventions (closure of schools, restaurants and other public places, etc.) may affect the results in the opposite direction.

The assumptions required to estimate the reproduction ratio must also be taken into account. As already mentioned, the generation interval is unknown for the outbreak in Mexico, but of major importance for quantitative estimates. This illustrates the importance of estimating as soon as possible the generation time distribution to calibrate estimates of R [6]. As expected, longer generation time generally led to larger estimated R [3]. We believe the PAN GI should be favoured in the interpretation of the results, as it was determined from household data during past influenza pandemics.

A second limitation arises from arbitrary deciding which part of the epidemic curve displayed exponential growth, namely a minimum duration (five days), a starting and ending date. Stochastic variations, especially in small time series, may cause large uncertainties in the estimates [10]. Observing that the real time reproduction ratio M2, which does not rely on the exponential growth assumption, yielded smaller reproduction ratio estimates, suggests that method M1 yielded upper bound estimates.

A comprehensive analysis of all available data has independently led to the range 1.4-1.6 for the reproduction ratio [11]. At least two factors contribute to this substantially lower estimate: underreporting was explicitly taken into account and reduced the

TABLE

Epidemic growth rates estimated for the new influenza A(H1N1) epidemic in Mexico and corresponding reproduction ratio estimates calculated with method M1 (see Methods)

Period length (days)	Start date (m/d/y)	End date (m/d/y)	R ²	Growth rate (/day)	CI 95%	R (PAN GI)	R (VIR GI)	R (ELV GI)
5	04/19/09	04/23/09	0.8777	0.29	[0.29, 0.21]	2.2	2.5	3.0
6	04/19/09	04/24/09	0.9159	0.27	[0.27, 0.21]	2.1	2.4	2.8
7	04/16/09	04/22/09	0.9361	0.37	[0.37, 0.3]	2.6	3.1	3.9
8	04/15/09	04/22/09	0.9500	0.38	[0.38, 0.31]	2.7	3.2	4.0
9	04/15/09	04/23/09	0.9583	0.35	[0.35, 0.3]	2.5	2.9	3.6
10	04/15/09	04/24/09	0.9598	0.32	[0.32, 0.28]	2.3	2.7	3.3
11	04/14/09	04/24/09	0.9524	0.31	[0.31, 0.27]	2.3	2.6	3.2
12	04/13/09	04/24/09	0.952	0.3	[0.3, 0.26]	2.2	2.6	3.1
13	04/12/09	04/24/09	0.9537	0.3	[0.3, 0.27]	2.2	2.6	3.1
14	04/11/09	04/24/09	0.9585	0.3	[0.3, 0.27]	2.2	2.6	3.1
15	04/10/09	04/24/09	0.9619	0.31	[0.31, 0.28]	2.3	2.6	3.2
16	04/09/09	04/24/09	0.9643	0.3	[0.3, 0.28]	2.2	2.6	3.1
17	04/10/09	04/26/09	0.9564	0.26	[0.26, 0.24]	2.0	2.3	2.7
18	04/09/09	04/26/09	0.9596	0.26	[0.26, 0.24]	2.0	2.3	2.7
19	04/08/09	04/26/09	0.9544	0.26	[0.26, 0.24]	2.0	2.3	2.7
20	04/07/09	04/26/09	0.9554	0.25	[0.25, 0.24]	2.0	2.2	2.6

Note: Each line reports the best fitting period of given duration, as measured by the deviance R-squared measure.

reproduction ratio, and the generation interval, estimated from the actual epidemic, seems to have been much shorter than considered here (mean 1.9 days).

Although sensitive to all uncertainties discussed above, our early estimates show that the reproduction ratio in Mexico was in a range similar to that of past influenza pandemics [12,13].

Acknowledgements

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CLUSTER OF NEW INFLUENZA A(H1N1) CASES IN TRAVELLERS RETURNING FROM SCOTLAND TO GREECE – COMMUNITY TRANSMISSION WITHIN THE EUROPEAN UNION?

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On 26 and 27 May, the Hellenic Centre for Disease Control and Prevention in Greece reported two confirmed cases of new influenza A(H1N1) virus infection in travellers returning from Scotland. The two cases had no apparent traceable links to an infectious source. Herein we report details of the two cases and potential public health implications.

Case report

Case 1

A 21-year old Greek man developed mild influenza-like illness on 24 May while in Edinburgh where he studies. Symptoms included cough and fever (39°C). On 25 May, he travelled to Athens in Greece and the next day, 26 May, he visited the outpatient department of one of the hospitals designated for influenza A(H1N1) in Athens. The examining physician decided to take a pharyngeal swab, which was tested at the National Influenza Reference Laboratory for Southern Greece, although the patient did not meet the European Union (EU) and national criteria for the new influenza A(H1N1) testing (“case under investigation”) [1]. The result of real time PCR was positive for the new influenza A(H1N1) virus (CDC kit). The patient reported no travel history to another place in the past 15 days. To his knowledge, he had no contact with a known case of influenza A(H1N1) or any sick person. However, on 21 May, he met a large number of people, mainly students and attended three student parties in the evenings of 21, 22 and 23 May. Furthermore, he spent a lot of time with his two room-mates and at least two other close friends, one of whom is case 2. The patient has not developed any complications and is in good condition.

Case 2

A 20-year old Greek man, a close friend and fellow student of case 1, developed mild influenza symptoms without complications, with fever (38°C), mild cough and myalgia, on 24 May. He travelled from Edinburgh to Thessaloniki in Greece on the previous day, 23

May. On 26 May he visited the AHEPA hospital in Thessaloniki, after he had learnt about his friend’s (case 1) illness. A pharyngeal swab was taken and tested at the National Influenza Reference Laboratory for Northern Greece, and the real time-PCR test was positive for the new influenza A(H1N1) virus (CDC kit). This patient had also attended many of the same social events as case 1, including the party of 21 May, but he had not participated in the parties on 22 and 23 May. The last time he met his friend (case 1) was in the morning of 23 May, when he was leaving Edinburgh.

Contact tracing was carried out for close family members, room-mates, close friends and social contacts of both the confirmed cases, as well as for flight contacts of case 1, who was symptomatic during his airway travel. Chemoprophylaxis (oseltamivir) was administered to close contacts in Greece according to the national guidelines. All known contact details were communicated to Health Protection Scotland.

Discussion

Cases of human infection with influenza A(H1N1) are currently affecting geographically diverse areas around the world [2-4]. Person-to-person transmission has led to increasing numbers of cases in North America that are attributed mainly to local clusters especially in schools [3]. Nevertheless it appears that in areas with high population density sustained transmission within the community has occurred, mainly in Mexico and the United States, to date [2-3, 5]. So far, no sustained community transmission has been reported in Europe. However the situation is characterised as rapidly evolving [6] and similar clusters have been reported in Europe [7].

We herein report two cases of influenza A(H1N1) who most probably were not infected from one another, as their symptoms

started almost simultaneously and their last person-to-person contact took place about 30 hours before symptom onset. It is likely they had a common exposure during one of their several community gatherings in Scotland with no traceable (at this point) link to the source of infection.

The two Greek cases of new influenza A(H1N1) who acquired infection in Scotland raise two possibilities. It is possible that a seeding event from an as yet unidentified traveller from an affected area with widespread sustained transmission (e.g. United States or Mexico) occurred. Whether this exposure happened during one of the gathering events both cases attended or in the community (since both cases had extensive and wide exposure to other community events) is unclear at this point. Secondly, there is a chance that institution-wide transmission has been taking place in the university the cases attend or widespread transmission exists in the community in the specific geographical area in Scotland that has led to the exposure of the two cases.

Several public health implications arise from the cases presented here. Firstly, cases of the new influenza A(H1N1) infection are for the first time confirmed in travellers from one European country to another, with no specific history of exposure to a traveller from Mexico or the United States and no traceable link to the source of infection. Although sustained human-to-human transmission within the country has not been confirmed in Scotland, a number of cases infected within the country have been reported from the United Kingdom [8].

Secondly, if measures for containment of the new virus continue to be implemented for some time in some of the less affected countries to delay spread, there is a need for an efficient mechanism – at an international or at least European level – for updating information about areas with “sustained community transmission”.

Thirdly, at this stage of the new influenza A(H1N1) epidemic, community transmission can be established in any country without a known and well identified chain of transmission. This risk increases as we are entering the tourist season and as the number of countries reporting large numbers of confirmed cases is increasing. It is of concern that with the present EU definition of “cases under investigation” [1], and with the practice this definition implies of testing for A(H1N1) of people with clinical symptoms and travel history to an “affected area” (epidemiological link to a confirmed case or laboratory worker are exceptional at this stage in Europe), we are by definition going to miss cases infected locally in the event of established community transmission without known and identified chain(s) of transmission. For the present period (late spring-summer, minimal seasonal influenza activity), it is probably necessary to modify the present EU definition of “cases under investigation” to also include clusters of patients with influenza-like illness, irrespective of travel history. If this were the case, our patients would have met the criteria for specific influenza A(H1N1) testing.

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NEW INFLUENZA A(H1N1) VIRUS INFECTIONS IN FRANCE, APRIL – MAY 2009

New influenza A(H1N1) investigation teams*^{1,2}

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Since the emergence of a new influenza A(H1N1) virus in North America and its international spread, an active surveillance of cases of infection due to this virus has been set up in France in order to undertake appropriate measures to slow down the spread of the new virus. This report describes the epidemiological and clinical characteristics of the 16 laboratory confirmed cases diagnosed in France as of 20 May 2009.

Background

Human cases of new influenza A(H1N1) virus infection have been identified recently in many countries [1,2]. After the detection of the first cases in Mexico and in the United States and the spread of infection to further countries, the World Health Organization (WHO) declared the outbreak of a new influenza A(H1N1)swl (swine-like) virus infection to be a “public health emergency of international concern”. On 27 April 2009, the first cases were reported in the United Kingdom and in Spain in travellers returning from Mexico [3,4]. In response to the risk of spread of the disease in France, national active surveillance of respiratory illness among recent travellers in the affected areas (see definition below) has been set up. On 1 May 2009, the first cases were identified in France, and on 20 May 2009, the number of confirmed cases in France has reached a total of 16 cases.

Methods

Organisation of the surveillance

The objective of the surveillance is to detect cases of influenza due to the novel virus in travellers coming back from the affected areas in order to implement control measures around each case and contain the indigenous spread of the virus.

A case definition triggering case investigation has been established and widely diffused [5]. A possible case is defined as a person with acute respiratory illness (defined as the occurrence of fever ($\geq 38^{\circ}\text{C}$) or myalgia or asthenia and at least one respiratory symptom (cough or dyspnea)) and a history of travel in an affected area or a history of a close contact with a confirmed or possible case during the seven days before the onset of symptoms. Taking into account the international situation, the affected areas mentioned in the case definition are updated when needed [5]. On 20 May 2009, Mexico, United States, Canada, Panama, Dominican Republic and Japan were considered as affected areas.

A probable case is defined as a person with a positive PCR for influenza A virus or a possible case with a close contact with

a confirmed or probable case. A confirmed case is defined as an individual tested positive for the new influenza A(H1N1) virus with a specific PCR. As long as a possible case is neither confirmed nor discarded, he/she is considered as “currently under investigation”.

Protocols for case and contact management and for infection control were developed and distributed by the French Ministry of Health and the French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS). Symptomatic persons coming from an affected area are advised to call the local hospital based mobile emergency unit (Centre 15). A medical practitioner assesses the case by phone and if the person meets the case definition for a possible case the Centre 15 calls the InVS, to validate the classification and guide the case management. Detailed information is available on flights coming from affected areas and at international airports and a 24/24 and 7/7 duty service by trained epidemiologists has been set up at InVS to answer calls from the Centre 15 or other health professionals. Hospitalisation of all possible or probable cases is recommended whatever the severity of symptoms. Nasal swabs from such cases have to be sent to one of the 24 laboratories which have been approved by the Ministry of Health to test those specimens for influenza A by PCR under BSL3 conditions. When the specific A(H1N1)swl PCR have been sent to all 24 laboratories, positive results have to be confirmed and further viral identification to be done by one of the two French National Reference Centres (NRC) for influenza viruses.

Curative treatment by neuraminidase inhibitor is recommended for cases, even those classified as possible ones. Prophylactic treatment by neuraminidase inhibitor is recommended for close contacts of probable or confirmed cases only. These close contacts are asked to follow a quarantine at home and to avoid unnecessary contacts with other people. In case of appearance of fever or respiratory signs, they should consult a medical professional immediately.

Case-base epidemiological and virological data are collected through an interactive application (adapted from Voozano®, Epiconcept®) allowing a real time exchange of information between epidemiologists from InVS, from the 15 French Interregional epidemiology units (Cire) located in mainland France, the two Cire located overseas and virologists of the NRCs.

Results

On 1 May 2009, France reported its first two laboratory-confirmed cases of the new influenza A(H1N1) virus infection in travellers returning from Mexico. By 20 May 2009, InVS and Cire had been involved in 1,613 reportings (41 located overseas). Among these, 348 were classified as possible or probable cases and 16 have been laboratory-confirmed for the new influenza A(H1N1) swl.

The rest of the analysis concerns the 16 confirmed cases. All cases acquired the infection abroad: 11 cases had a history of travel to Mexico and five cases travelled to United States: two came back from California and three from New-York (Figure). To date, no secondary case has been identified in France. Five cases were

symptomatic before return to France. Among the remaining 11 cases, disease onset occurred up to four days after return (mean and median: 2 days) and these cases reported themselves up to six days after disease onset (mean: 1.5 day, median: 1 day).

Cases were identified in the following regions: Alsace (3), Aquitaine (1), Auvergne (1), Ile-de-France (9) and Languedoc-Roussillon (2). No case has been identified in the French departments of America (French Guiana, Martinique, Guadeloupe) or in Reunion Island located in the Indian ocean.

The cases were reported to InVS by the Centre 15 (10 cases), a hospital (four cases), an individual (one case) and a virological laboratory (one case).

Of the 16 confirmed cases, 10 are male and six are female. Ages range from 18 months to 65 years (mean: 32 years, median: 29 years). The age distribution by age group is as follows: [0-9 years]: one case, [10-19 years]: two cases, [20-29 years]: five cases, [30-39 years]: four cases, [40-49 years]: two cases, [50-59 years]: one case, [60-69 years]: one case.

The clinical features of cases show common symptoms for influenza disease (Table).

No complications have been reported and no death occurred. Underlying conditions were reported for four cases: asthma (two cases), physical and mental impairment (one case) and heart disease with dislipemia (one case).

All cases received antiviral curative treatment once diagnosed; 15 patients took oseltamivir alone and one was administered zanamivir and oseltamivir. Fifteen cases were admitted to hospital and the duration of hospitalisation ranged from three to seven days (median: 5 days).

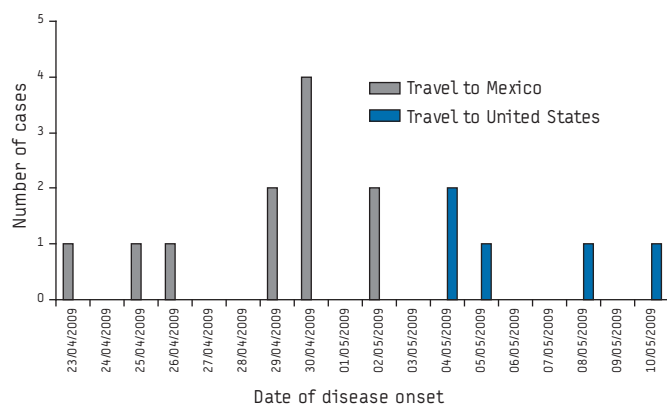
Discussion

France, as other European countries, has identified laboratory-confirmed cases of the new influenza A(H1N1) virus infection through an active surveillance set up as a response to the international situation as soon as the alert was given. As reported in other countries, symptoms in laboratory-confirmed cases resemble those of seasonal influenza. To date no secondary case has been identified among close contacts of the confirmed cases. Systematic hospitalisation of cases with strict implementation of control measures may have contributed to this result. Sporadic cases or self limited chains of transmission may have occurred, though, and gone unnoticed despite the measures taken to detect them. This may happen if a sick traveller prefers not to report to a health professional or when the infection passes to close contacts from an asymptomatic traveller. In order to improve the sensitivity of the surveillance system, a complementary modality of surveillance has been implemented. Health professionals have to notify to public health authorities about clusters of at least three cases of respiratory tract infection occurring within one week in a small community (such as a hospital ward, a nursing home, a classroom or a family) without other aetiology identified as well as to report an unexpected increase of such cases among their patients. Virological investigations are required in these cases in order to exclude a possible infection due to the new influenza A(H1N1)swl virus. So far, all such notified events have been discarded as being due to A(H1N1)swl.

To date, no increase in seasonal influenza activity (based on data from general practitioners sentinel networks, on data on

FIGURE

Cases of laboratory-confirmed new influenza A(H1N1) by day of disease onset and travel history, France, as of 20 May 2009



TABLE

Clinical features of confirmed cases of new influenza A(H1N1) virus infection, France, as of 20 May 2009

Symptom	Cases with symptoms / Cases for whom information is available	Percentage
Cough	16*/16	100%
Fever ($\geq 38.0^{\circ}\text{C}$)	10**/16	62%
Asthenia	9/15	60%
Sore throat	8/14	57%
Myalgia	8/15	53%
Headache	3/15	20%
Sneezing	2/14	14%
Diarrhoea	2/16	13%
Conjunctivitis	2/15	13%
Joint pain	1/14	7%
Vomiting	1/16	6%
Shortness of breath	1/16	6%
Insomnia	1/16	6%

*Cough was reported to be dry for 14 cases (93%) and was associated with a productive cough in three cases.

** Fever was reported to be between 38°C and 39.5°C . Furthermore three more cases reported elevated temperature to 37.5°C (one case) and to 37.7°C (two cases).

consultations for influenza like illness in a network of hospital emergency units and on mortality data surveillance) has been reported.

*The investigating team is composed of more than 90 members of staff of the Institut de Veille Sanitaire and its regional units (Cellules Interrégionales d'Epidémiologie [CIRE]), and it was constituted to manage the response to the epidemic, to assess suspected cases imported from affected areas and to regularly update international information. We are thankful to laboratories, Centre 15, clinicians, public health authorities, UMR707 INSERM – Université Pierre et Marie Curie, for collecting and kindly providing additional clinical data. The corresponding author is S Vaux, InVS (s.vaux@invs.sante.fr).

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CLUSTER ANALYSIS OF THE ORIGINS OF THE NEW INFLUENZA A(H1N1) VIRUS

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In March and April 2009, a new strain of influenza A(H1N1) virus has been isolated in Mexico and the United States. Since the initial reports more than 10,000 cases have been reported to the World Health Organization, all around the world. Several hundred isolates have already been sequenced and deposited in public databases. We have studied the genetics of the new strain and identified its closest relatives through a cluster analysis approach. We show that the new virus combines genetic information related to different swine influenza viruses. Segments PB2, PB1, PA, HA, NP and NS are related to swine H1N2 and H3N2 influenza viruses isolated in North America. Segments NA and M are related to swine influenza viruses isolated in Eurasia.

Introduction

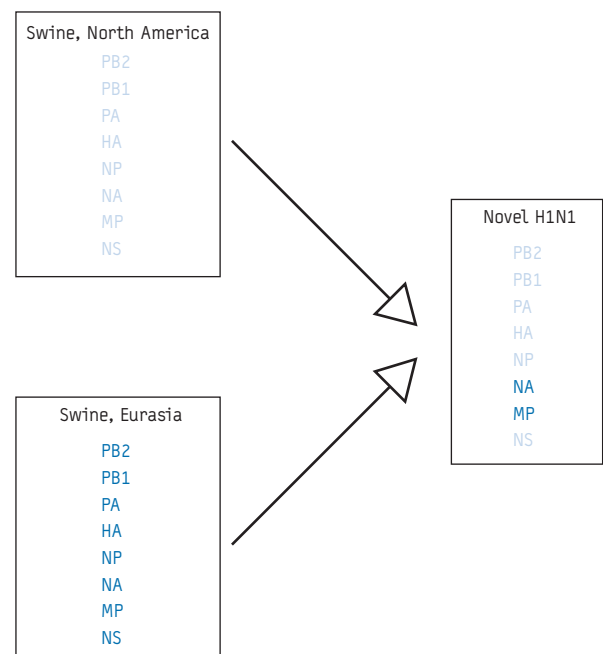
Influenza A virus is a single stranded RNA virus with a segmented genome. When different influenza viruses co-infect the same cell, progeny viruses can be released that contain a novel mix of segments from both parental viruses. Since the first reported pandemic in 1918, there have been two other pandemics in the 20th century. In both cases, the pandemic strains presented a novel reassortment of genome segments derived from human and avian viruses [1-3]. The origins of the 1918 strain are so not clear, although different analyses suggest that this virus had an avian origin [4,5].

When and where pandemic reassortments happen remains a mystery. Avian viruses often undergo reassortment events among different subtypes. Several reports suggest that reassortments are also frequent between human viruses [6,7]. Swine have been found frequently with co-infections and reassortment of swine, human, and avian viruses has been reported [8-10,3]. In addition, cell surface oligosaccharide receptors of the swine trachea present both, a *N*-acetylneuraminic acid- α 2,3-galactose (NeuA α 2,3Gal) linkage, preferred by most avian influenza viruses, and a NeuA α 2,6Gal linkage, preferred by human viruses [11]. Co-infection combined with co-habitation of swine and poultry on small family farms all over Asia, and the presence of avian as well as human receptor types in pigs have led to the "mixing vessel" conjecture [12,13] that suggests that most of the inter-host reassortments are produced in pigs.

Recently, a new A(H1N1) subtype strain has been identified initially in Mexico, then rapidly reported in all continents. As

of 27 May, 12,954 cases of the new influenza A(H1N1) virus infection, including 92 deaths have been reported to the World Health Organization [14,15]. Several approaches have been used to understand the origins of this strain. Searches in public databases containing influenza A genomes using sequence alignment tools indicated that the closest relatives for each of the eight genomic segments are from viruses circulating in swine for the past decade [16-19]. These include genome segments derived from "triple reassortant" swine viruses that combined in the late 1990s genome

FIGURE 1
Origins of the new influenza A(H1N1) virus



Schematic representation of the main results of the cluster analysis. The analysis shows that the recent A(H1N1) virus is a reassortment of at least two swine influenza viruses from North America (in light blue) and Eurasia (in dark blue).

segments from viruses previously identified in humans, birds, and swine [20]. Similar conclusions were drawn by the application of phylogenetic techniques [16,21].

Here we present a cluster analysis using Principal Component Analysis and unsupervised clustering. Clustering methods are particularly robust under changes in the underlying evolutionary models. Our results substantiate previous reports [16,21], and demonstrate that for each of the genome segments of the new influenza A(H1N1) virus the closest relative was most recently identified in a swine, compatible with a reassortment of Eurasian and North American swine viruses (Figure 1).

Materials and methods

Influenza sequences were obtained from the National Center for Biotechnology Information (NCBI) [22] in the United States. We performed a search using Basic Local Alignment Search Tool (BLAST) for each of the eight A/California/04/2009(H1N1) segments separately, recording the 50 best matches. Then we constructed the union of all these matches, taking the sequences for all their segments available in the database. We aligned these sequences using the stretcher algorithm as implemented in the EMBOSS package.

After the alignment we translate the sequences into the binary data, comparing them to the reference sequence site by site. A mutation maps to 1, while a nucleotide identical to that in a reference sequence maps to 0. Whenever there are masks, they map to the corresponding fractional numbers. Gaps are not counted as polymorphisms. Therefore, if there are the S sequences restricted to the P polymorphic sites, these data translate to the SxP matrix. Each row of this matrix can be thought of as a vector in a P-dimensional space, and it represents one of the sequences.

We perform the Principal Component Analysis (PCA) in order to determine the most significant coordinates in this P-dimensional space. After this we leave the principal components which capture 85% of the total variance, discard the remaining ones and project the data onto this relevant coordinate subset.

This procedure is followed by the consensus K-means clustering. Namely, if one targets for K clusters, one repeats the K-means clustering procedure N times, and forms the matrix n whose elements n_{ij} ($i, j=1, \dots, S$) represent the number of times out of the N trials when the i-th and j-th sequences were clustered together. In our analysis we set $N \geq 100$. The matrix of the distances between the samples is:

$$D_{ij} = 1 - \frac{n_{ij}}{N}$$

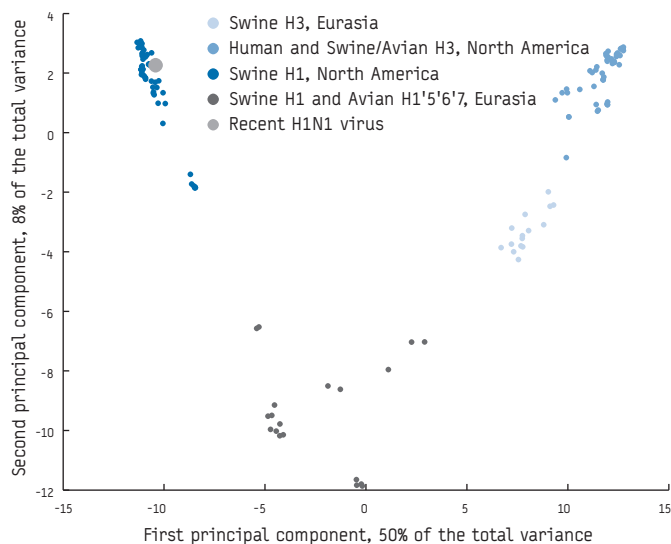
One then performs the standard hierarchical clustering with this matrix, targeting for the K clusters. This procedure does not depend on any assumptions made by the phylogenetic models. Note that these techniques can be used for inferring phylogenies as well [23], though this is beyond the scope of the present note.

Results

Sequence comparison of available sequences of the new A(H1N1) virus (as of 27 May 2009) did not identify significant sequence variation, except for a few point mutations. Hence A/

FIGURE 2A

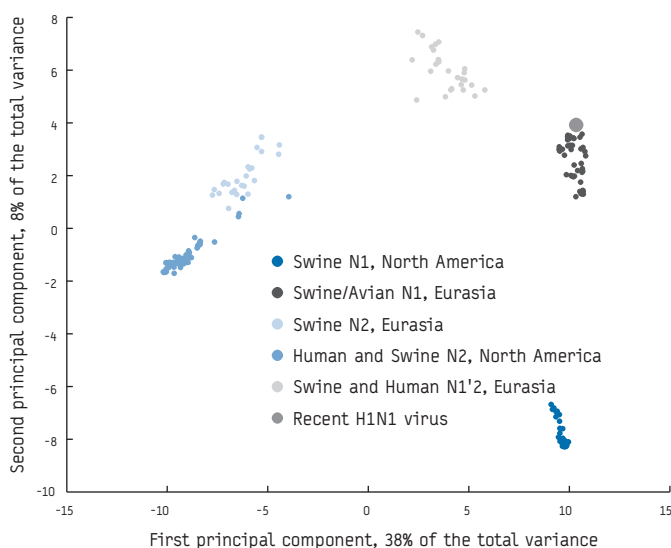
Cluster analysis of the new influenza A(H1N1) virus. HA segment; data projected onto the first two principal components



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2B

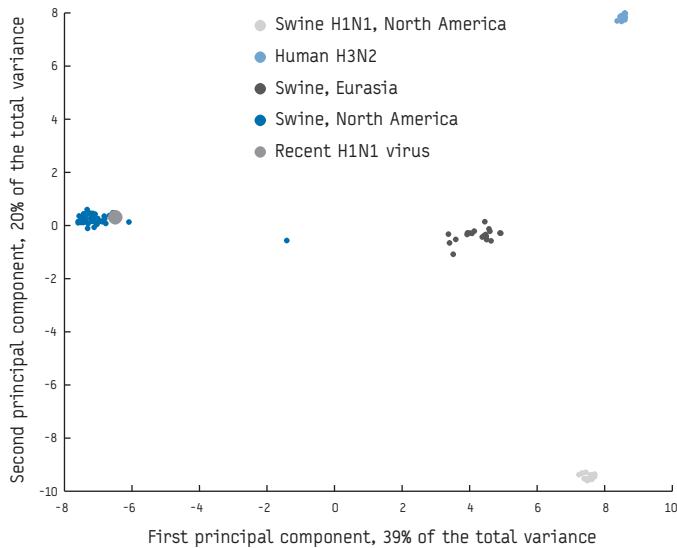
Cluster analysis of the new influenza A(H1N1) virus. NA segment; data projected onto the first two principal components



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2C

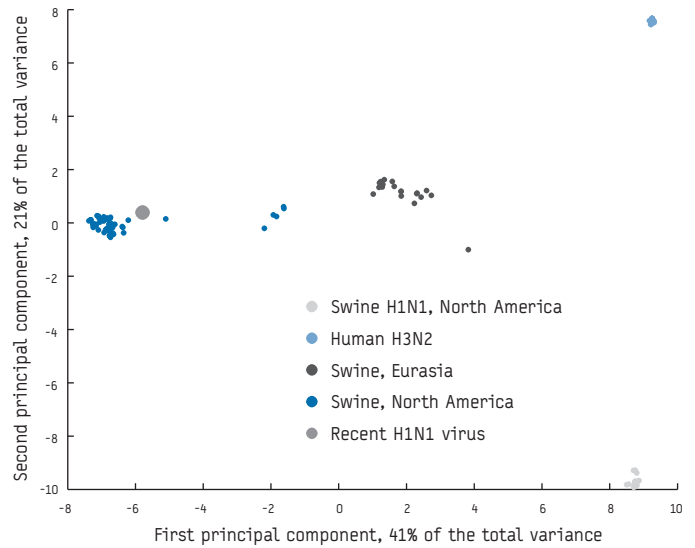
Cluster analysis of the new influenza A(H1N1) virus. PB2 segment; data projected onto the first two principal components



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2E

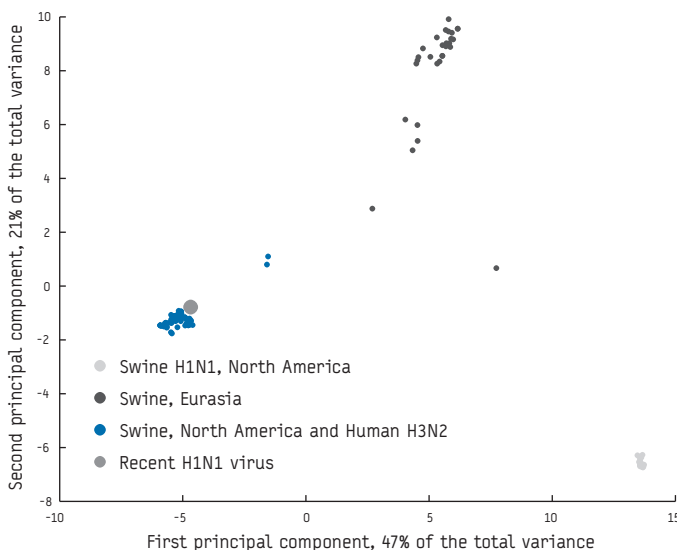
Cluster analysis of the new influenza A(H1N1) virus. PA segment; data projected onto the first two principal components



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2D

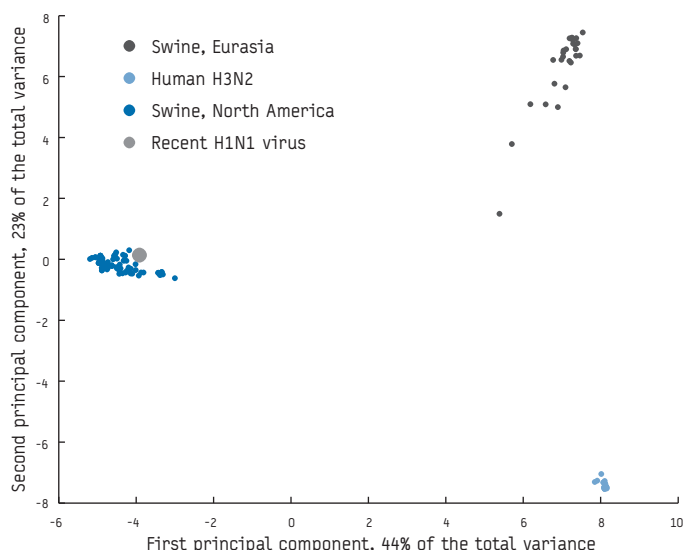
Cluster analysis of the new influenza A(H1N1) virus. PB1 segment; data projected onto the first two principal components



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2F

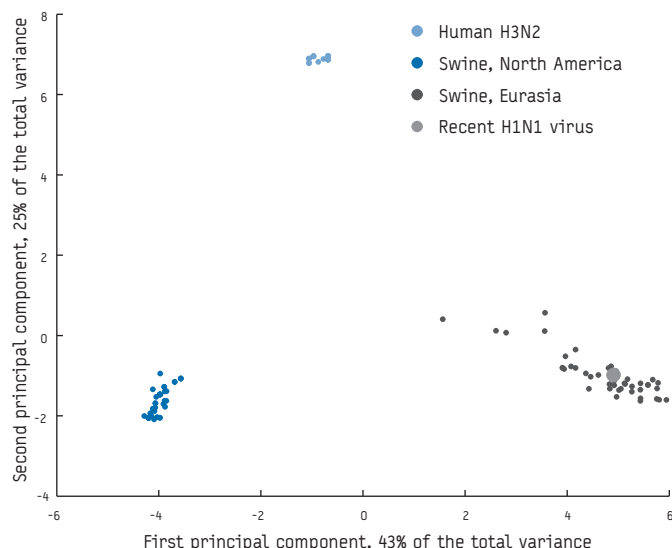
Cluster analysis of the new influenza A(H1N1) virus. NP segment; data projected onto the first two principal components



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2 G

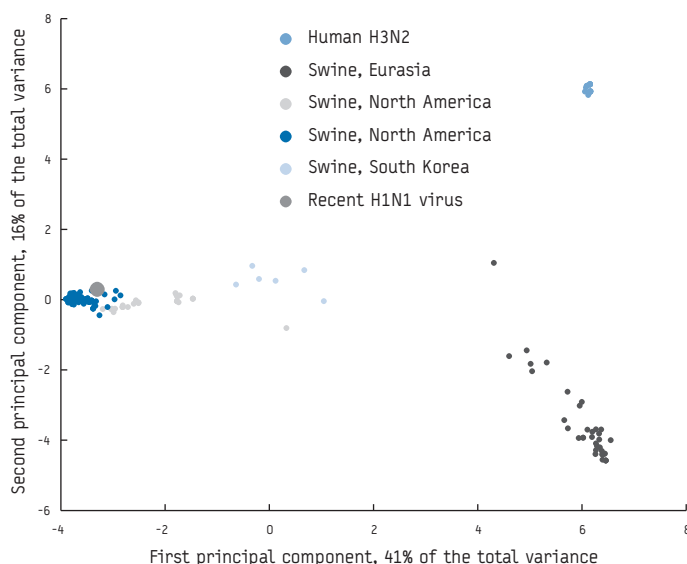
**Cluster analysis of the new influenza A(H1N1) virus.
MP segment; data projected onto the first two principal components**



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

FIGURE 2 H

**Cluster analysis of the new influenza A(H1N1) virus.
NS segment; data projected onto the first two principal components**



Representation of the segment by segment analysis of the closest relatives to the 2009 H1N1 influenza viruses. Data is projected in the two axes of maximal variation. Clusters in different colors represent a distinct host and geographic location. Segments PB2, PB1, PA, HA, NP and NS are related to viruses isolated in swine in North America and NA and MP to swine viruses in Eurasia

California/04/2009(H1N1) was chosen as the representative for further analyses. There are many different phylogenetic techniques, each of them with their own assumptions about evolutionary models that vary in the way of computing genetic distances, probabilities, etc. As opposed to phylogenetic techniques, cluster methods do not have a need for evaluation of a tree, which is a more complicated structure than a set of clusters. Clustering techniques do not provide a detailed phylogenetic structure because they analyse group features of the sequence data. That is why the clustering analysis is more robust to the assumptions we make, for instance, the choice of genetic distance. Unsupervised methods provide a way of identifying clusters without relying on previous information about the origins, host and time isolation.

Figures 2a-2h show the data projected onto the first two principal components with the corresponding percentage of variation. The figures clearly show that in all cases the new virus sequences clustered with those of swine viruses. The closest matches for each of the segments are summarised in the Table.

Our analyses support the hypotheses whereby the 2009 pandemic influenza A(H1N1) virus derives from one or multiple reassortment(s) between influenza A viruses circulating in swine in Eurasia and in North America. It is schematically illustrated in the Figure 1.

Supplementary Tables 1 to 8 show the results of the clustering for each of the eight segments (PB2, PB1, PA, HA, NP, NA, M NS):

- http://www.eurosurveillance.org/public/public_pdf/Table_1_Cluster_analysis_HA.pdf
- http://www.eurosurveillance.org/public/public_pdf/Table_2_Cluster_analysis_NA.pdf
- http://www.eurosurveillance.org/public/public_pdf/Table_3_Cluster_analysis_PB2.pdf
- http://www.eurosurveillance.org/public/public_pdf/Table_4_Cluster_analysis_PB1.pdf
- http://www.eurosurveillance.org/public/public_pdf/Table_5_Cluster_analysis_PA.pdf
- http://www.eurosurveillance.org/public/public_pdf/Table_6_Cluster_analysis_NP.pdf

TABLE

Closer clusters to the new influenza A(H1N1) virus.

Segment	Closest match	Years
PB2	Swine, North America	1998-2007
PB1	Swine, North America	1998-2007
PA	Swine, North America	1998-2007
HA	Swine H1, North America	1985-2007
NP	Swine, North America	1985-2007
NA	Avian/Swine N1, Eurasia	1982-2007
M	Swine, Eurasia	1980-2005
NS	Swine, North America	1998-2007

Closer clusters to each of the segments of the new influenza A(H1N1) virus. The analysis reveals two clusters of related viruses: North American swine viruses (in light blue) and Eurasian swine viruses (in dark blue).

http://www.eurosurveillance.org/public/public_pdf/Table_7_Cluster_analysis_MP.pdf

http://www.eurosurveillance.org/public/public_pdf/Table_8_Cluster_analysis_NS.pdf

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TRANSMISSION POTENTIAL OF THE NEW INFLUENZA A(H1N1) VIRUS AND ITS AGE-SPECIFICITY IN JAPAN

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On 16 May 2009, Japan confirmed its first three cases of new influenza A(H1N1) virus infection without a history of overseas travel, and by 1 June, 361 cases, owing to indigenous secondary transmission, have been confirmed. Of these, 287 cases (79.5%) were teenagers (i.e. between 10 and 19 years of age). The reproduction number is estimated at 2.3 (95% confidence interval: 2.0, 2.6). The average number of secondary transmissions involving minors (those under 20 years of age) traced back to infected minors is estimated at 2.8. That is, minors can sustain transmission even in the absence of adults. Estimates of the effective reproduction number R_t moved below 1 by 17 May. Active surveillance and public health interventions, including school closures most likely have contributed to keeping R_t below one.

Introduction

The reproduction number R , the average number of secondary cases generated by a single primary case, of the new influenza A(H1N1) virus, is a key quantitative measure for assessing pandemic potential [1]. In the ongoing epidemic of the new influenza A(H1N1) virus, early studies suggested that R ranged from 1.4-1.6 [2] and some estimated it to be as high as 2.2-3.1 [3]. Estimates in 1.4-1.6 range for the new influenza A(H1N1) virus are lower than estimates based on data from, for example, the fall wave of the 1918 influenza pandemic [4,5]. The present study investigates indigenous secondary transmissions of the new influenza A(H1N1) virus in Japan, not only estimating R but also exploring its age-specificity.

Methods

Epidemiological description of the epidemic

On 16 May 2009, three high school students in Kobe city, Hyogo prefecture, without a history of overseas travel, were confirmed as infected with the new influenza A(H1N1) virus. Confirmatory diagnosis in Japan requires influenza-like symptoms and a laboratory diagnosis which is made either by virus isolation, real-time PCR or a significant increase in neutralising antibody titre against the virus. Further confirmed diagnoses followed predominantly in Hyogo and Osaka prefectures. The increased number of infections among particular age groups was most evident in the data from prefectures where most secondary cases were found among high school students attending different schools.

By 1 June, the Ministry of Health, Labour and Welfare of Japan had reported 371 confirmed cases, including nine imported cases and one case traced back to a distant international airport (i.e. a

worker at Tokyo-Narita airport) [6]. Figure 1 shows the geographic distribution of 361 indigenous cases. Cases outside Osaka and Hyogo prefectures had travel histories to Osaka or Hyogo before their illness onset. The index case(s) (who may have remained asymptomatic [7]), with a history of overseas travel, has (have) yet to be identified. Furthermore, there are no known cases prior to the five confirmed cases that developed the disease on 9 May in Hyogo (Figure 2A). The triggering event may be associated with Japan's two-week festive break, the "golden week", just before 9 May, when people may have travelled to and returned from Mexico, United States and Canada.

FIGURE 1

Spatial distribution of the epidemic of new influenza A(H1N1) virus infection in Japan. Cumulative number of confirmed indigenous cases, as of 1 June 2009 (n = 361)



Note: Cases in Tokyo, Saitama, Shiga and Kyoto had travel history to either Hyogo or Osaka prefecture before illness onset. Kobe city, where first three cases were diagnosed, is a capital city of Hyogo prefecture.

We analysed the temporal incidence distribution of confirmed cases for this epidemic (Figure 2A). The known dates of illness onset are used except for a fraction of the confirmed cases in Kobe city (45; 12.5%) whose dates of onset have yet to be fully clarified. Since the known median time from onset to diagnosis in Kobe has been estimated at 1.0 day [8], it is assumed that the dates of onset among the 45 cases in Kobe were 1 day before their date of diagnosis. We observed that by the time the first three cases had been confirmed (16 May), the epidemic curve was just about at its peak. 16-17 May fell on a weekend, and all schools in Osaka and Hyogo were officially closed for one week starting on 18 May. Figure 2B displays the age-distribution of the 361 confirmed cases, which is concentrated in the teenage population. We see the age-specific window (10-19 years of age) that includes 287 confirmed cases (79.5%; 95% confidence interval (CI): 75.3, 83.7).

Epidemiological analysis

Taking into consideration the high levels of uncertainty related to the invasion of a population by a novel influenza virus, three different methods are used to estimate the transmission potential of the new influenza A(H1N1) virus. To concentrate on the transmission potential in Japan, all nine imported cases and one case that is not associated with indigenous transmission in Hyogo and Osaka were removed from the following analyses.

Model 1 (M1)

Estimation of R using the intrinsic growth rate [3,5]. The intrinsic growth rate r , is estimated via a pure birth process [9]. The likelihood is proportional to:

$$\exp\left(-r \sum_{i=0}^{t-1} C(i)\right) (1 - \exp(-r))^{C(t) - C(0)}$$

where $C(t)$ denotes the cumulative number of cases on day t . $C(0) = 5$ and $t = 0$ represents 9 May. The generation time (GT) is assumed to follow a gamma distribution with mean $\mu = 1.9$ days and coefficient of variation $v = 47\%$ [2]. R is subsequently estimated using the estimator [10]:

$$(1 + r\mu v^2)^{\frac{1}{v^2}}$$

Given that many serial intervals reported from Spain are longer than 1.9 days [7], the uncertainties surrounding GT estimates are partially addressed through a sensitivity analysis of R to variations in the mean GT in the range from 1.3-4.0 days. The exponential growth phase is assumed to have a mean duration of 8 days but windows in the 8 ± 2 days were also used.

Model 2 (M2)

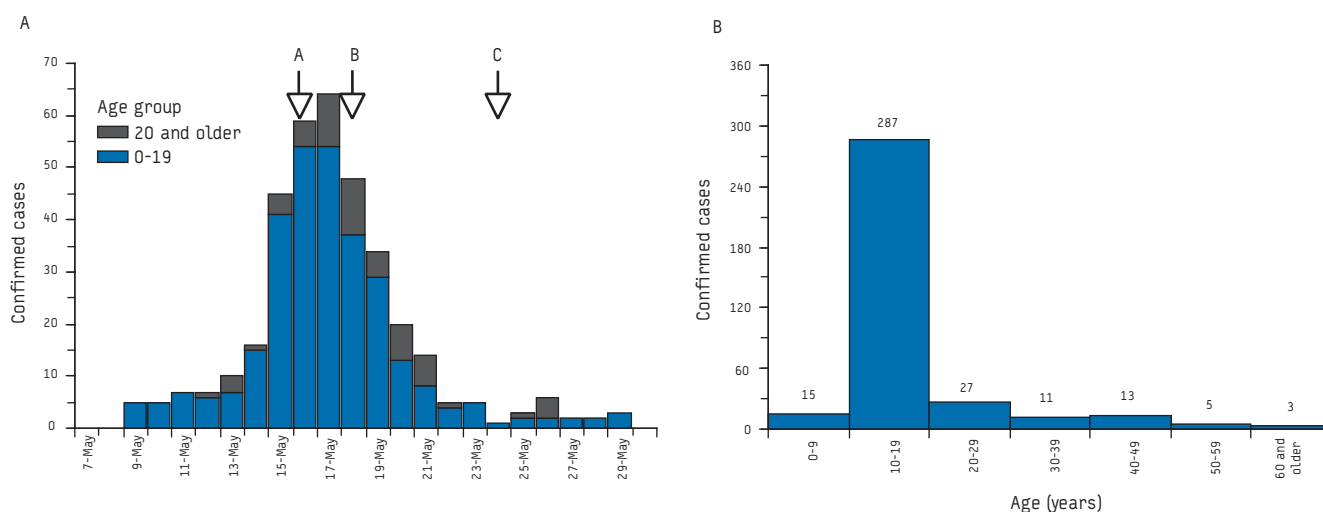
The effective reproduction number R_t , the average number of secondary cases generated by a primary case at time t , is estimated. The daily growth rate rt is used to estimate R_t following the approach described elsewhere [11]; the distribution of GT and the estimator of R used are the same as those used in M1. The mean GT is assumed to be 1.9 days but varying in the 1.3 to 2.5 days range [2].

FIGURE 2

Time- and age-specificity of the epidemic of new influenza A(H1N1) virus infection in Japan

A) Epidemic curve of confirmed indigenous cases according to the date of illness onset, as of 1 June 2009 (n = 361)

B) Age distribution of confirmed indigenous cases, as of 1 June 2009 (n=361)



Note: None of the confirmed cases had recent history of overseas travel (except for one case in Wakayama). The nine cases, believed to have become infected abroad, and one case, arising in a worker at Tokyo-Narita airport, are excluded from these figures. The dates of illness onset for each confirmed case are reported by prefectural governments, except for a fraction of cases in Kobe city where cases with unknown dates of onset are assumed to have developed the disease one day before the confirmatory diagnosis (based on published median estimate [8]). It should be noted that the dates of onset are based on preliminary reports and have yet to be refined. Arrow A indicates the date on which the first three cases were diagnosed in Kobe city. All schools in Hyogo and Osaka were closed between the dates signalled by the arrows B and C.

Model 3 (M3)

The role of age-specificity in transmission is analysed using estimates of the next-generation matrix, K (Figure 3). First, we aggregate the population in two age groups, minors and adults. Second, since the mean GT is approximately 2 days [2], the daily number of cases during the exponential growth phase (i.e. first 8 days) uses as its unit of time, two-day intervals (i.e. cases, c , in days 1 & 2, 3 & 4, 5 & 6 and 7 & 8 are grouped). Third, the expected value of cases in age-group i of grouped-generation τ , $E(c_i(\tau))$, is modelled by $R_{ij}c_j(\tau-1) + R_{ij}c_j(\tau-1)$ (for $\tau = 2, 3$ and 4) where R_{gh} is the element of K that corresponds to the average number of secondary cases in group g caused by an infected individual in group h . We estimate the entries in the matrices, assuming two different mixing patterns modelled via two unknown parameters by means of Poisson regression (Figure 3).

Results

The intrinsic growth rate r , is estimated at 0.47 (0.40, 0.56) per day. Accordingly, M1 gives an R estimate of 2.3 (95% CI: 2.0, 2.6). Figure 4A illustrates the sensitivity of R to variations in the mean GT in the range 1.3-4.0 days. The corresponding R estimates lie in the 1.8 to 4.8 range. Variations in the initial growth phase (i.e. ± 2 days) do not greatly influence R ; i.e. the expected values of R lie in the 1.9 to 2.3 range. The exclusion of the less documented cases in Kobe lead to an R estimate of 2.0 (95% CI: 1.7, 2.3).

Use of M2 suggests that R_t peaked on 14 May (Figure 4B). On 17 May, the day after a press release announced the first three confirmed diagnoses, R_t declined below 1. Under active surveillance efforts and school closures, R_t was kept below 1 thereafter. Consistent temporal patterns of R_t are seen using different values, except for slight increase and decrease in R_t estimates, for GT mean values in the 1.3-2.5 day-range.

Using M3, the next-generation matrix, K_1 estimate, under the separable mixing assumption is

$$\hat{K}_1 = \begin{pmatrix} 2.82 & 0.32 \\ 0.32 & 0.04 \end{pmatrix}$$

while our K_2 estimate based on a qualitative assumption of WAIFW (who acquired infection from whom) matrix is

$$\hat{K}_2 = \begin{pmatrix} 2.82 & 0.29 \\ 0.29 & 0.29 \end{pmatrix}$$

The host-specific reproduction number [12] for minor, i.e. the average number of secondary minor cases generated by a single primary minor case was 2.8 under K_1 and K_2 . Hence a population of minors can sustain the chains of secondary transmission even in the absence of adults (i.e. for this epidemic “minors” are the “core” group). Our estimate of R based on M3 is the largest eigenvalue of K , and R is estimated at 2.9 for both matrices. These estimates are slightly greater than R estimates based on M1; when the mean and variance of GT is 2.0 days and 0 days² (i.e. if GT is constant, following a delta function), our R estimate is 2.6.

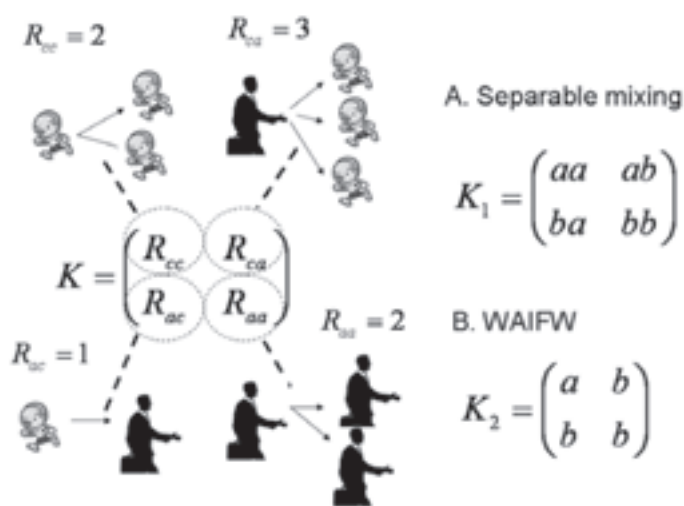
Discussion

Two important conclusions can be drawn from our epidemiological analyses. Firstly, the reproduction number R of the new influenza A(H1N1) virus in Japan is estimated to be as high as 2.3, a value that is significantly higher than that recently reported [2]. The pandemic potential of this virus in Japan may be higher in terms of transmission potential than in other areas of the world. In particular, it should be noted that our estimate of R is greater than published estimates for seasonal influenza epidemics in temperate countries [13]. Given that our R estimate has been tested for robustness to uncertainty to mean GT, it seems plausible that high contact rates among teenagers (when compared to other populations) may be one of the main drivers of this epidemic. From a transient increase in R_t around 14 May, our high estimate of R may reflect the existence of few highly connected clusters of cases among “cliques” of high school students. There may be additional contributing factors to variations in our R estimates, including cross-protective immunity due to previous exposure to other closely related influenza viruses.

Secondly, our age-specific estimates support the view that minors can sustain transmission of the new influenza A(H1N1) virus among themselves. Available data are not enough to investigate the precise role of age-specific effects (e.g. different roles of transmission among infants, primary-school, high-school and university students) due to small case counts. Nevertheless, we believe that the population of minors could play a key role as a “reservoir” for sustained chains of secondary transmission, despite the fact that cases in this group include those infected in some atypical school clusters. Should further data confirm these results then the value of public health interventions targeting minors (closing schools and further contact restrictions between minors) could be effective in controlling further outbreaks in Japan and other countries.

Our estimates of R_t provide a quantitative measure of the time-evolution of the “force” of the epidemic. Although the dates of onset have yet to be refined and, thus, the precision of R_t estimate may have been influenced by possible delay in diagnosis and reporting, R_t declined below 1 one day after the news of the first

FIGURE 3
Next-generation matrix



Note: Each element of the next-generation matrix, i.e., R_{cc} , R_{ca} , R_{ac} and R_{aa} , denotes the average number of secondary transmissions caused by a single primary case for child-to-child, adult-to-child, child-to-adult and adult-to-adult transmissions, respectively (note that here “child” represents “minor”, aged from 0 to 19 years). The reproduction number R , for the whole population, is given by the largest eigenvalue of the next-generation matrix. By making qualitative assumptions A and B, two parameters, a and b , are estimated.

three confirmed diagnoses. Thereafter, the implementation of active surveillance programmes, including contact tracing, combined with school closures, most likely have contributed to keeping R_t below 1.

R is useful for assessing transmission potential, and it is one of the ways of assessing pandemic potential. This study puts emphasis on quantifying the impact of contact patterns on the transmission potential, factors that vary across space and time. Thus, further analyses of R for the new influenza A(H1N1) virus in different settings are needed to better quantify the role of uncertainty and heterogeneous patterns of transmission in these estimates. Validation of our quantitative understanding of the role of age-specific transmission should lead to improved effectiveness of age-specific control measures.

Acknowledgements

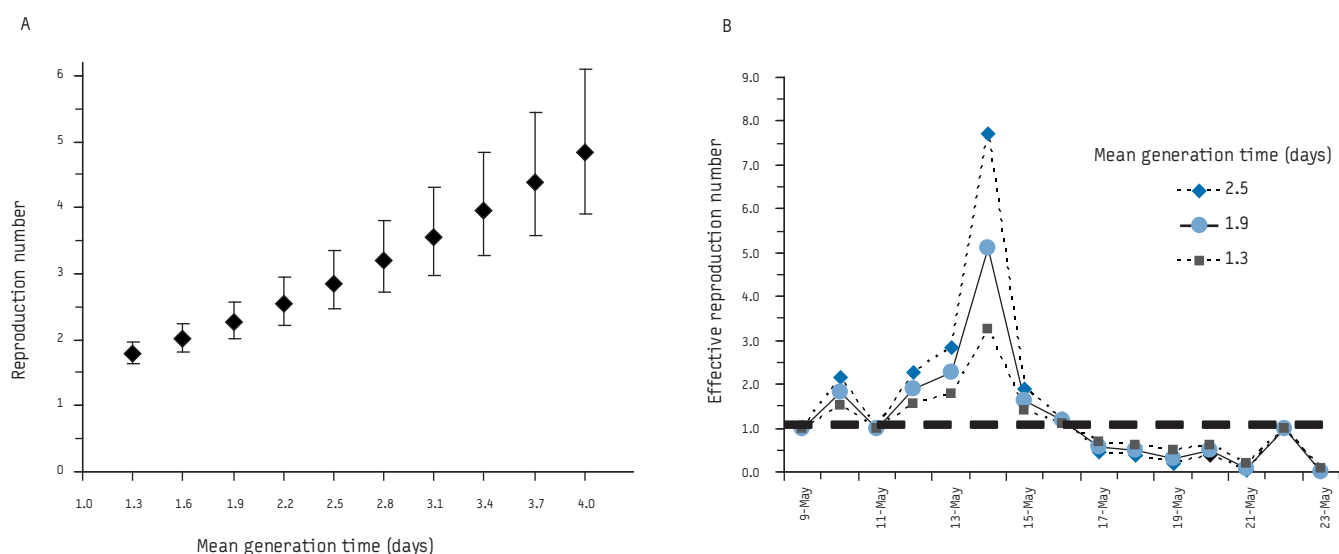
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FIGURE 4

Estimates of the reproduction number for the epidemic of new influenza A(H1N1) virus infection in Japan
A) Estimated reproduction number R , based on the initial growth phase of the epidemic (i.e. first eight days)
B) Effective reproduction number R_e , as a function of time



Note:
A) Mean and variance of the generation time were 1.9 days and 0.8 days² (given a coefficient of variation of 47%), and the sensitivity of R to different mean generation times is examined. Coefficient of variation is kept constant when the mean generation time is varied.
B) $R_e > 1$ indicates growth of cases at a given point of time, while $R_e < 1$ indicates that the epidemic is in declining trend and may be under control. The horizontal dashed line represents the threshold value, $R_e = 1$. It should be noted that the dates of onset in Japan have yet to be refined, and the precision of R_e estimate may have been influenced by possible delay in diagnosis and reporting

EPIDEMIOLOGY OF NEW INFLUENZA A (H1N1) VIRUS INFECTION, UNITED KINGDOM, APRIL – JUNE 2009

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Following the previous report to Eurosurveillance on 14 May 2009, the number of confirmed cases of new influenza A(H1N1) has continued to increase in the United Kingdom. By 31 May, UK surveillance activities had detected a total of 252 confirmed cases. Seventy (28%) were related to travel to the United States and Mexico. There is evidence of spread in households, schools and the community with increases in secondary (n=40), tertiary (n=125) and sporadic (n=13) cases. The new influenza A(H1N1) virus infection continues to cause a mild illness predominately affecting younger age-groups with a low rate of hospitalisation.

Since the identification in late April of cases of acute respiratory infection due to a new influenza A (H1N1) virus in the United States and Mexico [1], the same strain has been detected in an increasing number of countries. By 31 May, the World Health Organization (WHO) had reported 15,510 cases in 53 countries.

The first two confirmed cases of new influenza A(H1N1) virus infection in the United Kingdom (UK) were reported in travellers returning from Mexico to Scotland. The UK response and preliminary

epidemiological findings have previously been described [2]. This article provides an update to that report.

During the period from 27 April to 31 May, a total of 252 confirmed cases have been detected (Figure 1). Initially cases were reported amongst travellers returning from Mexico, and then from the United States. The first indigenously acquired infections in the UK were reported on 1 May and since then the proportion and number of indigenously acquired cases has steadily increased.

Of the 252 confirmed cases, 118 (47%) are female (Figure 2). Cases range in age from 0 to 73 years, with a mean age of 20 years and median age of 12 years.

FIGURE 1
Cumulative number of laboratory-confirmed new influenza A(H1N1) cases by day of report and travel history, United Kingdom, 31 May 2009 (n=252)

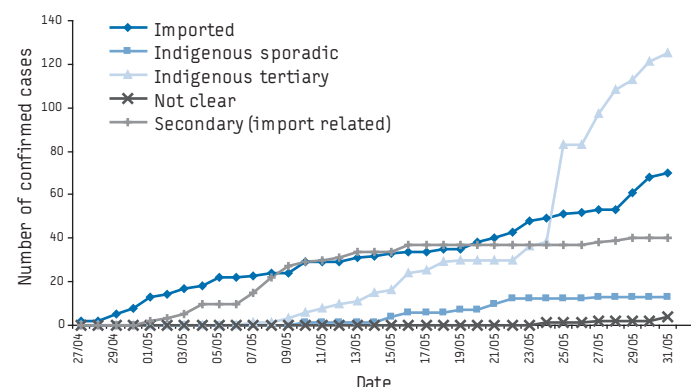
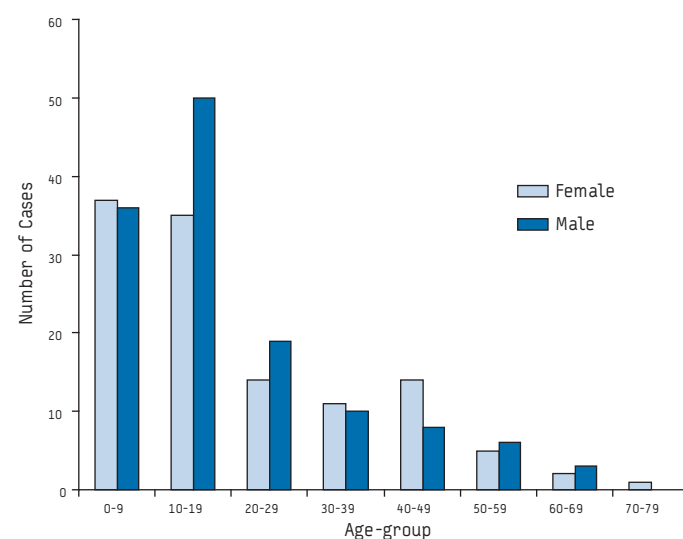


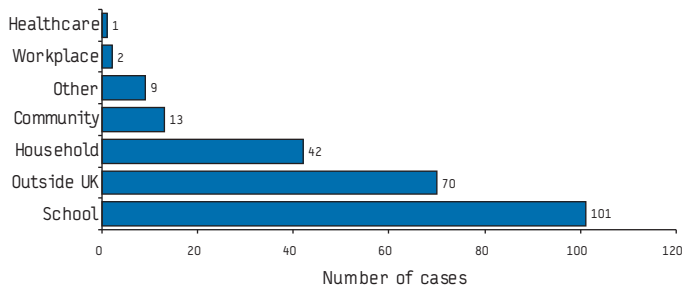
FIGURE 2
Cases of laboratory confirmed new influenza A(H1N1) by age-group and sex, United Kingdom, 31 May 2009 (n=251*)



*Age missing for one case.

Of the 252 cases, 28 reported a history of travel in the seven days before disease onset to Mexico and 42 to the United States.

FIGURE 3
Setting/source of acquisition of new influenza A(H1N1) virus infection, United Kingdom, 31 May 2009 (n=238*)

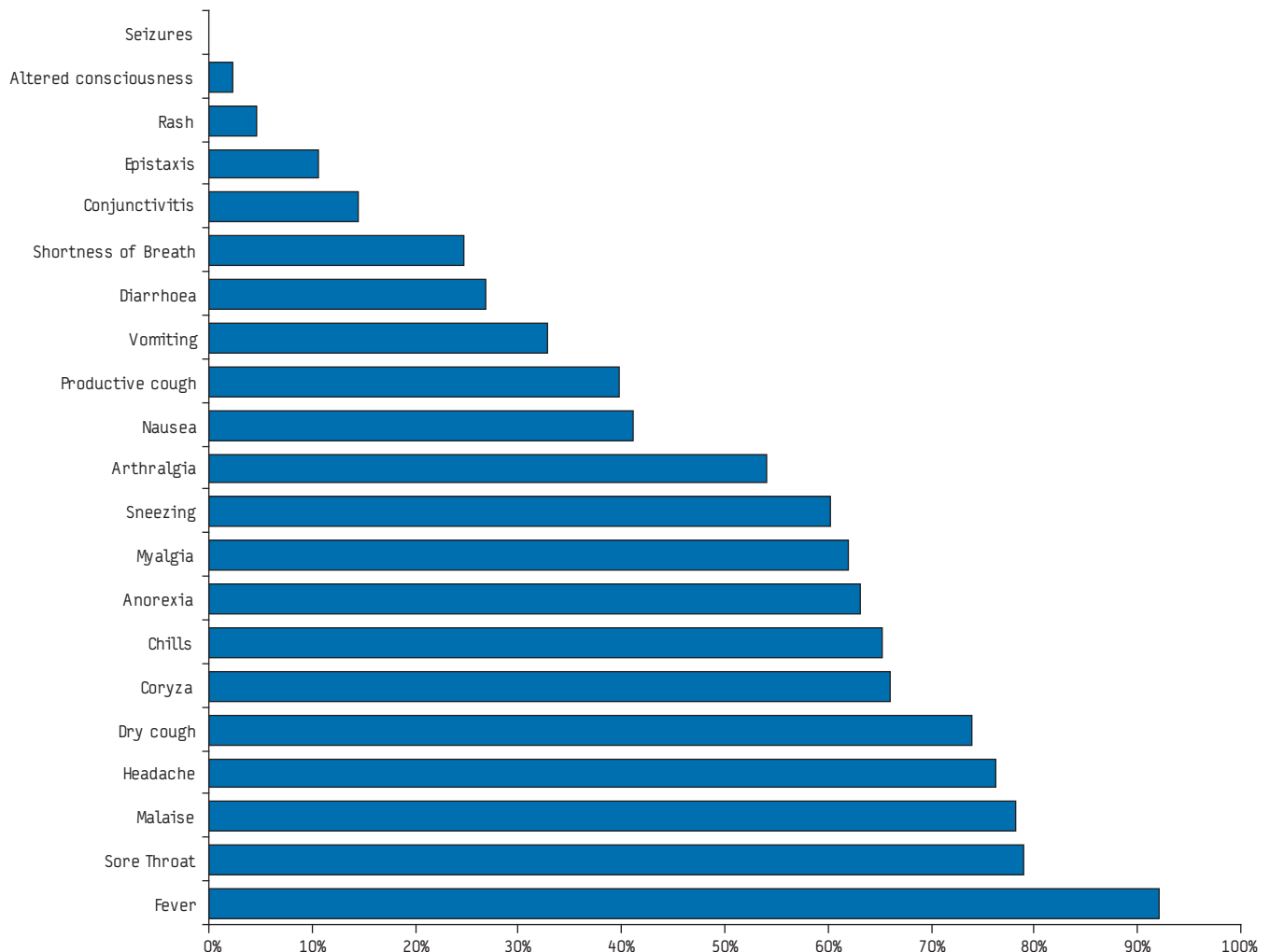


* Investigation is still underway for 14 cases.

Of the remaining 182, 178 cases reported no recent overseas travel and acquired their infection within the United Kingdom. Of these 178 indigenous cases, 40 were secondary (contact within seven days of onset with a travel-associated case); 125 were tertiary (contact within seven days of onset with a secondary case) and 13 sporadic (no travel or contact with a confirmed case in the seven days before onset). Follow-up is still underway for four cases. Amongst the indigenous cases, infection has been linked to likely transmission in a school setting for 101 cases, a household setting for 42 cases, workplace for two cases and health care setting for one case (Figure 3).

The First Few Hundred (FF100) project aims to collect information about a limited number of the earliest laboratory-confirmed cases of new influenza A(H1N1) and their close contacts [3] to gain an early understanding of some of the key clinical, epidemiological, and virological parameters of this infection and to facilitate real time modelling efforts. By 31 May, 175 confirmed cases had been entered into the FF-100 database. Clinical information gathered on these cases shows they continue to present with symptoms typical for influenza (Figure 4).

FIGURE 4
Clinical presentation of confirmed cases of new influenza A(H1N1) virus infection, United Kingdom, 31 May 2009 (n=175)



Up to 31 May, four cases have been hospitalised for clinical reasons. No UK case is known to have died.

HPA and the Health Protection organisations for Scotland, Wales and Northern Ireland have a number of enhanced influenza surveillance systems that are currently operational [4] and that provide an indication of influenza activity in the general population:

- A number of general practitioner (GP) sentinel schemes that collect information on patient consultation rates with influenza-like illness;
- National Health Service (NHS) direct and NHS-24 telephony systems which monitor call rates for colds/flu in the community;
- GP sentinel virological surveillance schemes to monitor circulating respiratory viruses in the community;
- Mortality surveillance based on routine death registration data.

To date, there have not been significant signals of increased influenza activity through these systems, which have established thresholds for widespread circulation of influenza. Outputs from these systems are published on a daily and weekly basis on the HPA website [5]. Further work is on-going to describe more fully the emerging epidemiological, virological and clinical characteristics of this novel influenza virus including in-depth field investigations of individual cluster events in settings such as schools.

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EVALUATION OF FOUR REAL-TIME PCR ASSAYS FOR DETECTION OF INFLUENZA A(H1N1)v VIRUSES

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The sensitivity and specificity of four real-time PCR assays (HPA A(H1)v, CDC A (H1)v, HPA A(N1)v and NVRL S-OIV assays) were evaluated for detection of influenza A(H1N1)v viruses. Nose and throat swab samples containing influenza A(H1N1)v viruses, seasonal influenza AH3N2, AH1N1, influenza B viruses, or negative for influenza viruses were tested by the four assays. Specificity was also analysed using influenza A viruses of different subtypes and non-related respiratory viruses. The sensitivities and specificities of the four assays were in a similar range and suitable for diagnostic use. The HPA (H1)v and the S-OIV assays were the most sensitive assays for use as a first line test, but the S-OIV assay was less specific, detecting all avian subtypes of influenza A viruses tested. The results of this study demonstrate that the concurrent use of primary diagnostic and confirmatory assays provides rapid and accurate assessment of confirmed cases, and allows appropriate management of patients.

Introduction

The recent emergence of new influenza A(H1N1) virus (henceforth: influenza A(H1N1)v virus, where v stands for variant, according to nomenclature agreed by the World Health Organization Global Influenza Surveillance Network – WHO GISN) in humans [1-2] has led to the requirement for sensitive and specific assays for the differential diagnosis and confirmation of influenza A(H1N1)v virus infections, necessary to guide public health actions. Real-time PCR is widely considered the gold standard for molecular detection of influenza viruses due to its high assay specificity, sensitivity and broad linear dynamic range. In the present study, the performance (including sensitivity and specificity) of four real-time PCR assays designed to detect influenza A(H1N1)v viruses in respiratory specimens has been evaluated. Two assays are based on detection of haemagglutinin (HA), one on the detection of neuraminidase (NA) and one on the matrix (M) gene.

HPA (H1)v assay

The influenza A(H1)v specific assay of the Health Protection Agency (HPA) contains primers and a dual-labelled TaqMan MGB probe (Applied Biosystems) targeting conserved sequences in the HA gene of A(H1N1)v viruses, and the positive control swine A(H1N1) virus A/Aragon/3218/2009, in a 1-step TaqMan PCR assay [3]. The advantage of using a genetically distinct positive control virus (A/Aragon/3218/2008) is that false positives can be differentiated by sequence from true positives.

CDC (H1)v assay

The Centers for Disease Control and Prevention (CDC) real-time RT-PCR kit designed for the detection and characterisation

of influenza A(H1N1)v viruses contains a panel of oligonucleotide primers and dual-labelled hydrolysis probes [4]. The CDC (H1)v primer and probe set evaluated in this study has been designed to specifically detect A(H1)v influenza in a one-step RT-PCR assay.

HPA (N1)v assay

The influenza A(N1)v real-time assay (HPA) is a two-step TaqMan PCR assay incorporating oligonucleotide primers and a dual-labelled MGB TaqMan probe for the detection of the NA gene of influenza A(H1N1)v viruses and the positive control virus A/Aragon/3218/2008 [5]. The assay has been designed to be performed in conjunction with the influenza A(H1)v specific assay, to provide confirmation of diagnosis of influenza A(H1N1)v virus infection.

S-OIV assay

The swine-origin influenza virus (S-OIV) assay (National Virus Reference Laboratory, NVRL, Dublin) is a real-time one-step RT-PCR assay containing primers and a dual-labelled hydrolysis probe targeting the M gene of influenza A viruses other than seasonal A(H1N1) and A(H3N2) viruses [6].

Methods

Respiratory samples (85 nose or throat swabs) were submitted as part of the influenza A(H1N1)v virus investigation in the United Kingdom. Of these, 43 influenza A-positive, untypable, M gene sequence-confirmed cases of influenza A(H1N1)v, and 42 A(H1N1)v-negative samples containing seasonal influenza A(H1N1), A(H3N2) or influenza B, or negative for influenza viruses, were analysed using the real-time assays. In addition, specificity was evaluated using representative influenza A viruses of HA subtype H5, H6, H7 and H9, and a panel of non-related respiratory viruses: respiratory syncytial viruses (RSV A and RSV B), parainfluenza viruses, rhinoviruses, human metapneumoviruses (hMPV) and corona viruses. Viral RNA was purified from clinical samples and viral cultures using the Biomerieux NucliSens easyMAG system.

Specimens were tested according to the protocol provided for each assay. All assays were run on an ABI Taqman 7500 Fast Thermal Cycler in standard (one-step assays) or Fast (two-step) mode. All samples were tested in duplicate. Discrepant results were confirmed by repeat testing. Ct values of <40.00 were considered to be positive for detection of viral RNA.

Results

The relative sensitivity of the assays was compared by analysing a 10-fold dilution series of A/England/195/2009(H1N1)v (nose swab sample).

No cross-reaction was observed when the four real-time assays were used to test 22 seasonal influenza viruses, or other respiratory viruses. A panel of representative influenza A viruses of different subtypes was also analysed (Table 2).

The HPA (H1)v and CDC (H1)v specific assays showed no cross-reactivity with any of the other influenza A subtypes analysed. The HPA (N1)v confirmatory assay detected one influenza A(H5N1) virus, but showed no cross-reactivity with other subtype viruses. The S-OIV assay showed cross-reactivity with all of the influenza A viruses analysed.

When 43 true positive samples were analysed, 36 were positive in all four real-time PCR assays (Table 3).

Four false negative and two equivocal results were observed with the CDC (H1)v assay. One equivocal result was observed with the S-OIV assay. Two samples were negative with either the HPA (H1)v or (N1)v assays, but when these assays were performed in parallel, as recommended, one false negative result was observed. No false-positives were detected in the 42 influenza A(H1N1)v virus-negative samples with any of the four real-time assays.

The Ct values obtained by analyses with the real-time assays of the 43 confirmed influenza A (H1N1)v virus samples are shown

in Figures 1a-c. A total of 42 true negative and 43 true positive samples were tested in all assays. Comparison of the HPA (H1)v and CDC (H1)v assays showed that of the 43 true positives tested, 41 were detected in the HPA (H1)v assay (Figure 1a). Thirty seven were positive and 2 equivocal in the CDC (H1)v assay. Three samples positive in HPA (H1)v assay were negative in the CDC assay and 1 sample positive in the HPA (H1)v assay was equivocal in the CDC (H1)v assay.

Of the 43 true positives, 41 were positive in the HPA (H1)v assay and 42 in the S-OIV assay (Figure 1b). One sample gave an equivocal result with the S-OIV assay.

Comparison of the HPA (H1)v diagnostic assay with the HPA (N1)v confirmatory assay demonstrated that the two assays correlate well, with a correlation coefficient of $r = 0.97$ (Figure 1c).

The precision of the HPA (H1)v and (N1)v real-time assays was assessed by the coefficient of variation (CV) and standard deviation (SD) of the replicate Ct measurements ($n=37$ and $n=9$ respectively) for the assay-positive control on diagnostic assay runs. The CV for the mean Ct values obtained with the (H1)v and (N1)v assay-positive controls was 3% and 2% respectively.

TABLE 1

End-point detection of A/England/195/2009 (H1N1)v by four real-time PCR assays

Dilution A/Eng/195/2009(H1N1)v	Mean Ct values			
	HPA (H1)v	CDC (H1)v	HPA (N1)v	S-OIV
1.00E-03	18.35	24.85	23.50	21.85
1.00E-04	21.35	28.25	27.15	25.30
1.00E-05	24.60	31.75	30.60	28.45
1.00E-06	27.95	35.20	34.25	31.70
1.00E-07	30.65	38.70	36.10	37.60
1.00E-08	32.95	Neg	38.80	36.85
1.00E-09	Neg	Neg	Neg	Neg

TABLE 2

Specificity of four real-time PCR assays with representative influenza A subtype virus isolates

Influenza A virus subtype	HPA (H1)v	CDC (H1)v	HPA (N1)v	S-OIV
A/Cambodia/R0405050/2007 RG ^a H5N1	Neg	Neg	Neg	28.02
A/Indonesia/6/2005 H5N1	Neg	Neg	31.77	27.27
A/Chicken/Turkiye/Av05/2006 H5N1	Neg	Neg	Neg	25.92
A/Vietnam/1203/2004 H5N1	Neg	Neg	Neg	27.36
A/Duck/Singapore-Q/F119-3/97 H5N3	Neg	Neg	Neg	22.53
A Turkey/England/198/2009 H6N1	Neg	Neg	Neg	30.61
A/AfricanStarling/Q-England/983/79 H7N1	Neg	Neg	Neg	29.06
A/Chicken/Wales/306/2007 H7N2	Neg	Neg	Neg	30.54
A/Quail/HongKong/G1/97 H9N2	Neg	Neg	not done	26.08

^a derived by reverse genetics

TABLE 3

Comparison of HPA (H1)v, CDC (H1)v, HPA (N1)v, and S-OIV real-time PCR assays on sequence confirmed swine-lineage samples

Number of samples	HPA (H1)v	CDC (H1)v	HPA (N1)v	S-OIV
36	+	+	+	+
1	+	-	+	Equiv*
2	+	-	+	+
1	-	+	+	+
1	-	-	-	+
1	+	Equiv*	+	+
1	+	Equiv*	-	+
Sensitivity (%)	95.4	90.7	95.4	100

* Weak positive in one replicate

FIGURE 1A

Comparison of HPA (H1)v and CDC (H1)v assay Ct values

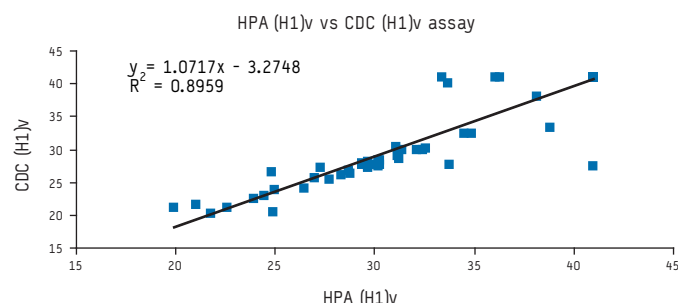


FIGURE 1B

Comparison HPA (H1)v and S-OIV assay Ct values

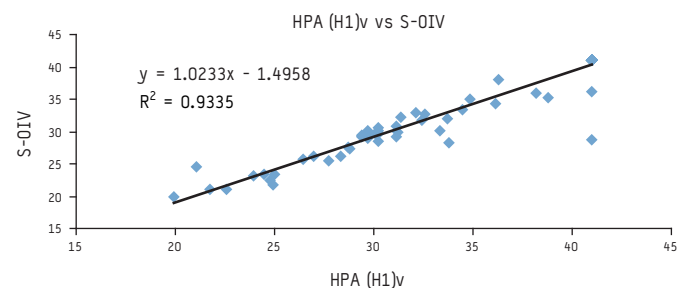
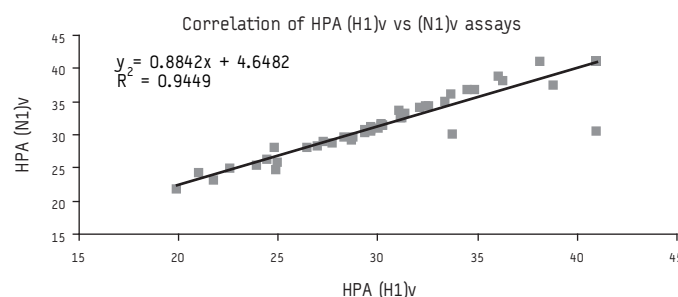


FIGURE 1C

Correlation of Ct values obtained with HPA (H1)v and (N1)v assays



Conclusions

The sensitivities and specificities of the four assays were in a similar range and suitable for diagnostic use. The HPA (H1)v and the S-OIV assays were the most sensitive assays for use as a first line test, but the S-OIV assay was less specific, detecting all avian subtypes of influenza A viruses tested. For confirmation, an assay in another gene such as the HPA (N1)v could be employed. The results obtained with the HPA (H1)v and (N1)v assays correlated well and, in addition, intra-assay variability of the HPA (H1)v and (N1)v assays was shown to be acceptable with values for the coefficient of variation (CV) <5%.

Because the security of a diagnostic result for influenza A(H1N1) v virus is important for public health actions, the use of primary detection and confirmatory assays as described here is appropriate. The use of the HPA (H1)v and (N1)v assays together provides rapid and accurate assessment of confirmed cases, and enables appropriate management of patients.

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ORIGINS OF THE NEW INFLUENZA A(H1N1) VIRUS: TIME TO TAKE ACTION

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To gain insight into the possible origins of the 2009 outbreak of new influenza A(H1N1), we performed two independent analyses of genetic evolution of the new influenza A(H1N1) virus. Firstly, protein homology analyses of more than 400 sequences revealed that this virus most likely evolved from recent swine viruses. Secondly, phylogenetic analyses of 5,214 protein sequences of influenza A(H1N1) viruses (avian, swine and human) circulating in North America for the last two decades (from 1989 to 2009) indicated that the new influenza A(H1N1) virus possesses a distinctive evolutionary trait (genetic distinctness). This appears to be a particular characteristic in pig-human interspecies transmission of influenza A. Thus these analyses contribute to the evidence of the role of pig populations as “mixing vessels” for influenza A(H1N1) viruses.

Introduction

On 24 April, the World Health Organization (WHO) released the first alert indicating the occurrence of confirmed human cases of swine influenza A(H1N1) in North America [1]. A few days later, the Centers for Disease Control and Prevention in the United States confirmed that these human influenza cases were caused by the same new influenza A(H1N1) virus [2]. Soon after, it was proposed that the current flu outbreak is caused by a new influenza A(H1N1) virus generated from a triple reassortment of human, swine and avian viruses [2-8]. Other publications, including our study presented here, demonstrate that this new influenza A(H1N1) virus most likely evolved from recent swine viruses [9-11].

Methods and results

Protein homology analysis

We used more than 400 protein sequences to analyse the genetic evolution of the new influenza A(H1N1) virus. This set of protein sequences included polymerases PB2, PB1 and PA, hemagglutinin (HA), nucleocapsid (NP), neuraminidase (NA), matrix 1 (MP1), nonstructural 1 (NS1) encoded by the new influenza A(H1N1) virus as well as other homologous proteins from influenza viruses from past flu seasons. Phylogenetic tree topologies revealed that the closest homologies for the new influenza A(H1N1) virus are swine influenza viruses that have been circulating in the United States and Asia for the last decade (Figure 1, Supplementary materials: Figure 1 and Table 1).

Figure 1. Possible origins of the influenza 2009 A(H1N1) virus: a) hemagglutinin and b) neuraminidase proteins (See Below)

These findings indicate that domestic pigs in North America may have a central role in the generation and maintenance of this virus. This idea is also supported by the observation that protein sequences of the new influenza A(H1N1) virus have close homology to proteins of swine influenza viruses that infected humans in the recent past (Supplementary materials: Figure 1, Figure 2 and Table 2). In fact, a common element of these swine influenza zoonotic transmissions was that humans (mostly swine farm workers) were in direct contact with infected pigs [12-15].

Phylogenetic analysis

To further examine the possible genetic origins of the new influenza A(H1N1) virus, we compared all the available sequences of influenza A(H1N1) viruses circulating in North America for the last two decades (from 1989 to 2009). Protein sequences from avian, swine and human influenza viruses were obtained from the Influenza Virus Resource [16], a database that integrates information gathered from the Influenza Genome Sequencing Project of the National Institute of Allergy and Infectious Diseases (NIAID) and the GenBank of the National Center for Biotechnology Information (NCBI). A total of 5,214 protein sequences were found in this database. After removing identical sequences, a set of 1,699 influenza A proteins including PB2, PB1, PA, HA, NP, NA, MP1, and NS1 proteins were used for analyses of the genetic evolution of influenza A(H1N1) viruses. These analyses provide additional evidence of the role of pig populations as “mixing vessels” for influenza A(H1N1) viruses (Figure 2).

Figure 2. Genetic distinctness of the influenza 2009 A(H1N1) virus: a) hemagglutinin (HA) and b) neuraminidase (NA) proteins; c) phylogenetic trees for PB2, PB1, PA, NP, MP1, and NS1 proteins (See Below)

Secondly, our analyses also revealed that the new influenza A(H1N1) virus possesses a distinctive evolutionary trait (genetic distinctness), that seems to be characteristic in pig-human interspecies transmission of influenza A (reported cases occurred in Iowa, Maryland and Wisconsin, United States between 1991 and 2006) (Figure 2, Supplementary materials: Figure 2 and Table 3).

Discussion and conclusion

Although limited in sample size, our analyses substantiate the value of molecular screening and phylogenetic assessment for understanding the evolution of influenza viruses and, most importantly, for the early detection of emerging novel viruses that

could lead to influenza pandemics. Notably, our analyses revealed that the new influenza A(H1N1) virus is genetically distinct from other influenza A(H1N1) viruses that have been circulating for the last twenty flu seasons (Figure 2 and Supplementary materials: Figure 2). Influenza viruses with novel antigens (genetic drift) can escape from immune responses induced by prior infection or vaccination and can lead to a pandemic [17].

These observations also reiterate the potential risk of pig populations as the source of the next influenza virus pandemic. Although the role of swine as “mixing vessels” for influenza A(H1N1) viruses was established more than a decade ago [18,19], it appears that the policy makers and scientific community have underestimated it. In fact, in 1998 influenza experts proposed the establishment of surveillance in swine populations as a major part of an integrated early warning system to detect pandemic threats for humans [18,19] but, to some extent, this task was overlooked. For example, a search of influenza sequences in the Influenza Virus Resource [16] revealed that the total number of swine influenza A sequences (as of 19 May 2009) is ten-times smaller than the corresponding number of human and avian influenza A sequences (4,648 compared to 46,911 and 41,142 sequences, respectively). More significantly, in some countries, such as the United States, the national strategy for pandemic influenza [20] assigned the entire preparedness budget (3.8 billion US dollars) for the prevention and control of avian A(H5N1) influenza, overlooking the swine threat [20-22]. In our (the authors’) opinion, in this plan, a substantial effort was dedicated to prevent and contain the foreign threat of Asian avian flu, neglecting the influenza threat that the North American swine population presents [23]. Specifically, we believe that the aforementioned strategy ignores the swine farm and industry workers which constitute the population at higher risk of contracting and spreading the hypothetical pandemic influenza virus [24-26].

The current new influenza A(H1N1) outbreak caused by a virus of swine origin represents a new challenge for animal and human health experts. Our institution, the College of Veterinary Medicine at the National Autonomous University of Mexico (Universidad Nacional Autónoma de México, UNAM) is placing a strong emphasis on the establishment of influenza surveillance in swine and avian species to identify novel genetic assortment of the new influenza A(H1N1) and other influenza viruses circulating in Mexico. For example, since 2002, we have been monitoring the genetic evolution of influenza A viruses circulating in Mexican poultry farms [27]. Now, a similar surveillance system will be applied to swine farms. This effort prioritises the use of genetic distinctness as a marker for the detection of novel viruses that could lead to influenza pandemics.

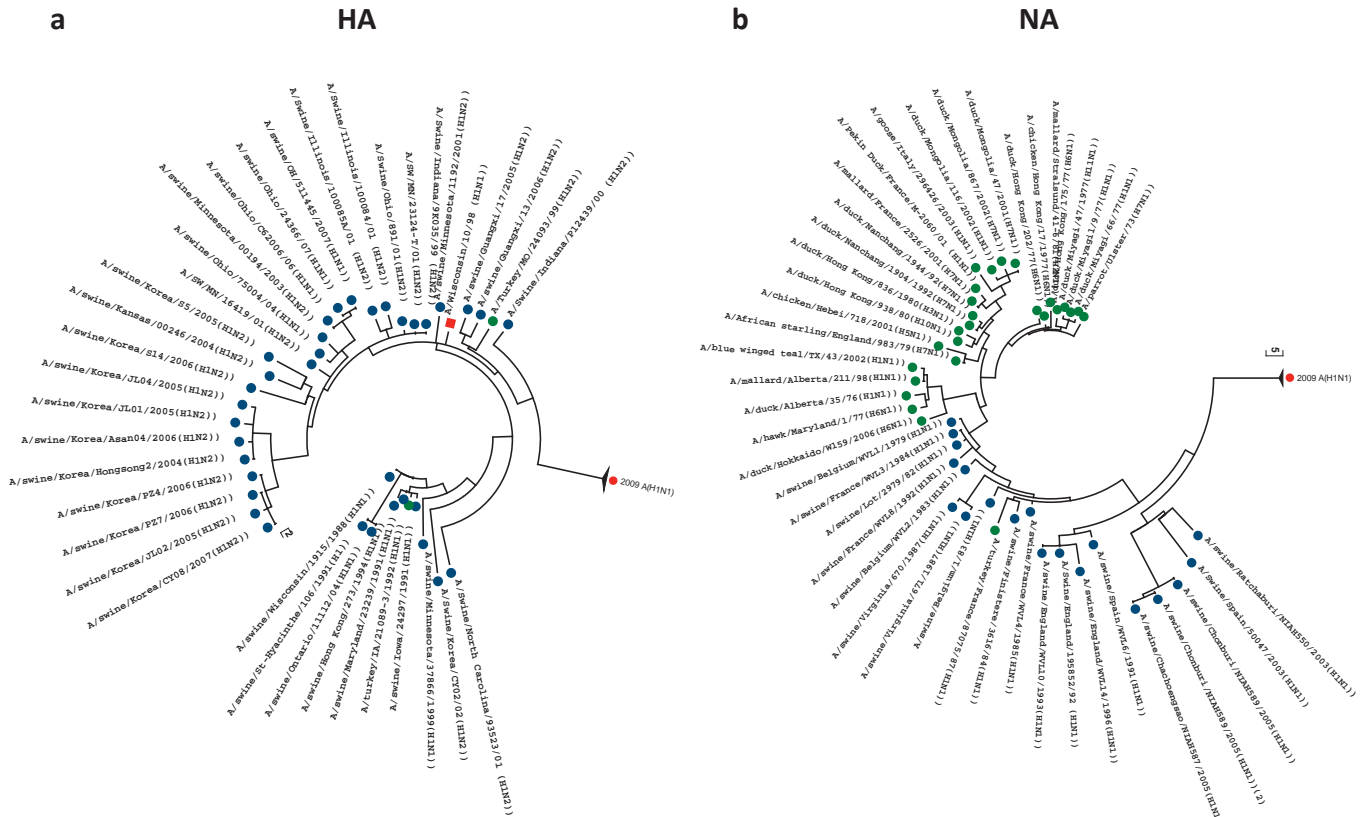
The recent influenza pandemic threat in North America reveals that it is time to take action towards the development of a systemic surveillance system which integrates phylogenetic information of influenza viruses circulating in humans and livestock.

Supplementary materials: Figure 1, Figure 2, Table 1, Table 2, Table 3, and available online from: www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19228

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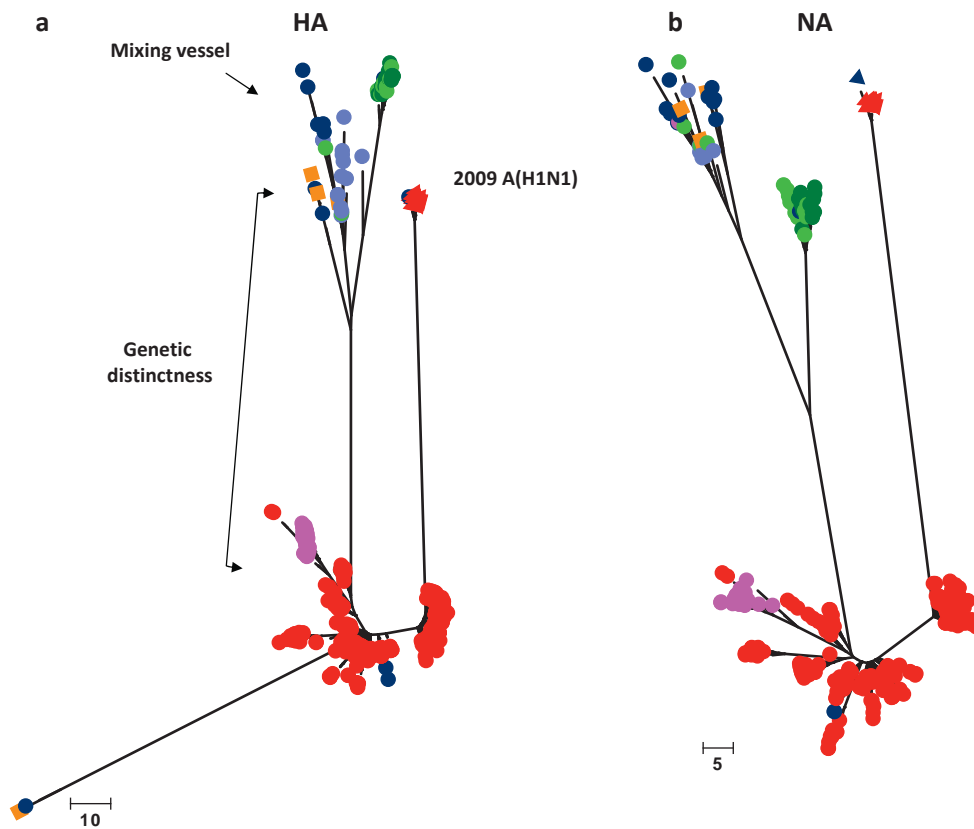
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Figure 1. Possible origins of the influenza 2009 A(H1N1) virus: a) hemagglutinin and b) neuraminidase proteins



Protein sequences from the 2009 A(H1N1) virus were retrieved and used for BLAST searches versus the all-species NCBI nr protein database. Top-fifty best hits were retrieved from GenBank and used for phylogenetic tree reconstruction using the maximum parsimony method. Phylogenetic trees were rooted using the earliest influenza virus found with the analysis. Proteins from the 2009 A(H1N1) virus (red circles) showed close homology to proteins from swine influenza viruses circulating in Asia, Europe and US (blue circles) and swine influenza viruses that have infected humans in recent past (red squares). Protein relationships with avian influenza virus (green circles) were more distant. Scale bar indicates the number of changes over the whole sequence. Phylogenetic trees for PB2, PB1, PA, NP, MP1, and NS1 proteins, and details of statistical significance of branch order are provided in Supplementary Materials - Figure 1.

Figure 2. Genetic distinctness of the influenza 2009 A(H1N1) virus: a) hemagglutinin (HA) and b) neuraminidase (NA) proteins; c) phylogenetic trees for PB2, PB1, PA, NP, MP1, and NS1 proteins



PRELIMINARY ANALYSIS OF INFLUENZA A(H1N1)v INDIVIDUAL AND AGGREGATED CASE REPORTS FROM EU AND EFTA COUNTRIES

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Since the first importation of influenza A(H1N1)v virus to Europe in late April of this year, surveillance data have been collected in the Member States of the European Union and European Free Trade Association. This is the first preliminary analysis of aggregated and individual data available as of 8 June 2009 at European level.

Introduction

On 21 April 2009, the United States Centers for Disease Control and Prevention (US CDC) reported two cases of influenza due to a new virus strain of mixed swine, avian and human origin, the so-called new influenza A(H1N1) virus (hereafter named A(H1N1)v virus) [1]. On 25 April, the European Centre for Disease Prevention and Control (ECDC) published a risk assessment, started developing tools to monitor the situation and support the countries of the European Union (EU) and European Free Trade Association (EFTA), and initiated its first situation report distributed daily to more than 700 stakeholders since then. After the World Health Organisation (WHO) raised its pandemic alert level to phase 4 on 27 April and up-scaled again to phase 5 on 29 April, ECDC was monitoring the situation around the clock and provided epidemiological updates on global case numbers three times a day. Subsequently, the European Commission published a case definition for surveillance of the new disease [2], ECDC published information for travellers, updated its risk assessment on 8 May, published several documents on case and contact management, and coordinated the surveillance of influenza A(H1N1)v at EU level.

The objective of this paper is to present the epidemiological situation in the 27 EU and the three countries in the European Economic Area (EEA) and EFTA, Iceland, Liechtenstein and Norway, hereafter called the EU+3 countries, on the basis of the surveillance data provided by the EU+3 countries through individual and aggregated case reports.

Methods

Data used in this analysis of the epidemiological situation in the EU+3 countries, as of Monday 8 June 2009, 08:00 CEST, include individual case reports posted by countries in the Early Warning and Response System (EWRS) and aggregated case reports provided daily through the EWRS or through other official communication channels.

Confirmed cases are defined as persons in whom the infection has been confirmed by RT-PCR, or by viral culture or by a four-fold rise in influenza A(H1N1)v-specific neutralising antibodies. The latter implies, according to the EU case definition, the need for paired sera from the acute phase of illness and from the convalescent stage 10-14 days later [2].

While countries with fewer cases are uploading data on their cases directly into the surveillance database at ECDC, Spain and the United Kingdom (UK), who both have high number of cases, and Belgium are providing extracts from their own national databases, which are then entered into the ECDC database. Re-coding of some of the variables was necessary for Spain and the UK, and data were subsequently validated by the countries. The data from Belgium were imported manually after re-coding the variables.

Cases which are not explicitly reported as having been exposed during travel in an affected country (imported cases) are considered to have been infected in their own country.

Results

As of 8 June, 1,128 laboratory-confirmed cases of influenza A(H1N1)v have been reported from 25 of the EU+3 countries through aggregated case reports. Spain (26%) and the UK (49%) together account for 75% of confirmed cases. Of those 1,128 cases, 498 (44%) were also reported through individual case reports (Table 1). Latvia, Liechtenstein, Lithuania, Malta and Slovenia have not reported confirmed cases so far.

Epidemic curves

The first confirmed case in EU+3 countries was a traveller returning from Mexico to the UK. He was identified on 27 April 2009 and reported onset of symptoms on 16 April. Figure 1 compares the distribution of cases by date of onset from the individual case reports (n=498) with the distribution of cases by reporting date from the aggregated case reports (n=1,024). It shows a delay of one week between date of onset and date of reporting in the first weeks of the outbreak, up to 20 May, followed by an increasing discrepancy in the number of cases reported by the two systems.

Figure 2 shows the distribution of imported and domestic cases in EU+3 countries by date of onset. The first case reported as in-

TABLE 1

Distribution of confirmed cases of influenza A(H1N1)v reported until 8 June 2009 by source of information, EU+3 countries (n=1,128)

Member State	Aggregated case reports	Individual case reports	Percentage
Austria	6	6	100
Belgium	14	14	100
Bulgaria	2	0	0
Cyprus	1	1	100
Czech Republic	2	2	100
Denmark	5	4	80
Estonia	3	3	100
Finland	4	4	100
France	57	18	32
Germany	63	63	100
Greece	5	0	0
Hungary	3	3	100
Iceland	1	0	0
Ireland	11	11	100
Italy	50	39	78
Luxembourg	1	1	100
Netherlands	10	6	60
Norway	9	9	100
Poland	5	5	100
Portugal	2	2	100
Romania	9	9	100
Slovakia	3	3	100
Spain	291	113	39
Sweden	14	13	93
United Kingdom	557	169	30
Total	1128	498	44

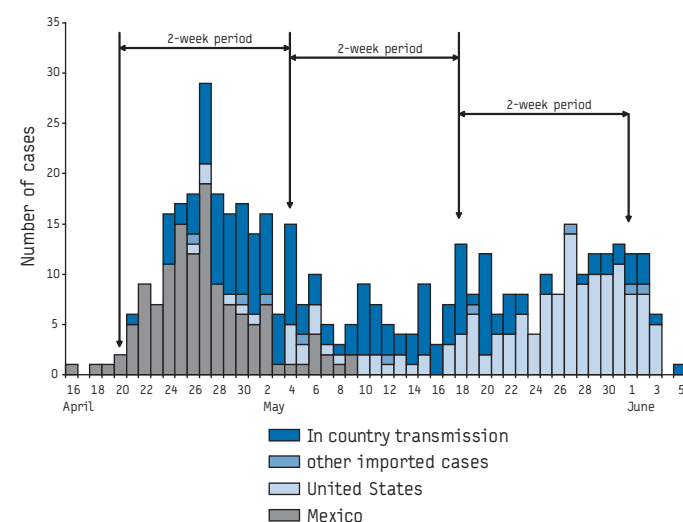
country transmission had onset of symptoms five days after the first imported case. During the first two-week period, 65% of cases were reported to have been imported, compared to 40% during the second and 73% during the third two-week period. The majority of imported cases in the first two-week period were imported from Mexico and in the third two-week period from the United States (US).

Demographic characteristics of cases

The male to female ratio was 1.1. The median age was 23 years (range: eight months to 73 years). Seven cases were younger than

FIGURE 2

Distribution of confirmed cases of influenza A(H1N1)v infections by date of onset and type of transmission, as of 31 May 2009*, EU+3 countries (n=457)



* Individual case reports from Spain were last updated on 14 May, from the UK and France on 29 May, from Italy on 4 June and from Germany on 6 June

FIGURE 1

Distribution of confirmed cases of A(H1N1)v infections by date of onset (n=498) and date of reporting (n=1,024), as of 5 June 2009, EU+3 countries

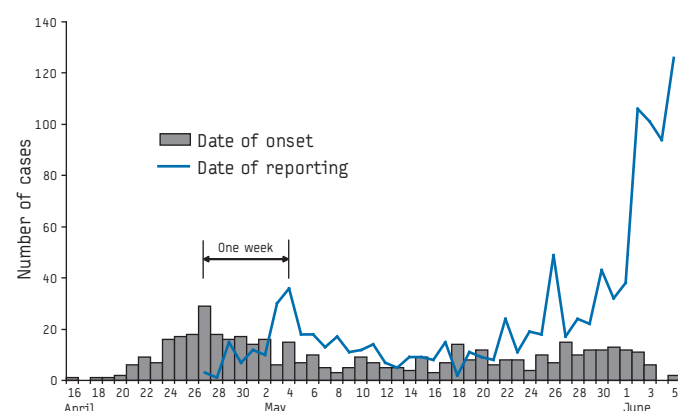
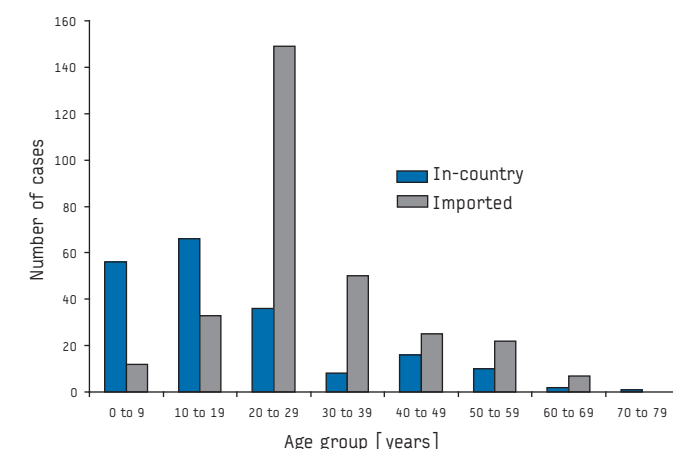


FIGURE 3

Distribution of cases of influenza A(H1N1)v infection by age group and type of transmission, as of 8 June 2009, EU+3 countries (n=493)



two years. Of 494 cases with known age, 168 (34%) were under the age of 20 years. The most affected age group was the group of 20-29 year-olds and accounted for 37% of cases.

The proportion of imported cases older than 20 years (78%) was significantly higher than the proportion of over 20 year-old cases who were infected in their own country (27%, $p < 0.0001$). The median age of imported cases was 25 years compared to 13 years for non-imported cases (Figure 3).

Symptoms

In the analysis of symptoms, the data from Spain and Belgium were excluded due to recoding issues, leaving 371 cases for analysis. Asymptomatic cases constituted 8% of reported cases (28/371), and were more common among cases under the age of 20 years (11%) when compared with older cases (5%, $p = 0.02$).

The most commonly reported symptoms were respiratory symptoms (79%), followed by fever or history of fever (78%). Gastro-intestinal symptoms were reported from 86 cases (23%). Presence of gastro-intestinal symptoms was not significantly associated with travel exposure but was significantly more common among cases under the age of 20 years (32%) than among older cases (18%, $p = 0.001$). Table 2 shows the distribution of symptoms by category of symptom.

Pre-existing conditions

Underlying disease was reported for 24 cases: lung disease for 12, heart disease for four, renal disease from three, human

immunodeficiency virus (HIV) infection from three, and seizures from two cases (one of these two also had a not further specified cancers). One 14 months-old child was reported with combined heart, lung and renal disease. None of the cases was reported to be pregnant. Several cases with other underlying conditions such as hypertension, iodine sensitivity, allergic rhinitis or facial paralysis were reported, which are not considered classical risk groups for seasonal influenza [3].

Treatment and prophylaxis

Of 292 cases for whom information is available, 258 (88%) received antiviral treatment. Oseltamivir was the most commonly used drug (255), zanamivir was reported to have been used for treatment of three cases. Post-exposure prophylaxis was reported to have been administered to 13 (7%) of 198 cases for whom information was available. Twelve received oseltamivir and one received zanamivir as prophylaxis. Six of the cases who received prophylaxis were imported cases.

Complications

Seven (2%) of the 286 cases for whom information is available were classified as having complications. Four patients were reported with pneumonia, one with otitis, one with elevated liver enzymes and one with the need for steroid treatment. Fifty-three cases reported shortness of breath, one of whom had underlying heart disease.

Previous influenza vaccination

Twenty (8%) of the 260 cases for whom information is available were reported to have received seasonal influenza vaccination in the past season. Vaccinated persons were aged between 8 months and 76 years. Eighty percent of vaccinated persons were returning travellers. Two were reported to have asthma, one with underlying heart disease, one with chronic disease not further specified and one with myalgic encephalopathy.

Hospitalisation

Among 291 cases, 36% (105) were reported to have been hospitalised. The rate of hospitalisation varies by country. In several countries, e.g. France, Austria, Belgium and Romania, cases were hospitalised for isolation purposes.

Discussion

On the basis of the aggregated case reporting, two EU Member States account for 75% of the cases reported in the EU+3 countries. It is unlikely that a difference in the sensitivity of surveillance systems alone could explain such a difference. The one-week delay between date of onset (individual case reports) and reporting date (aggregated case-reports) observed in the first weeks of the epidemic probably reflects the delay in seeking medical care after onset and getting laboratory confirmation (see Figure 1). The discrepancy observed since the third week of May in the numbers reported through aggregated case reports versus individual case reports highlights the increasing difficulties of the Member States in investigating and reporting individual cases as the number of case increases.

This preliminary analysis does not allow an accurate description of the level of in-country transmission, as the data are still incomplete. However, a recent Eurosurveillance article suggests that in the UK, most of the recent cases are due to in-country transmission, although sustained community transmission still has to be confirmed [4].

TABLE 2

Distribution of symptoms among cases of influenza A(H1N1)v infection, as of 8 June 2009, EU+3 countries (n=371)

	Number	Percentage
At least one symptom	344	93
GENERAL	317	85
Fever or history of fever	290	78
Headache	160	43
Muscle pain	145	39
Joint pain	79	21
RESPIRATORY	295	80
Dry cough	188	51
Productive cough	60	16
Sore throat	172	46
Runny nose	120	32
Sneezing	72	19
Shortness of breath	34	9
GASTRO INTESTINAL	34	24
Diarrhoea	45	12
Vomiting	49	13
Nausea	57	15
OTHERS	146	39
Conjunctivitis	21	6
Nose bleeding	9	2
Altered consciousness	2	1
others (various)	117	32

The age distribution of cases is significantly different among imported and domestic cases. Imported cases tend to be young adults, exposed while travelling abroad, and their demographic characteristics are more representative of travellers than of the population susceptible to A(H1N1)v infection. Domestic cases tend to be younger (median age 13 years) and reflect school children and teenagers among whom transmission is amplified. Therefore, the demographic characteristics of cases documented in the EU so far do not reflect the overall population at risk of infection, but rather the population contributing to seeding events (travellers) and amplification of transmission (school children and teenagers) in the early stage of the spread of a new influenza virus strain.

The relatively high proportion of asymptomatic cases, especially among under 20 year-olds, is probably due to intensive contact tracing during school outbreaks. The difference in the number of cases with gastro-intestinal symptoms observed in under 20 year-olds compared to older cases has been previously described for seasonal influenza and is not significantly associated with an exposure abroad [3]. The hospitalisation rate cannot be considered as a factor of severity because many of the cases were reported to be admitted to hospital for isolation. There was great variation among countries in this respect.

Information on the interval between exposure and the start of prophylaxis is not available and therefore no conclusions can be drawn regarding the effectiveness of antiviral prophylaxis.

Individual case reports for less than half of the cases (498/1,128) were available for this analysis, which may bias the results. The bias will particularly affect conclusions drawn on cases from the last three weeks of the dataset, for which information from the most affected Member States were not available. Bias may have been introduced in the age distributions and the frequencies of symptoms and underlying conditions, since the missing data particularly concern in-country transmission. Therefore, the comparisons between cases affected in their own country and travel-associated cases should still be considered preliminary and a change in disease patterns during the period for which data are missing cannot be ruled out. Due to delay in reporting from the Member States to ECDC, the Europe-wide picture presented here may not fully represent the reality of what was known at country level on 8 June.

With the currently available information, conclusions about the severity of the infection are limited. In addition, if cases deteriorate while they are ill, this information would probably not be reported to the ECDC.

Conclusions

The preliminary analysis of the initial few hundred cases reported at European level shows that the epidemiological pattern in the EU+3 countries does not differ from what was documented in the Americas. Currently, the disease seems to be relatively mild and comparable with seasonal influenza. However, it is still too early to define, on the basis of this analysis, the age groups most at risk of infection.

These data are important to guide appropriate policy decisions. In 2008, a working group on surveillance in a pandemic, including ECDC, WHO and experts from the Member States, identified nine strategic parameters which would need to be assessed early in an influenza pandemic [5]. Out of these, six parameters (including

disease severity, incidence by age-group and known risk-factors, confirmation/modification of case definition and modes of transmission) can only be properly evaluated using individual case reports.

As the number of cases grows, it will become increasingly difficult for the Member States to investigate and report individual cases. The surveillance currently in place may soon reach its limits. It may well be that targeted outbreak studies will provide better information on risk factors for more severe disease. A switch to sentinel surveillance and/or surveillance of severe cases, as implemented by countries outside the EU, has to be considered. However, the case-based reporting should be continued at least until countries experience community spread or large-scale epidemics. ECDC is currently working with the Member States to automate the upload of data in their own national formats.

In the meantime, aggregated case reporting complementing individual case reports has proven very useful in describing recent trends and anticipating future developments. As recent trends suggest that Europe may be entering the acceleration phase [6], it is important to continue collecting aggregated case reports.

Acknowledgements

These data were provided by the national focal points for the Early Warning and Response System and the contact points for influenza surveillance of the EU and EFTA countries. ECDC wishes to acknowledge the serious commitment and effort of all these individuals and their teams in ensuring the timely reporting of case-based data from their respective countries. The full list of names is indicated below.

The final preparation of the report was made by ECDC working group on influenza A(H1N1)v, see below.

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The ECDC working group on influenza

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Rapid communications

ENHANCED INFLUENZA SURVEILLANCE ON RÉUNION ISLAND (SOUTHERN HEMISPHERE) IN THE CONTEXT OF THE EMERGENCE OF INFLUENZA A(H1N1)v

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With the winter season on the southern hemisphere that starts in Réunion Island in June seasonal influenza activity usually increases shortly afterwards. The new influenza A(H1N1)v virus is rapidly spreading worldwide and may reach the island during the coming winter season. We have therefore enhanced influenza surveillance to detect the introduction of influenza A(H1N1)v, monitor its spread and impact on public health and characterise potential viral changes, particularly if seasonal influenza A(H1N1), resistant to oseltamivir, co-circulates with A(H1N1)v.

Background

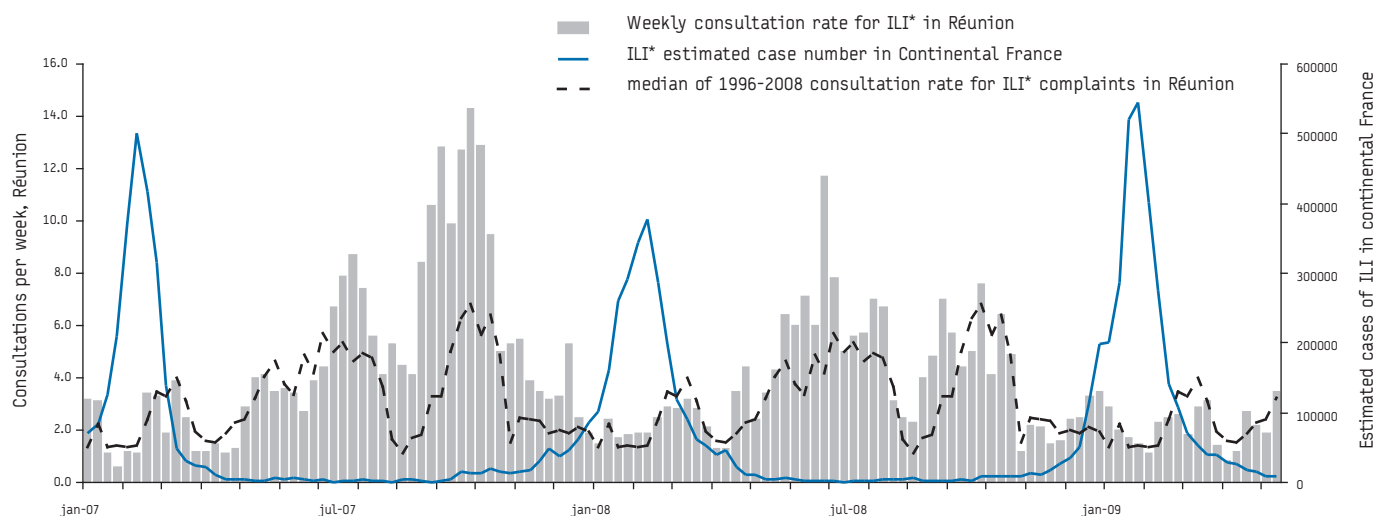
Influenza virus type A is associated with annual epidemics and occasional large-scale global pandemics. Both are characterised by increased morbidity and mortality [1]. In temperate regions, a clear seasonality exists in the influenza activity with a marked peak in cold winter months. In tropical regions however, where there is

less fluctuation in seasonal temperature this is not noticeable to the same extent [2].

Réunion Island, a French overseas administrated territory with 800,000 inhabitants, is located in the southern hemisphere in the south-western Indian Ocean, 700 km east of Madagascar and 200 km south-west of Mauritius, at a longitude of 55°3 east and latitude of 21°5 south, above the Tropic of Capricorn. In Réunion Island, influenza activity has been monitored since 1996 [3], but influenza virus circulation remains poorly documented. Results of past monitoring suggest that annual influenza activity increases in June-July [4] and the last reported seasonal influenza epidemic occurred in August-October 2007 [5]. The island is presumed to have a double exposure to seasonal influenza, one from the southern hemisphere and the other one from the intense link with metropolitan France [4,6] (Figure 1).

FIGURE 1

Seasonal influenza activity on Réunion Island and in continental France, 2007-2009



*Influenza like illnesses

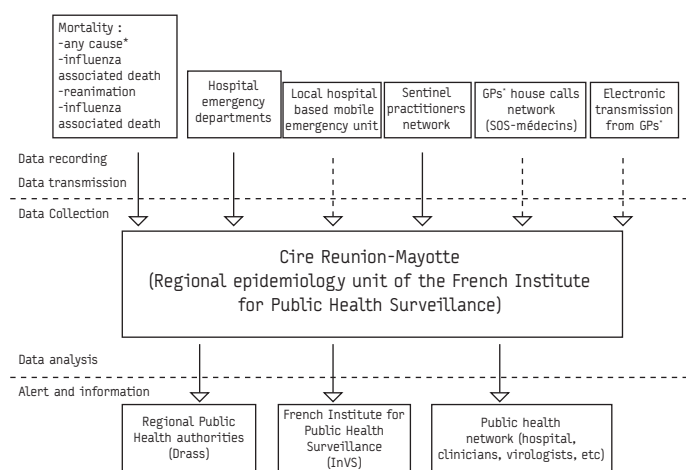
Source for continental France data: Réseau Sentinelle, France ; Source for Réunion Island data: Observatoire Régional de la Santé and réseau sentinelle, Réunion

In April 2009, a new strain of human influenza A(H1N1) virus, the influenza A(H1N1)v virus, was identified in USA and Mexico [7]. As of 10 June 2009, a total of 74 countries reported 27,737 cases and 141 associated deaths to the World Health Organization (WHO) demonstrating the pandemic potential of the virus [8]. Anticipating the start of the influenza season in Réunion Island sometime in June (Figure 1), the Regional epidemiology unit of Réunion-Mayotte (Cellule interrégionale d'épidémiologie, Cire) of the French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS) is implementing an enhanced surveillance system to face the likely

introduction and spread of influenza A(H1N1)v during the coming winter months in Réunion. The aim of this system is to detect the introduction of influenza A(H1N1)v timely on the island, monitor its spread and impact on public health and characterise potential viral changes, particularly if seasonal A(H1N1) resistant to oseltamivir co-circulates with A(H1N1)v. Furthermore, the surveillance we describe here is an attempt to include the specific surveillance of influenza A(H1N1)v virus into the global influenza surveillance system. It could be an example for other countries in the tropics and results will provide useful data about the effectiveness and limits of such system. Our experience might guide northern hemisphere countries in how to adapt their surveillance system before the upcoming influenza season in the winter.

FIGURE 2

Organisation of the influenza surveillance on Réunion Island, 2009



Organisation of the influenza surveillance on Réunion Island, 2009

Figure 2 shows the organisation of the enhanced surveillance for imported cases of influenza A(H1N1)v. Timely detection of the introduction of cases by travellers coming or returning from affected areas is crucial to implement control measures around each case and limit the indigenous spread of the virus. Our enhanced surveillance is based on the national protocol set up by InVS [9] and the management of patients follows recommendations of the French pandemic plan [10]. Case definitions of possible, probable, confirmed, excluded and close contacts of cases are shown in the Table.

Community surveillance

Sentinel practitioners network

A sentinel network, consisting of 40 general practitioners (GP) and two paediatricians, scattered across the island conducts prospective influenza surveillance on Réunion Island [3,4]. On a weekly basis, they report the percentage of consultations for influenza-like illness (ILI) using the following case definition: sudden onset of fever > 38°C AND cough OR breathing difficulty. Every physician is expected to perform a nasal swab for each first patient of the week presenting with ILI symptoms that started within less than 48 hours.

→ Existing surveillance systems which may be reinforced

→ Surveillance systems in creation

* Will be activated only in case of massive influenza outbreak on Réunion Island

TABLE

Case definition and classification, influenza A(H1N1)v infection, France, 10 June, 2009

Clinical criteria	Any person with an acute respiratory illness: -Fever (>38°C) OR myalgia OR asthenia -AND respiratory symptoms: cough OR dyspnoea
Epidemiological criteria	At least ONE of the following in the seven days prior to disease onset: -travel to an area where sustained human-to-human transmission of influenza A(H1N1)v is documented (as of 10 June 2009: Argentina, Australia, Canada, Chile, Dominican Republic, Japan, Mexico, Panama, United Kingdom, United States). -close contact to a possible, probable or confirmed case of influenza A(H1N1)v infection while the case was contagious (24h prior to symptom onset until seven days after).
Close contact definition	At least one of the following: -a person living with a case: family, roommate etc. -a person who had direct contact with a case, within 1 m while the case was coughing, sneezing or talking ; flirt ; close friends ; classmate, working neighbour; plane or train neighbour
Case classification	1- Possible case: Any person meeting the clinical and epidemiological criteria. 2- Probable case: At least one of the following: -Any possible case with a positive RT-PCR for influenza A virus -Any possible case with a severe symptomatology (acute respiratory distress syndrome or death with an acute respiratory infection) -Any possible case which was a close contact to a probable or confirmed case while the case was contagious. 3-Confirmed case: Any possible case with a positive RT-PCR for influenza A(H1N1)v virus. 4-excluded case: At least one of the following: -Any person who does not meet possible case criteria. -Any possible case with a negative influenza A virus RT-PCR

Hospital emergency departments

Data are collected daily directly from patients' computerised medical files that are filled in during medical consultations regardless of the diagnosis. All data are extracted automatically and transmitted electronically in real-time to the InVS. Items collected include diagnosis, coded according to ICD-10, with a severity score ranked from 1 to 5 after medical examination, date of admission to emergency department, orientation (hospitalisation or discharge), age, sex, postal code, and main symptoms. Each patient corresponds to a single record, including all variables [11]. Moreover, data concerning ILI patients will be extracted using influenza associated ICD-10 diagnosis codes (codes for influenza and more acute respiratory tract infections). On Réunion Island three out of the four existing hospitals participate in the network. The fourth one is being integrated and should participate starting in July 2009. Nasal swabs will be performed daily for every first adult and paediatric patient seen in emergency departments.

General practitioner house calls network (SOS Médecins)

In the western coast of Réunion Island, SOS Médecins is composed of eight GPs that are involved in more than 100 interventions per day for a population of about 100,000 inhabitants (one eighth of the population). Telephone calls are handled by a call center and logged in a local database. This database is linked via internet to electronic notebooks held by GPs who can update the database with additional information following the visit of a patient. The data collected include: date of the visit, postal code, age, sex, symptoms of the patient and the medical diagnosis. Each morning, data for all visits logged during the previous 24-hour period (midnight to midnight) are downloaded [12].

Local hospital based Mobile Emergency Unit (Samu Centre 15)

On Réunion Island, a single 'Samu Centre 15' operates for the entire island. This mobile unit receives emergency calls and provides emergency healthcare and medical transport of patients. Total phone calls (regardless of diagnosis), phone calls for ILI and for advice on influenza will be analysed weekly.

Hospital surveillance

To monitor and describe severity, cases hospitalised for ILI will have a nasal swab for viral testing. Clinical and epidemiological information will be collected by Cire in collaboration with a clinical research project for hospitalised cases currently under preparation.

Mortality surveillance

The National Institute for Statistics (Institut National de la Statistique et des Etudes Économiques, Insee) conducts the administrative recording of deaths from all causes in France. For several years, Insee has been monitoring and centralising daily mortality in France including Réunion Island. In case of an influenza epidemic on the island, we will analyse this total number and excess of deaths from all causes. This system will be completed by analysis of all death certificates received by the regional public health authority that mention 'influenza'. These certificates will be recorded as influenza-associated deaths. Electronic death certification which is being implemented in France will be used by the Intensive Care Department of Saint-Denis Hospital, and be analysed in real-time by the Cire.

Cluster identification

Despite a well functioning surveillance system, imported cases of influenza A(H1N1)v might be missed and result in outbreaks of ILI in closed communities (schools, children, workers, elderly). In order to prevent this from happening, reporting of outbreaks in such

communities, particularly in the early phase of the influenza season, has been fostered and will lead to prompt investigation including virological testing. Furthermore, to improve self-notification of clusters, healthcare professionals have been informed on the relevance of such measures.

Virological surveillance

An enhanced virological surveillance will be implemented in order to identify and characterise circulating influenza viruses during the coming winter season in Réunion Island. Specimens will be collected by members of the sentinel network and hospitalised patients with ILI symptoms will also be tested. We estimate an average of 80 specimens to be tested weekly at the Laboratory of Virology of Saint-Denis Hospital, one of the 24 laboratories approved by the French Ministry of Health. Specimens will be tested for influenza A and B virus by RT-PCR. For positive influenza A specimens, specific RT-PCR for influenza A(H1N1)v will be performed. All positive influenza specimens (A(H1N1)v and others) will be sent for further viral isolation and complementary analysis, including oseltamivir resistance monitoring, to one of the two French National Reference Centres (NRC) for influenza.

Discussion

The beginning of the winter season in Réunion Island in June is usually followed by an increase of seasonal influenza activity shortly afterwards. As influenza A(H1N1)v is rapidly spreading worldwide, it can be expected that it emerges very soon in the upcoming winter season in the southern hemisphere (as it already has for example in Australia), including Réunion Island. Therefore, the surveillance of influenza on the island has been enhanced to be able to detect the introduction of influenza at an early stage and to monitor the spread and impact of the infections in order to guide the implementation of control measures foreseen in the French national pandemic plan. The usefulness of our enhanced surveillance will be guaranteed by a good collaboration between clinicians, virologists, epidemiologists and public health authorities. Close viral monitoring is of paramount importance since the circulation of seasonal influenza A(H1N1) resistant to oseltamivir with the A(H1N1)v virus is possible during the winter in the southern hemisphere. Such virological approach combined with epidemiologic description of a potential outbreak will assist local public health authorities to adapt control measures to limit the spread of the infection and mitigate the epidemic including use of information on the effectiveness of antivirals. Results of our enhanced surveillance, if an influenza epidemic occurs in Réunion Island, could provide relevant information for continental France or other European countries in preparation for the coming influenza season in the northern hemisphere.

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* Erratum: On 12 June 2009 Figure 2 was replaced and the titles in the References were translated into English.

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VIROLOGICAL SURVEILLANCE OF HUMAN CASES OF INFLUENZA A(H1N1)v VIRUS IN ITALY: PRELIMINARY RESULTS

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In this report we describe the findings of laboratory-based surveillance of human cases of influenza A(H1N1)v virus infection in Italy, following the recent worldwide detection of this new virus among human population and the decision of the World Health Organization (WHO) to raise the level of pandemic alert.

Background

In late April 2009, in California, the United States, the Centers for Disease Control and Prevention (CDC) identified two human cases of infection with a new swine-like influenza virus A(H1N1), recently named influenza A(H1N1)v virus [1]. The virus isolates showed a unique combination of gene segments, not identified previously among either human or swine influenza A viruses. Similar virus strains were identified in Mexico [2], where a large outbreak of influenza-like illness had been ongoing since mid-March. On 25 April 2009, the World Health Organization (WHO) declared the outbreak as a 'Public Health Event of International Concern' (PHEIC) under the International Health Regulations (2005) [3]. As of 10 June 2009, the number of cases of influenza A(H1N1)v virus infection reached 27,737 in 74 different countries, with 141 deaths. On 11 June 2009 the WHO raised the level of pandemic alert to phase 6.

Hereby we report the characteristics of the first 54 cases of influenza A(H1N1)v virus infection identified in Italy and describe the virological surveillance activities carried out by the National Influenza Centre and the Italian Surveillance Influenza Network (INFLUNET).

Enhanced influenza surveillance

In Italy, influenza surveillance is routinely based on integrated epidemiological and virological national networks. Seasonal virological surveillance is carried out by the WHO National Influenza Centre (NIC) located at the National Institute of Health (Istituto Superiore di Sanità, ISS), which coordinates the activities of 15 collaborating laboratories. In case of emergency, further 12 hospital laboratories are involved in the surveillance activities. The NIC performs quality control assessment and laboratory validation activities specifically aimed to strengthen the diagnostic capabilities of the Italian laboratory network. When a pandemic

occurs, the major task of the NIC is to rapidly detect and/or confirm cases of influenza and perform virus characterisation.

In response to the spread of the A(H1N1)v virus in the United States and Mexico, virological surveillance activities throughout Italy were maintained effective beyond the usual deadline (week 17) of seasonal influenza surveillance.

Since 28 April 2009, the Ministry of Health (MoH) undertook a number of actions, including the recommendations to enhance surveillance activities and laboratory confirmation of suspected and probable cases, which were published as a national guidance document [4]. The case definitions used were based on those adopted by the European Commission [5]. The main scope of the guidance was the early identification of individuals presenting with influenza-like illness and recent history of travel to the affected areas and the adoption of population distancing measures (early isolation of cases and precautionary school closure) and antiviral prophylaxis of close contacts of cases, in order to contain the spread of A(H1N1)v virus cases in the country. In particular, a seven-day period of isolation at home of travellers coming back from affected areas, although asymptomatic, was initially recommended.

According to the above document, pharyngeal and/or nasal swabs should be collected by family and/or hospital doctors from each suspected case (i.e. a case fitting the clinical and epidemiological criteria [5]) and two separate aliquots of the samples should be sent – one to the regional reference laboratory and another one to the NIC. Since 20 May 2009, following the updated MoH recommendations [4], only specimens from probable cases (i.e. cases with positive test results for influenza A virus) should be sent for influenza A(H1N1)v confirmation by NIC.

The notification of confirmed A(H1N1)v cases of infection to the MoH is done by the NIC.

Laboratory confirmation of cases of influenza A(H1N1)v virus infection

The well-established seasonal surveillance network made it possible to identify the first suspected cases of influenza A(H1N1)v

virus infection in Italy as early as 27 April 2009. However, although WHO had promptly provided the national influenza centres with updated molecular diagnostic protocols for influenza A(H1N1)v virus detection, at the time no specific diagnostic reagents were available at the Italian NIC. For this reason, a differential diagnostic test was urgently needed in order to confirm the cases reported by the collaborating laboratories.

In order to assess whether the primer and probe sets, available at NIC for molecular influenza diagnosis, could be useful also to detect infection with the new influenza A(H1N1)v virus, we performed sequence homology studies (by ClustalW program/EMBL-EBI) of the matrix (M), hemagglutinin (HA), neuraminidase (NA) and nucleoprotein (NP) genes among influenza A(H1N1) strains of human and swine origin, downloaded from GenBank or available at the NIC database, together with the first complete viral genome sequence of the reference A/California/4/2009 (H1N1)v virus, made available in the publicly accessible GISAID sequence database (www.gisaid.org). Following the above studies, we decided to analyse the clinical samples collected from the Italian cases using a one-step in-house TaqMan (MGB)-real time RT-PCR (RRT-PCR), already in use at NIC for the detection of the M gene of type A human influenza viruses. Primers and probe used for the above RRT-PCR were available at the website of the United Kingdom Health Protection Agency [6], although conditions used at NIC were adapted to a singleplex reaction. To confirm the results, the amplified product of the M gene (about 200bp) was sequenced and

used for a differential diagnostic analysis to discriminate between seasonal and A(H1N1)v viruses. Furthermore, each sample was also tested in a RRT-PCR assay specific for both seasonal A/H1 and A/H3 human subtypes. A traditional RT-PCR assay, which was routinely used at NIC for seasonal surveillance and updated with specific primers (either suggested by CDC or designed by NIC) for A(H1N1)v virus detection and sequencing, was also employed.

Since 12 May 2009, clinical samples have been tested by the specific RRT-PCR reagent kit from CDC [7]. Virus isolation attempts of laboratory-confirmed cases were also performed, and genes coding for viral protein M, HA1, NA and NP of the first three virus isolates were sequenced and phylogenetically analysed.

Results

Clinical and epidemiological findings of virologically confirmed cases

Information on the epidemiological characteristics and the geographical distribution of the 54 cases of influenza A(H1N1)v virus infections, reported in Italy up to 10 June, is summarised in Figure 1.

Of the 54 confirmed cases, all of whom presented with a self-limiting influenza-like illness (ILI), six were reported among travellers returning from Mexico, 42 in travellers from the United States, two from Canada and one from the Bahamas. Only three cases were due to in-country transmission (specifically household transmission). About 30% of patients were isolated in hospital and 70% were advised to stay at home for the period of seven days. All 54 patients received antiviral treatment.

Figure 2a shows the distribution of all samples analysed and the laboratory-confirmed cases by day of sample collection, whereas Figure 2b shows the distribution of cases by day of symptoms onset and travel history. The median age of the patients was 27.5 years (Figure 1), ranging from 2 to 69 years, and 28 (52%) of the confirmed cases were females. Thirty-three cases were identified in central Italy, 19 in the north and only two in the south of the country. Interestingly, 12 of the cases identified in central Italy involved a group of high-school students from two schools in Rome, returning from a United Nations meeting held in New York and travelling back to Italy on 19 May on the same flight. The index case was a girl who showed typical ILI-symptoms as early as 15 May when still in New York, but whether she was the source of infection for the other students or whether they had acquired the infection during the meeting attended by about 10,000 students from all over the world remains unknown. One of the students was asymptomatic, 11 developed mild clinical symptoms consistent with those of seasonal influenza. Following these cases, the two schools in Rome were closed for one week.

Specificity analysis of the primer and probe sets and laboratory results

The viral gene sequence alignment analyses showed that the specific primers and probe set used by NIC in the RRT-PCR to detect the M gene of type A human influenza, was also able to detect the M gene of A(H1N1)v virus. The two primers corresponded to nucleotide positions 3-29 and 190-207, respectively, in the influenza A/California/6/09 sequence obtained from GISAID (EPI176497). The MBG-probe nucleotide positions were 152-167. The specific region recognised by the above primers was well-conserved among human and swine strains, although a sequence discrimination between the two groups could be obtained on the

FIGURE 1

Geographical distribution and epidemiological characteristics of cases of laboratory-confirmed A(H1N1)v virus infection in Italy, by 10 June 2009 (n=54)

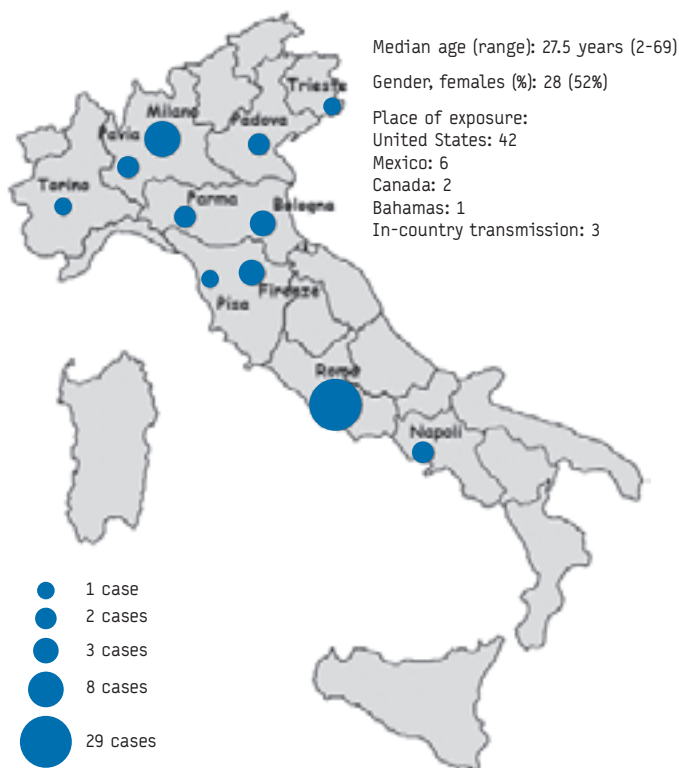
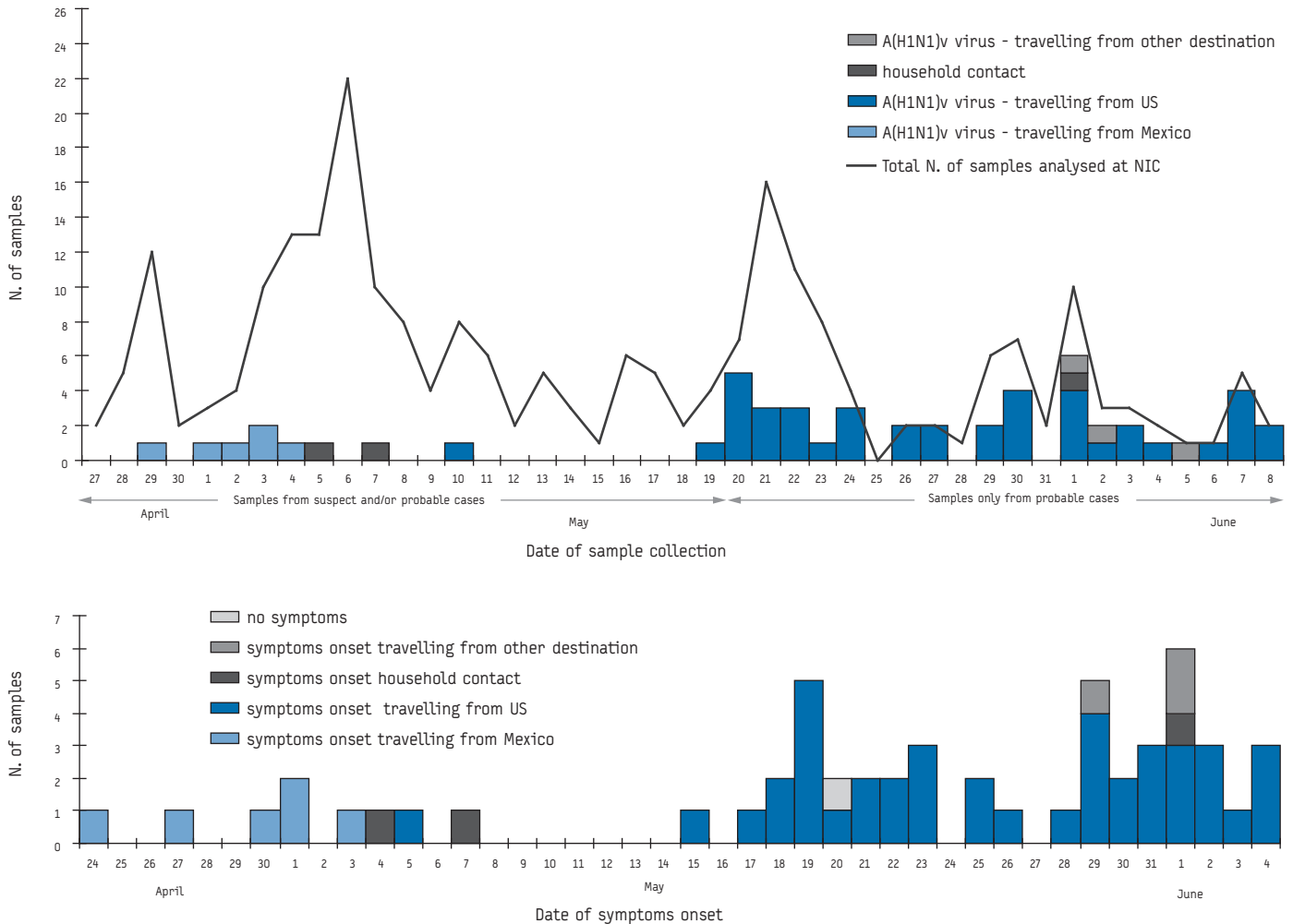


FIGURE 2

Number of clinical samples analysed at the National Influenza Centre and of laboratory-confirmed cases of influenza A(H1N1)v virus infection by (A) day of sample collection and (B) day of symptoms onset; Italy, as of 10 June 2009



basis of the sequence analysis of the final amplification M fragment (about 200 bp); along this region it was possible to highlight at least 12 nucleotide changes clearly distinguishing the A(H1N1)v virus from the currently circulating human influenza isolates. This was the method initially employed to identify the novel A(H1N1) strain in the clinical material. When the regional laboratories were able to provide viral sequences, a confirmatory BLAST analysis was performed by the NIC to confirm A(H1N1)v virus cases.

Sequence analyses

Preliminary studies showed that six genomic segments of the virus, including the HA, were related to swine viruses from North America and the remaining two (coding for the NA and M proteins) were from swine viruses isolated in Europe and Asia [8,9]. Figure 3 shows the evolutionary relationships of the M1, HA1, NA and NP gene segments of the first three A(H1N1)v virus isolates, obtained in Italy from patients without epidemiological link, compared to other recent A(H1N1)v virus sequences obtained from GenBank

and to some recent Italian swine and European human seasonal isolates. The phylogenetic trees confirmed that both the M and the NA gene segments of the new A(H1N1) strains were closely related to the Italian swine strains. In contrast, the HA1 and NP nucleotide sequences of these viruses appeared to be quite different from the Italian swine strains and more related to the swine strains belonging to the North-American lineage (A/Sw/Ohio/511445/07 in Figure 3), although forming a clade with human seasonal viruses.

Antiviral susceptibility

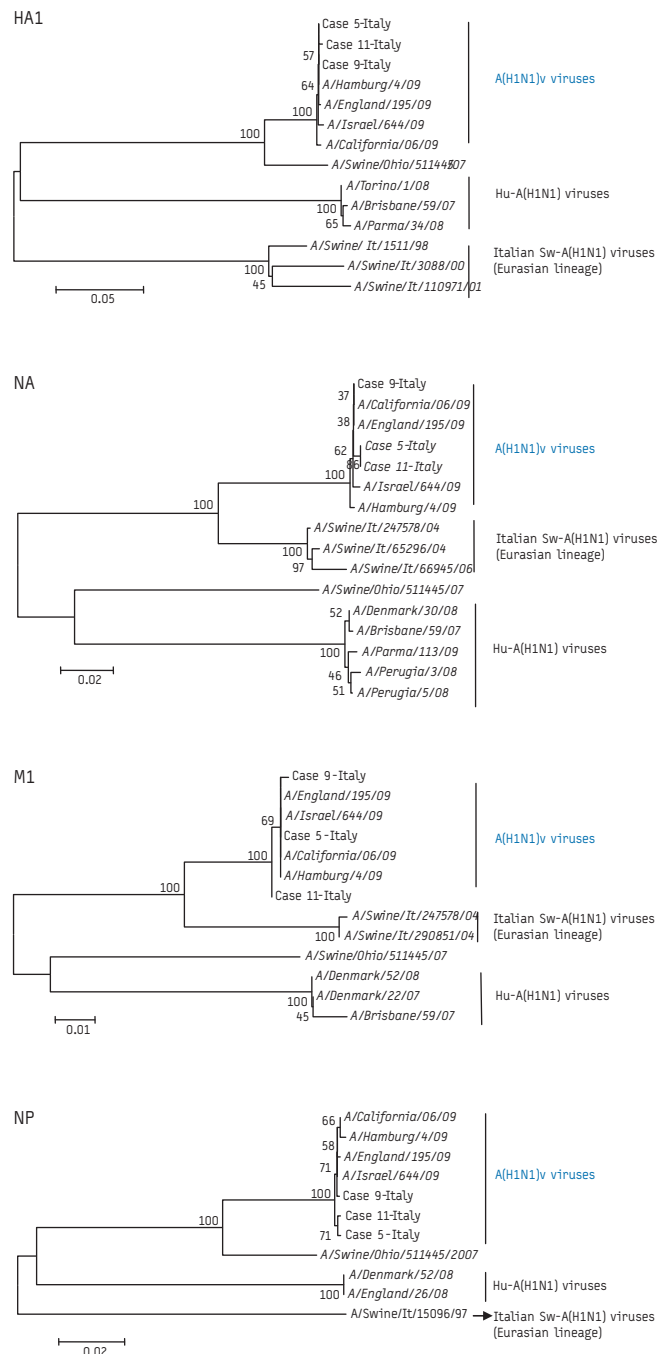
The sequence analyses of the NA and M genes, respectively, revealed that the above mentioned three A(H1N1)v virus isolates were resistant to adamantanes and sensitive to both neuraminidase inhibitors (oseltamivir and zanamivir).

Discussion

During a period of over one month between 27 April and 10 June, 54 laboratory-confirmed cases of influenza A(H1N1)

FIGURE 3

Phylogenetic analysis of the M1, HA1, NA and NP gene segments of the first three A(H1N1)v virus isolates obtained in Italy in May 2009 compared to recent Italian swine and European human seasonal influenza isolates



MEGA software package (version 3.1) was used to estimate phylogenies from the nucleotide sequences and for the construction of phylogenetic trees, using Tamura-Nei method and the Neighbor-Joining algorithm. Bootstrap based on 1,000 replicates; Italian cases of A(H1N1)v virus are indicated in bold; GenBank sequences are in italics; Hu=human; Sw=swine

virus infection were identified in Italy. With the exception of three secondary cases (in-country transmission) in Rome, all cases of influenza A(H1N1)v virus infection reported in Italy, in this first phase, were acquired abroad, during travel to affected areas (Mexico, the United States, Canada, the Bahamas) and involved mainly young adults.

Laboratory-based surveillance represented a useful tool for early detection of influenza A(H1N1)v cases among travellers and their close contacts. Most laboratories developed methodologies for a rapid diagnosis of this novel virus infection, in close collaboration with the NIC which provided support for definitive diagnosis and data collection. It is expected that the sustainability of this system will decrease as the epidemic spreads and syndromic surveillance will prevail.

The very limited in-country transmission suggests that early diagnosis, antiviral prophylaxis and social distancing, including precautionary school closure, may have contributed to contain the spread of infection in the first phase of the epidemic. However, containment strategies are not realistic in the long-term, and mitigation remains the only option as the epidemic progresses.

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EPIDEMIOLOGY OF INFLUENZA A(H1N1)v VIRUS INFECTION IN JAPAN, MAY - JUNE 2009

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Between 9 May and 4 June 2009, a total of 401 laboratory-confirmed cases of influenza A(H1N1)v virus were reported in Japan, from 16 of the 47 Japanese prefectures. The two areas most affected were Osaka prefecture and Kobe city where outbreaks in high schools occurred leading to school closures. To date all cases have had symptoms consistent with seasonal influenza and no severe or fatal cases have been reported.

Following the emergence of a new influenza A(H1N1) virus (henceforth: influenza A(H1N1)v virus) and the relevant declarations by the World Health Organization (WHO) [1], the Ministry of Health, Labour and Welfare (MHLW) of Japan launched a case-based surveillance for influenza A(H1N1)v virus infection in addition to the existing sentinel surveillance system for seasonal influenza and imposed entry screening on travelers from affected areas (Canada, Mexico and the United States) starting from 28 April 2009 [2].

The following case definitions of suspected and confirmed cases have been used:

A **suspected case** of influenza A(H1N1)v virus infection is defined as a person with high fever (>38°C) OR at least two acute respiratory symptoms (nasal obstruction/rhinorrhea, sore throat, cough, fever/feverishness) AND who meets at least one of the following criteria:

- within the last seven days returned from a country or region with an epidemic of influenza A(H1N1)v;
- was in close contact (within two meters) with a confirmed case within the past seven days;
- handled samples suspected of containing influenza A(H1N1)v virus in a laboratory or other setting within the past seven days;

A **confirmed case** of influenza A(H1N1)v virus infection is defined as a person with high fever (>38°C) OR at least two acute respiratory symptoms (nasal obstruction/rhinorrhea, sore throat, cough, fever/feverishness) AND influenza A(H1N1)v virus infection that has been laboratory confirmed by real-time PCR and/or viral isolation.

For all travellers from the affected areas who are febrile at the entry, a quarantine officer performs a rapid diagnostic test for influenza. If the result of rapid test is positive for influenza A, a PCR test for influenza A(H1N1)v is done. The Quarantine Law and the Pandemic Influenza Preparedness Action Plan of the Japanese Government request confirmed cases and close contacts of confirmed cases to be hospitalised/isolated for seven days considered to be the infectious period [3,4].

The primers for conventional and real-time RT-PCR for the detection of A(H1N1)v virus were developed by the National Institute of Infectious Diseases and became available on 29 April. All 75 prefectural and municipal public health institutes and quarantine stations in Japan became ready to perform conventional and real-time RT-PCR test by 4 May. Since the first laboratory-confirmed cases were reported on 9 May, the number of cases of influenza A(H1N1)v increased continuously, resulting in a total of 401 laboratory-confirmed cases as of 4 June 2009. This report summarises the epidemiological characteristics of the confirmed cases reported in Japan from May to June.

The first four laboratory-confirmed cases of influenza A(H1N1)v were reported at the Narita International Airport quarantine station on 9 May 2009. The patients were travellers who returned from Canada on 9 May. Although all of them showed mild symptoms, they were hospitalised in an isolation ward of a designated hospital for seven days, in accordance with the Quarantine Law and the Pandemic Influenza Preparedness Action Plan of the Japanese Government [3,4].

The first laboratory-confirmed cases without travel history were detected on 16 May as follows:

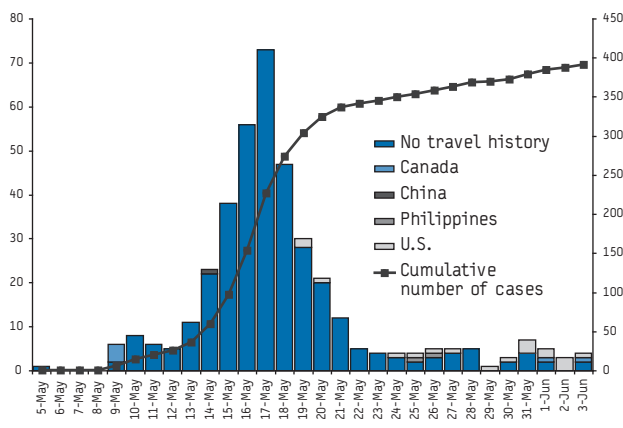
A high school in Ibaraki city, in Osaka prefecture near the border with Hyogo prefecture, noticed an increase in the number of absentees due to influenza-like symptoms in the middle of May 2009. On 16 May the school was closed in conformity with the School Health Law [5]. According to this law (enacted in 1958), influenza-like illness/seasonal influenza is one of the infectious diseases that can trigger school closure. The number of absentees that leads to school closure is decided by the school authorities. In many cases, 5 to 10 absentees in a class may lead to closing the class; 2-3 closed classes may lead to school closure.

None of the sick high school pupils in Ibaraki had travel history to the countries affected by the new influenza. On 16 May, five teenagers were confirmed with influenza A(H1N1)v virus infection: one from the school in Ibaraki in Osaka prefecture, and four from Kobe City in the neighbouring Hyogo prefecture. Subsequently, outbreaks in three schools were reported during the next few days in these adjacent prefectures. The local governments of Kobe City and Osaka prefecture implemented extensive school closures, deciding to close not only schools with infected students but all schools in both districts, for one to two weeks from 16 May. As a result, over

4,200 schools with around 650,000 children/students were closed. By 19 May, the number of confirmed cases reported in the two districts reached 172. However, after school closures, the number of new confirmed cases decreased (Figure 1). By 4 June a total of 357 cases were reported from the two prefectures.

Outside these two prefectures only sporadic cases were reported, the majority of whom had a travel history abroad or an epidemiological link to a traveller from affected areas including

FIGURE 1
Confirmed cases of influenza A(H1N1)v virus infection in Japan, by date of onset and cumulative number as of 4 June 2009 (n=392*)



* Nine cases without the record of onset of illness were excluded

FIGURE 2
Geographical distribution of confirmed cases of influenza A(H1N1)v virus infection in Japan as of 4 June 2009 (n=401)



Osaka (Figure 2). In all, confirmed cases were reported from 16 of the total of 47 Japanese prefectures.

Reflecting the outbreaks in high schools described above, confirmed cases in the age group of 15-19 years accounted for 64% (256) of all cases, followed by 10% (40) of cases in the age group of 10-14 years. Only four cases (1%) were over 60 years of age (Figure 3). Overall, the median age of cases was 16.0 (range 1-69 years). Male cases accounted for 63% (254) and female cases for 37% (147) of all cases. Large outbreaks observed in high schools may have contributed to the difference in gender (as more boys than girls attend the affected schools).

Information on clinical symptoms was available for 217 confirmed cases (Figure 4). The most frequent were fever (206, 95%), cough (128, 59%), and sore throat (85, 39%). Thirteen cases (6%) reported diarrhoea and five cases (2%) had nausea.

FIGURE 3
Age distribution of confirmed cases of influenza A(H1N1)v virus infection in Japan as of 4 June 2009 (n=401)

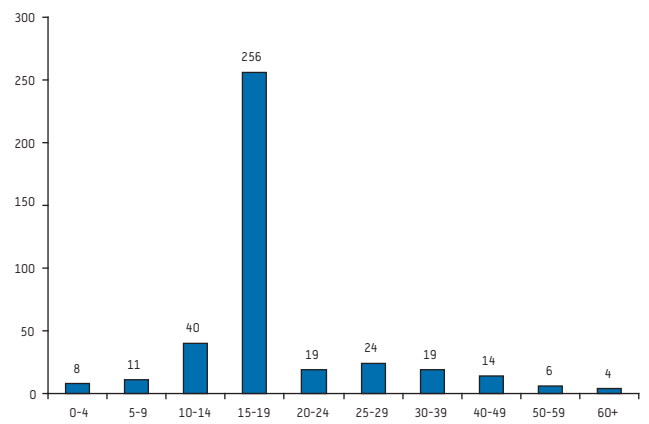
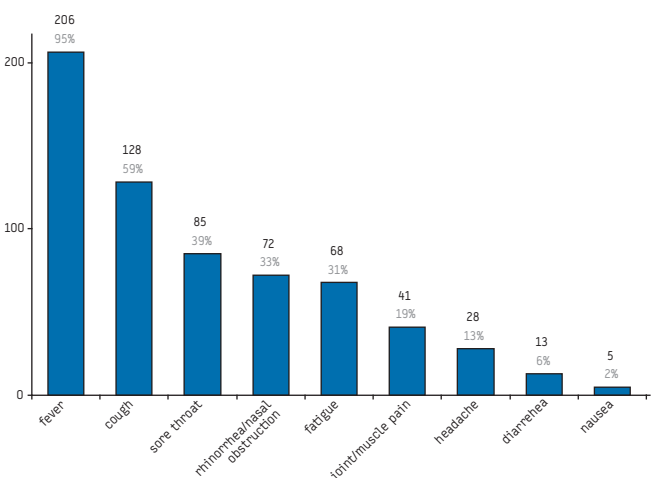


FIGURE 4
Clinical symptoms of confirmed cases of influenza A(H1N1)v virus infection in Japan as of 4 June 2009 (n=217)



Antiviral treatment of either oseltamivir or zanamivir was prescribed to about 90% of the 217 confirmed cases with known clinical symptoms.

No cases with pneumonia and/or respiratory failure, requiring ventilatory support, were reported. Other severe symptoms such as multiple organ failure were not reported either. Only three cases required hospitalisation due to underlying medical conditions, although a total of 135 cases were hospitalised for the purpose of isolation based on the Quarantine Law and the Pandemic Influenza Preparedness Action Plan of the Japanese Government [3,4].

Among the confirmed cases, six (including two cases aged over 60 years) had underlying diseases: asthma (3), asbestosis (1), epilepsy (1), myodystrophia (1); and one case was pregnant. As of 4 June 2009, no severe or fatal case had been reported.

The epidemiological characteristics of the patients with influenza A(H1N1)v virus infection have been reported by the investigation teams including members of IDSC/NIID and local government, who conclude that the severity of disease is similar to that of seasonal influenza [6,7].

The next steps include addressing the questions of how to improve the surveillance system to detect, monitor, and control the cases of influenza A (H1N1)v and how to prepare for the more severe cases as the epidemic is expected to expand in the winter season. We need to decide when the case-based surveillance for influenza A(H1N1)v should be ceased and integrated into the sentinel surveillance of seasonal influenza. To evaluate the pathogenicity, planned surveillance systems, such as severe pneumonia surveillance and ILI cluster surveillance, should be launched before the coming winter season. The Pandemic Influenza Preparedness Action Plan of the Japanese Government also needs to be amended so that medical resources would not be wasted by the patients with mild symptoms merely for the purpose of isolation.

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Rapid communications

SCHOOL CLOSURE IS CURRENTLY THE MAIN STRATEGY TO MITIGATE INFLUENZA A(H1N1)v: A MODELING STUDY

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Concerns about an imminent influenza pandemic have been intensified after the emergence of the new influenza A(H1N1)v strain. Mathematical modeling was employed on recent epidemiological data from Mexico in order to assess the impact of intervention strategies on the spread of influenza A(H1N1)v in the setting of the European region. When initiating the intervention of 100% school closure in a community of 2,000 people at a threshold of 1% cumulative attack rate, the total number of symptomatic cases is predicted to decrease by 89.3%, as compared to the non-intervention scenario. When this measure is coupled with treatment and home isolation of symptomatic cases as well as a 50% reduction of social contacts, a 94.8% decline in the cumulative attack rate is predicted along with a much shorter duration of influenza A(H1N1)v transmission. Active surveillance that will ensure timely treatment and home isolation of symptomatic cases in combination with school closure seem to form an efficient strategy to control the spread of influenza A(H1N1)v.

Introduction

The emergence of the new influenza A(H1N1)v strain in March-April 2009 prompted the World Health Organisation (WHO) to raise the pandemic alert level. Influenza A(H1N1)v has to date spread to 76 countries and has infected 35,928 individuals (confirmed cases as of 15 June 2009) [1]. Currently, there is uncertainty about key epidemiological parameters such as the age-specific attack rates, the case fatality rate and the basic reproductive number R_0 (i.e. the number of secondary cases attributed to one infected individual in a susceptible population) [2-4]. Since the epidemic in Mexico provides the most advanced insight into key epidemiological parameters [2], we used those parameters to simulate the potential spread of influenza A(H1N1)v in a model community situated in Greece and explored the effectiveness of various intervention strategies that could inform policies and decisions in the setting of the European region.

TABLE 1

Size of households and proportion of household members ≥ 65 or < 15 years-old according to household size, Greece, 2001

Household size	Total % of households	% without ≥ 65	% with one ≥ 65	% with two ≥ 65	% with three ≥ 65	% with four ≥ 65	% with five ≥ 65
1	19.8	56.03	43.97	0.00	0.00	0.00	0.00
2	28.1	49.48	22.44	28.08	0.00	0.00	0.00
3	21.1	73.44	15.71	10.01	0.84	0.00	0.00
4	20.5	86.20	10.04	3.43	0.28	0.05	0.00
5	6.8	68.93	24.82	5.85	0.33	0.06	0.01
6	2.5	53.92	26.94	18.50	0.55	0.07	0.02
7	0.8	48.02	27.41	22.91	1.50	0.14	0.03
8+	0.5	49.69	25.88	21.47	2.40	0.44	0.12
Household size		% without < 15	% with one < 15	% with two < 15	% with three < 15	% with four < 15	% with five < 15
1	19.8	100.00	0.00	0.00	0.00	0.00	0.00
2	28.1	97.45	2.55	0.00	0.00	0.00	0.00
3	21.1	65.88	32.36	1.76	0.00	0.00	0.00
4	20.5	44.08	18.30	37.37	0.25	0.00	0.00
5	6.8	34.96	24.97	20.43	19.48	0.16	0.00
6	2.5	22.85	22.79	32.33	11.61	10.33	0.08
7	0.8	17.55	19.76	27.39	22.44	7.32	5.55
8+	0.5	13.15	15.63	26.46	20.60	15.29	8.88

Source: General Secretariat of National Statistical Service of Greece. Available from http://www.statistics.gr/Main_eng.asp

The simulation model

Simulation parameters

We used a discrete-time stochastic individual-based simulation model, employed in previous studies on influenza [5,6], to simulate the spread of influenza A(H1N1)v. A structured model community of approximately 2,000 people was generated to match the age-distribution, household size and number and size of schools of the Greek population (Tables 1-2).

The model community of 2,000 people was divided into four neighbourhoods of approximately equal size that share one kindergarden, one primary school and one high school. Influenza is introduced at day 0 by randomly assigning a number of initial infective individuals, and person-to-person transmission probabilities are used to simulate influenza spread over time. The transmission probabilities used elsewhere [5] were modified to yield the age-specific attack rates of the influenza A(H1N1)v outbreak in the community of La Gloria in Mexico [2]. As the population was assumed to be structured (households, schools, neighbourhoods and community), different transmission probabilities applied to different mixing groups. They were highest for contacts within households and lower for contacts within schools, followed by neighbourhoods and, finally, the entire community (Table 3). The transmission probabilities published elsewhere [5,7,8] were modified to yield the age-specific attack rates observed in the influenza A(H1N1)v outbreak in La Gloria [2].

Each day, all susceptible individuals in the community were exposed to a number of infective children (I_{hc}) and adults (I_{ha}) of their household, their school (if they are children) (I_s), their neighbourhood (I_n) and the entire community (I_{com}), with corresponding probabilities of transmission. The probability of an adult not becoming infected by children at home was:

$$(1 - p_{hca})^{I_{hc}}$$

Thus, in the simple case of an adult exposed on a specific day to I_{hc} infected children at home, I_n infected people in their neighbourhood and I_{com} infected people in the entire community, the probability of not becoming infected was:

$$P(\text{not being infected}) = (1 - p_{hca})^{I_{hc}} (1 - p_n)^{I_n} (1 - p_{com})^{I_{com}}$$

Thus, each day, for each susceptible, the probability of becoming infected was calculated on the basis of who was infectious in their contact groups and of the group-specific transmission probabilities:

$$P(\text{infection}) = 1 - (1 - p_{hca})^{I_{hc}} (1 - p_n)^{I_n} (1 - p_{com})^{I_{com}}$$

Once these daily probabilities are calculated for each susceptible individual, a uniform (0,1) random number was generated. If this number was lower than the probability of infection of the susceptible individual, then this person became infected. If susceptible people had been given antiviral prophylaxis, the transmission probabilities

TABLE 2

Proportion of Greek population by age compared to the EU-27, the two most affected European countries, Spain and the United Kingdom, as well as Mexico (data for 2006)

	0 to 14 years	15 to 64 years	≥65 years
Greece*	14.3	67.2	18.5
EU-27*	16.0	67.2	16.7
Spain*	14.5	68.9	16.7
United Kingdom*	17.8	66.2	16.0
Mexico**	30.6	63.6	5.8

* Eurostat yearbook 2008. http://epp.eurostat.ec.europa.eu/portal/page/portal/publications/eurostat_yearbook

** United States Census Bureau, International Data Base. <http://www.census.gov/ipc/www/idb/tables.html>

TABLE 3

Transmission probabilities among children and adults, by mixing group

Contact group	Infected	Susceptible	Transmission probabilities
Household	Child	Child 0-4 years-old	0.6
Household	Child	Child 5-17 years-old	0.08
Household	Adult	Child 0-4 years-old	0.2
Household	Adult	Child 5-17 years-old	0.03
Household	Child	Adult	0.03
Household	Adult	Adult	0.04
School	Child 4-5 years-old	Child 4-5 years-old	0.015
School	Child 6-11 years-old	Child 6-11 years-old	0.0145
School	Child 12-17 years-old	Child 12-17 years-old	0.0125
Neighbourhood	Anyone	Child 0-11 years-old	0.00004
Neighbourhood	Anyone	Child 12-17 years-old	0.00012
Neighbourhood	Anyone	Adult 18-65 years-old	0.00048
Neighbourhood	Anyone	Adult >65 years-old	0.00035
Community	Anyone	Child 0-11 years-old	0.00001
Community	Anyone	Child 12-17 years-old	0.00003
Community	Anyone	Adult 18-65 years-old	0.00012
Community	Anyone	Adult >65 years-old	0.00009

were multiplied by 0.70 (protective efficacy: 30%). If an infected person was taking an antiviral drug, the transmission probability from that person to a susceptible person was multiplied by 0.38 (antiviral efficacy for infectiousness: 62%) [9].

We assumed an infectious period of four days and a latent period of one day, as data on influenza A(H1N1)v as well as volunteer challenge studies suggest a short latent period [2,10]. The probability of developing symptoms if infected was assumed 67% and asymptomatic people were 50% as infectious per contact as symptomatic people [11].

Interventions

The interventions considered are summarised in Table 4.

Antiviral treatment and targeted antiviral prophylaxis (TAP) of household contacts are administered one day after onset of

symptoms of the index case for a period of five and 10 days, respectively. Compliance with home isolation of symptomatic cases (90%) and of children during school closure (60%) was modeled by assuming that the compliant proportion stayed at home during the infectious period or during school closure, while non-compliant individuals continued circulation in the neighbourhood and the community as usual. Treatment and prophylaxis are assumed to reduce the probability of an infected person transmitting by 0.62 [9,12]. Prophylaxis is assumed to reduce the probability of being infected by 0.30 and, if infected, the probability of developing symptoms by 0.60 [9,12].

The threshold for initiating treatment and isolation of index cases and/or TAP in scenarios 1, 2, and 5-7 was set to 0.05% cumulative clinical attack rate (i.e. as soon as one symptomatic case occurs in the community of 2,000 people). The corresponding threshold for non-pharmaceutical interventions of scenarios 3-7

TABLE 4
Assumptions of the evaluated intervention strategies

	Treatment of symptomatic cases (Threshold: 0.05%)	Isolation of symptomatic cases (Threshold: 0.05%)	TAP (Threshold: 0.05%)	Social distancing (Threshold: 1%)	School closure (Threshold: 1%)
	% ascertainment of symptomatic cases / % compliance with receiving treatment	% compliance with staying home	% compliance with receiving prophylaxis	% reduction in community contacts	% of schools closing / % compliance of children with staying home
Scenario 0 (No intervention)	-	*	-	-	-
Scenario 1 (Treat and isolate)	80% / 100%	90%	-	-	-
Scenario 2 (Treat and isolate, TAP)	80% / 100%	90%	100%	-	-
Scenario 3 (Social distancing)	-	-	-	50%	-
Scenario 4 (School closure)	-	-	-	-	100% / 60%
Scenario 5 (Treat and isolate, Social distancing)	80% / 100%	90%	-	50%	-
Scenario 6 (Treat and isolate, School closure)	80% / 100%	90%	-	-	100% / 60%
Scenario 7 (Treat and isolate, School closure, Social distancing)	80% / 100%	90%	-	50%	100% / 60%

Threshold indicates the illness attack rate for initiating the interventions.

TAP: Targeted antiviral prophylaxis of household contacts.

* 80%, 75% and 50% of symptomatic preschool children, school children and adults, respectively, withdraw voluntarily to the home.

TABLE 5
Simulated illness attack rates of influenza A(H1N1)v outbreaks and proportion of cases by age group in a community of 2,000 persons in Greece when one infected person initially seeded into the population and the corresponding data from the outbreak in La Gloria, Mexico

Age group (years)	Clinical attack rate (%)		% of cases by age	
	Community in Greece	La Gloria, Mexico	Community in Greece	La Gloria, Mexico
0-18	59.7%	61.1%	31.7%	50.2%
19-65	32.1%	29.6%	57.0%	45.3%
65+	23.8%	22.0%	11.3%	4.5%
Overall	36.0%	39.1%	100.0%	100%

was set to 1% (20 cases per 2,000 population). We investigated the effect of these interventions in 200 simulations assuming five infected individuals initially seeded into the population.

Results

Simulated spread of H1N1 under the non-intervention scenario

In the case of an outbreak of influenza A(H1N1)v in Greece according to our model, and in the absence of intervention, individuals under the age of 18 years would account for 31.7% of cases, as compared to 50.2% in Mexico, and individuals over the age of 65 years are expected to account for approximately 11 out of 100 cases (11.3% versus 4.5% in Mexico) (Table 5) [2].

The simulated epidemic curve of the H1N1 outbreak is depicted in Figure 1 and is very similar to that obtained from La Gloria in Mexico [2]. The basic reproductive number R_0 was estimated in 1,000 simulations as described in Longini *et al.* [5] and its average value was 1.51.

We examined in 200 simulations the effect of introducing simultaneously more than one infected person in the community of 2,000 people on day 0. Introducing one infected individual resulted in an outbreak in only 35.2% of the simulations. As the

number of initially infected individuals increased to five and 10, the probability of an outbreak was 94.8% and 99.6%, respectively (Figure 2).

Impact of interventions

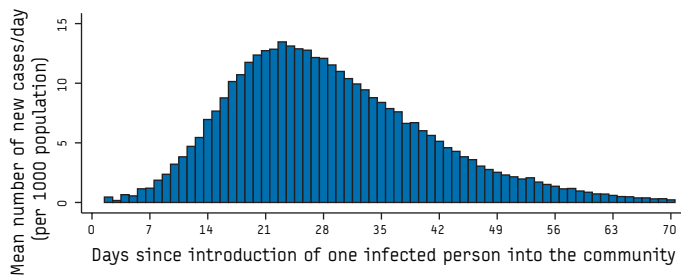
The effect of the intervention strategies is shown in Figure 3 and Table 6.

Compared to no intervention, the decrease in the illness attack rates when any of the intervention scenarios 1-4 were evaluated separately ranged from 40.9% to 89.3%. The combination of treatment, school closure and social distancing (scenario 7) resulted in an attack rate of 1.8% (decrease: 94.8%). Although school closure largely reduced the attack rate when used as a single intervention, transmission occurred over a prolonged period of time (day of occurrence of the last new infection: day 43). The addition of treatment and social distancing reduced the duration of virus transmission to 17 days. This scenario is predicted to limit the spread of influenza A(H1N1)v even in the case of 100 infected persons simultaneously introduced into the model community of 2,000 persons (Figure 4).

FIGURE 1

Simulated influenza A(H1N1)v outbreaks after the introduction of one infected person into the community (over 200 simulations)

A) Mean number of daily symptomatic infections per 1,000 population



B) Cumulative number of symptomatic cases per 1,000 population

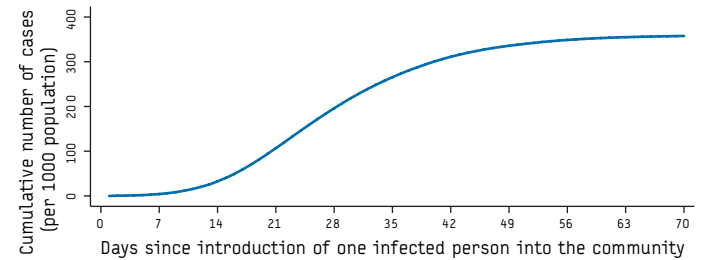


FIGURE 2

Distribution of the total number of secondary symptomatic cases in 200 simulations according to the initial number of infected persons seeded into the population

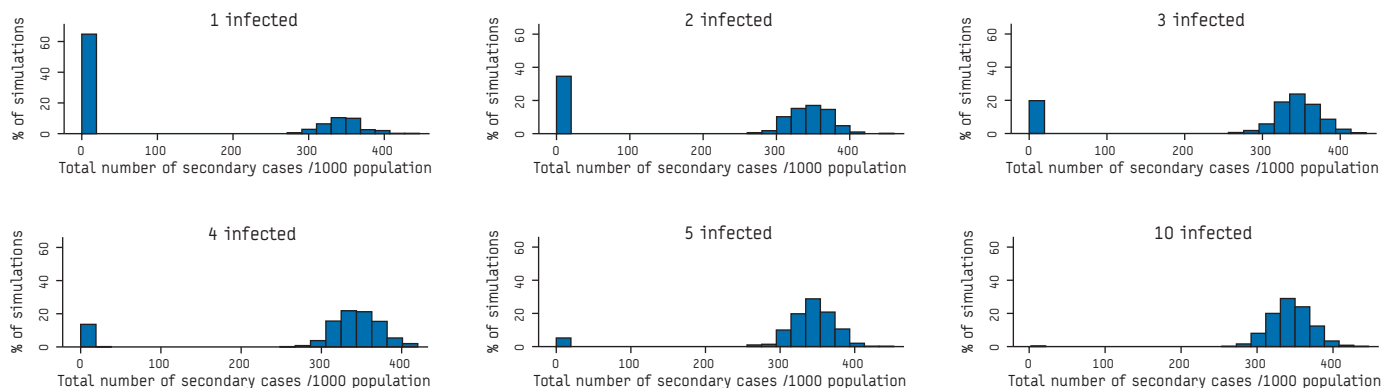
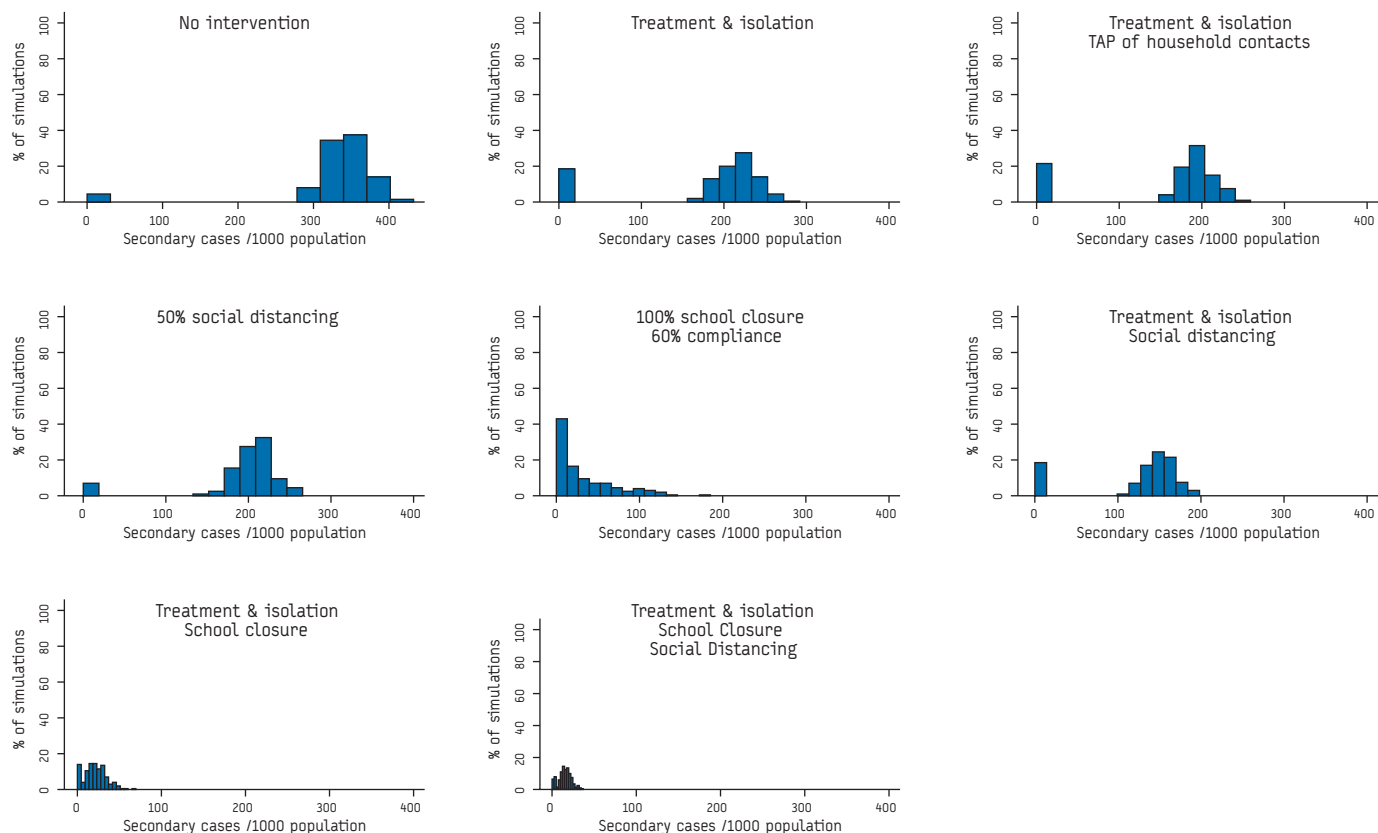


FIGURE 3

Distribution of the total number of secondary symptomatic cases in 200 simulations according to the intervention used (five infected individuals initially seeded into the population)



Threshold for initiating treatment and isolation of index cases, TAP of household contacts: 0.05%, for school closure and social distancing: 1% cumulative illness attack rate.
TAP: Targeted antiviral prophylaxis of household contacts.

TABLE 6

Simulated average illness attack rates and duration of influenza A(H1N1)v spread over 200 simulations according to different interventions used (five infected individuals initially seeded into the community)

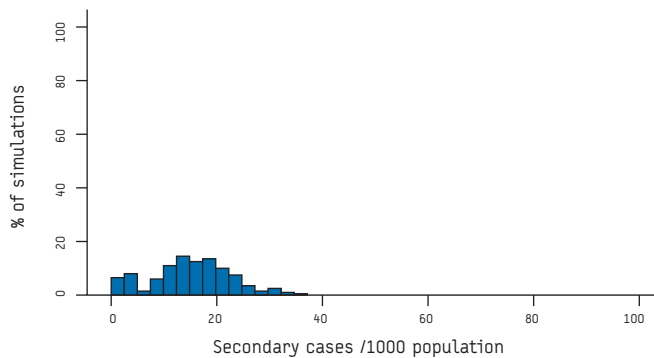
Intervention	Illness attack rates*		Day of the last infection*
	%	% decrease compared to no intervention	
0. No intervention	34.5%	-	54
Treatment-based interventions			
1. Ascertainment of 80% of cases, treatment and isolation of cases	18.8%	45.5%	41
2. Ascertainment of 80% of cases, treatment and isolation of cases, TAP of household contacts	16.3%	52.8%	40
Non-pharmaceutical interventions			
3. 50% social distancing	20.4%	40.9%	45
4. School closure (100% closure, 60% compliance)	3.7%	89.3%	43
Combination of treatment-based and non-pharmaceutical interventions			
5. Ascertainment of 80% of cases, treatment and isolation of cases and social distancing	13.1%	62.0%	35
6. Ascertainment of 80% of cases, treatment and isolation of cases and school closure	2.5%	92.8%	24
7. Ascertainment of 80% of cases, treatment and isolation of cases, school closure and social distancing	1.8%	94.8%	17

* The average estimates were computed over 200 simulations independently of whether an outbreak occurred or not.
TAP: Targeted antiviral prophylaxis of household contacts.

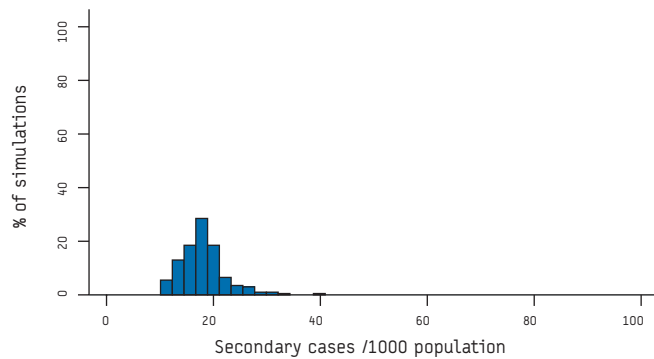
FIGURE 4

Distribution of the total number of secondary symptomatic cases (under intervention scenario 7 of Table 6) in 200 simulations according to the initial number of infected (secondary cases do not include the initial infected persons)

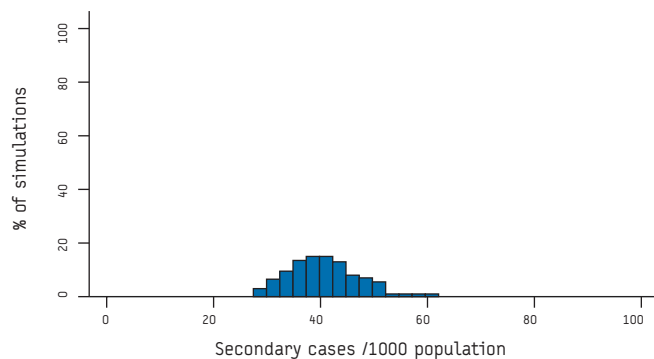
A) Five infected individuals initially seeded into the population



B) 40 infected individuals initially seeded into the population



C) 100 infected individuals initially seeded into the population



Discussion

A stochastic model was used to assess the impact of various intervention strategies on the spread of the new influenza A(H1N1) v in a Greek model community. Due to the similarity in the age structure of the Greek and the European population, it may be possible to apply the results to other communities in the European region. Uncertainty remains concerning key epidemiological parameters of influenza A(H1N1)v, such as the basic reproductive

number R_0 that has been estimated to be in the range 1.4-1.6 [2] and less than 2.2-3.1 [4] for Mexico, and 2.3 for Japan [3]. In our analysis, we have modeled an R_0 of 1.5 based on the first reported estimates [2]. Even with this low R_0 , simultaneous introduction of five infected individuals in the model community of 2,000 people almost always lead to an outbreak in the absence of any intervention.

The combination of antiviral treatment with school closure and social distancing at the assumed thresholds was found to control the spread of influenza A(H1N1)v. Although school closure was found to be an effective strategy even when it used as the sole intervention, sporadic transmission occurred over a prolonged period. As a prophylactic vaccine is not available yet, the effect of this intervention was not evaluated.

The simulation model has been applied to a community of 2,000 people. Therefore, our results concerning the anticipated duration and peak of the outbreak do not apply for an epidemic in the whole country. However, an epidemic in a country occurs in subpopulations or regions at different times [5], and this is the process we attempted to model. Similar small community models have been used widely in exploring the effectiveness of different intervention strategies [5,6,13,14]. A further assumption of the small community model is that after the initially infected persons have been seeded into the community, that population remains isolated. Furthermore, our model did not consider workplaces as mixing groups but rather used higher transmission probabilities for contacts between adults than for children within the community and neighbourhoods.

The findings on the impact of school closure in mitigating pandemic influenza are variable [12-17]. This is most probably due to different assumptions regarding the implementation of school closure (such as the delay in closing schools, the duration of school closure etc.) and regarding contact behaviour of pupils during school closure as well as to widely varied epidemiological parameters. Closing schools is more effective when R_0 is low and attack rates in children are high in comparison to adults [17]. In the current influenza A(H1N1)v epidemic, attack rates are particularly high in children [2] and the median age of non-imported cases in Europe is 13 years [18]. Our results agree with a recent paper suggesting that active surveillance and school closures in Japan most likely have contributed to controlling influenza A(H1N1) v transmission [3]. However, implementation of school closure is expected to lead to work absenteeism of working parents and considerable costs [19]. The potential benefits and costs of school closure need to be further considered.

The current epidemiological data obtained from the outbreak in Mexico are valuable in planning our response to the spread of influenza A(H1N1)v, provided that the epidemiological and clinical characteristics will not change substantially. Until the production and use of a prophylactic vaccine, active surveillance that will ensure timely treatment and home isolation of symptomatic cases in combination with school closure seem to form an efficient strategy to control influenza A(H1N1)v spread.

Acknowledgment

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Rapid communications

A VARIETY OF RESPIRATORY VIRUSES FOUND IN SYMPTOMATIC TRAVELLERS RETURNING FROM COUNTRIES WITH ONGOING SPREAD OF THE NEW INFLUENZA A(H1N1)V VIRUS STRAIN

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Clinical specimens from 79 symptomatic individuals with a recent history of travel to countries with verified transmission of influenza A(H1N1)v (North America) were tested with a multiple real-time PCR targeting a broad range of agents that may cause acute respiratory infection. This analysis revealed that besides four cases of influenza A(H1N1)v, other respiratory viruses were diagnosed in almost 60% of the samples. These observations are a reminder that many different viral transmissions occur simultaneously in countries with ongoing spread of influenza A(H1N1)v. The findings demonstrate that the definition of suspected cases by clinical and epidemiological criteria has only a poor capacity for discriminating influenza A(H1N1)v from other viral infections.

Background

A new influenza A(H1N1)v variant has spread globally since its first appearance in April 2009 [1,2] and as of 17 June 2009 there were 39,620 cases reported by the World Health Organization (WHO) [3]. On 30 April 2009, the European Commission suggested a case definition [4], which has been adopted and modified by most authorities in the European Union Member States. In agreement with this recommendation, testing for influenza A was recommended in Sweden for cases with a clinical presentation

including respiratory symptoms and fever above 38°C, and epidemiological circumstances such as recent travel (within seven days) to areas where the new influenza has been observed [5] or close contact with confirmed cases.

The regular sentinel surveillance for seasonal influenza has been extended and now focuses on identification of imported cases with influenza A(H1N1)v, and on preventing secondary transmission by contact tracing and antiviral medication in an attempt to delay sustained community transmission. In order to provide a better basis for the decision whether or not to initiate preventive measures, expanded testing, targeting a broad range of respiratory agents, has been applied to specimens from all suspected cases in the region Västra Götaland (1.5 million inhabitants). We report here the results of this expanded testing.

TABLE 1

Primers and probes for typing of influenza A virus by real-time PCR run in three parallel reactions

Oligonucleotide primers*	Sequence
IAH1_F	CYGACACTGTTGACACAGTACTTGAGA
IAH1_R	CGGCAACGCTGCAATTACC
IAH1_Probe	TGACAGTGACACACTCTGTCAACCTACTTGAG
IAH3_F	GCAACTGTTACCCTTATGATGTGC
IAH3_R	CATTGATAAACTCCARRGTGCKGA
IAH3_Probe	ATGCCTCCCTTAGGTCAGTGTGCTC
IAH1v_F	GGGGTAGCCCCATTGCATT
IAH1v_R	GTGGAGAGTGATTACACTCTGGA
IAH1v_Probe	CCCAGGATCCAGCCAGCAATGTTACA

* The oligonucleotide primers target type-specific regions of the haemagglutinin gene, and IAH1v oligonucleotides are specific for the new influenza A (H1N1)v variant.
Y: C/T mixture; R: G/A mixture.

TABLE 2

Viral aetiologies for the patients fulfilling definition of suspected cases of influenza A(H1N1)v, region Västra Götaland, Sweden, April-June 2009 (n=79)

Viral aetiology	Number	Percentage (%)
Rhinovirus	28*	34
Coronavirus	8	10
Influenzavirus B	3	4
Human parainfluenzavirus (1-3)	3	4
Adenovirus	2*	2
Influenzavirus A(H1N1)v	4	5
Metapneumovirus	1*	1
Enterovirus	1*	1
Respiratory syncytial virus	0	0
<i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i>	0	0
Negative	32	39
Total number	82*	100 %

* Three patients had double infections with rhinovirus together with enterovirus, metapneumovirus or adenovirus.

Material and methods

This report includes samples of patients who, during the period from 24 April to 10 June 2009 presented with influenza-like symptoms and a history of recent travel to the United States or Mexico, and therefore were recommended for examination and sampling. This clinical examination was performed by infectious disease clinicians on call at Sahlgrenska University Hospital/Östra in Gothenburg, and our report is based on their evaluation and laboratory results. In summary, of all 79 patients included with a travel history, 90% presented with respiratory symptoms, 5% without respiratory symptoms, and for the remaining 5% this information is not documented. Sixty-six percent had fever above 38°C, 29% had no fever, information on fever was missing for 5%. Nasopharyngeal swabs were sent to the molecular diagnostic unit at the virological laboratory at Sahlgrenska University Hospital for testing by a multiple real-time PCR targeting 13 viruses and two bacteria, run in six parallel multiplex PCRs on an ABI 7500 instrument [6]. Samples that were reactive for the influenza A component (matrix protein target, [7]) of this PCR were subtyped by an additional real-time PCR targeting the haemagglutinin gene, run in three parallel reactions specific for the H3N2 and H1N1 subtypes that have been circulating for a long time, as well as for the new H1N1v strain (Table 1).

Results and discussion

In total, samples from 79 patients were tested (42 males, 37 females; median age 30 years, range 1-75 years), with between 10 and 16 samples on average each week and most of them taken from patients with respiratory symptoms and a history of recent travel to North America (Figure). Four cases with the new influenza A (H1N1)v variant were diagnosed. Interestingly, in 56% of the cases, other aetiologies were identified (Table 2).

The most common finding was rhinovirus, observed in 28 of 82 cases (34%) and three of these patients also had a second viral infection (enterovirus, metapneumovirus and adenovirus). The frequent identification of rhinovirus and other viruses demonstrates that the criteria for suspected cases of influenza A(H1N1)v are relevant as indicators of a viral infection, but not specific for influenza A. On the other hand, applying more restrictive criteria would probably have excluded most infections with the new A(H1N1)v strain, considering that their clinical presentation has been reported to be relatively mild. This illustrates a dilemma

with surveillance actions aiming at revealing the spread of new respiratory infections. If the applied criteria are too strict (for example fever above 39°C, cough and muscle pain), the epidemic is likely to be underestimated, because only the severe cases are identified. If on the other hand the criteria are liberal, as illustrated by the current epidemic, most of the cases will probably have other aetiologies. The positive predictive value of clinical criteria for identification of influenza A is particularly low in the early phase of an epidemic, when the incidence of influenza A is low, but will become relatively high during the peak when a large proportion of respiratory infections will be due to influenza A virus. The value of broad virology testing decreases in the course of an influenza epidemic, when the detection rate of other aetiologies may decrease from above 50% as observed in this report to below 10% during the influenza peak (unpublished observations from our laboratory).

The cases with influenza A were analysed further by a typing PCR that within 4-5 hours could identify whether the strain was a traditional H1N1 or H3N2 virus, or the new H1N1 variant. This typing system targets specific regions of the haemagglutinin gene and has been developed in our laboratory (unpublished). It has proved to have a good sensitivity, as illustrated by cycle threshold (Ct) values that are typically lower than those obtained in the general PCR for influenza A, which targets a conserved region of the matrix protein gene.

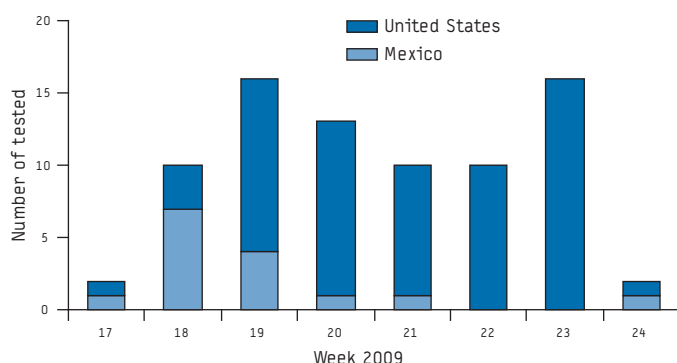
The results of the multiple PCR used in our setting were available within 24 hours after sampling and served at the same time as confirmation for the result of the first, general influenza A PCR. In cases that presented with typical influenza-like symptoms but were negative for influenza A in the first PCR, the finding of an alternative aetiology was helpful for the decision to refrain from preventive measures. Such measures include oseltamivir treatment of patients and influenza testing and prophylactic treatment of their close contacts. The clinical practice was not always different, but in some cases the identification of an alternative aetiology such as rhinovirus was helpful for the decision not to treat the patient of contacts, even when the patient had symptoms clearly indicative of possible influenza. From this experience we therefore conclude that a broad diagnostic test is a valuable tool in the early investigation of a new emerging respiratory virus like the new influenza A(H1N1)v.

Note added in proof:

On 17 June, Sweden changed to a stricter case definition for suspected cases. It now requires more than two symptoms besides epidemiology and fever.

FIGURE

Individuals tested each week, region Västra Götaland, Sweden, April-June 2009 (n=79)



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THE EMERGING INFLUENZA PANDEMIC: ESTIMATING THE CASE FATALITY RATIO

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To determine appropriate influenza pandemic containment and mitigation measures, health authorities need to know the approximate case fatality ratio (CFR) for this new infection. We present four different methods for very provisionally estimating the plausible range of the CFR for symptomatic infection by this pandemic strain in developed countries. All of the methods produce substantially lower values (range 0.06% to 0.0004%) than a previously published estimate for Mexico (0.4%). As these results have many limitations, improved surveillance and serological surveys are needed in both developed and developing countries to produce more accurate estimates.

Introduction

The first published estimate of the case fatality ratio (CFR) for those infected by the influenza A(H1N1)v pandemic strain was based on data from Mexico [1]. This work estimated the CFR to be 0.4% (range 0.3% to 1.5%) based on confirmed and suspected influenza A(H1N1)v-related deaths reported up to late April 2009. Since that date, the new pandemic strain has spread globally and new impact data are available, but we were unable to identify new estimates of the CFR in the literature. Yet this figure is critical if health authorities are to produce reasonable estimates of the likely impact of the pandemic in their particular countries. The estimated mortality burden is particularly useful for calibrating appropriate containment and mitigation measures that balance the likely health gains from interventions against their social and economic costs.

Methods

We considered four different ways to provide provisional estimates for plausible ranges of CFRs in developed countries for this pandemic.

Multiplier method

This method used confirmed deaths and cases reported to the World Health Organization (WHO), but with a range of multipliers for the latter to adjust for under-ascertainment. These multipliers were based on expert judgement that most symptomatic cases of the new pandemic involve relatively mild symptoms and that the great majority of cases were not being identified and reported. For example, spokespeople from the United States (US) Centers for Disease Control and Prevention (CDC) have announced “hundreds of thousands of cases that have occurred in the US” in late May and mid-June 2009 [2,3]. Similarly, one estimate for the United Kingdom was 30,000 cases in the community in May 2009 [4]. Regarding the choice of a multiplier to adjust data on laboratory-confirmed cases of pandemic influenza, we considered the above

assessments, which are specific to the current pandemic, to be more informative than past experience with seasonal influenza, which only provides very broad estimates of a potential multiplier. For example, it has been estimated for seasonal influenza in the US that there are 2.3 influenza cases in the community for every outpatient consultation, and 84.1 for every case that is hospitalised (derived from Molinari et al. [5]). But during a pandemic, patients are encouraged to remain at home unless they have “severe illness” or are “at high risk for influenza complications”. Additionally, laboratory testing capacity can be quickly saturated in a pandemic and priority is given to those who require hospitalisation or are at high risk for severe disease [6]. These processes will tend to push the ratio of community cases to laboratory-confirmed cases upwards to the multiplier in the range of 10-30 that we judged reasonable for this analysis.

In the calculations we used WHO data for cumulative cases and deaths as of 26 June 2009 [7] for all member countries of the Organisation for Economic Cooperation and Development (OECD), but excluding data from Mexico. The reason for this exclusion was that the epidemic appeared to have started in Mexico and we were concerned about the quality and sensitivity of numerator data in the early stages of the epidemic there, i.e. when it was not recognised that the new pandemic strain was spreading.

Community survey method

This method used an estimate for community cases from a telephone survey done by the New York City Department of Health [8]. It reported that 6.9% of New Yorkers had symptoms of influenza-like illness (ILI) between 1 and 20 May 2009. The report on this survey did not publish confidence intervals, so we calculated these to be 5.6% to 8.5% (for the survey of 1,005 households). Furthermore, at the time of this survey, only 90% of the influenza samples tested in the city were of the current pandemic strain [9], and so we adjusted the CFR estimate accordingly by this proportion. We conservatively used the cumulative death toll for New York City at three weeks after the time period used in this survey (when it was $n=12$) to allow for a lag in illness progression and then in reporting fatalities to health authorities [10]. We identified that there were no pandemic influenza deaths prior to May [11] and the New York City population of 8,274,500 used in our calculations was that for 2007 [12].

Method extrapolating from seasonal influenza mortality

This method was based on evidence that the elderly population appear to have a relatively low mortality rate compared to other age

groups in this pandemic. Data from Canada on hospitalisations and deaths [13] and US data indicate a median age of hospitalisation at 19 years and of death at 37 years [14]. Hence, we assumed that a CFR for seasonal influenza in the age group of under 65 year-olds could provide a crude approximation for the CFR of the new pandemic strain. To obtain this value we used the full range estimates that could be derived from a detailed US study [15] that used seven models for determining excess mortality attributable to influenza (Table 1).

Method extrapolating from a more 'mature' epidemic

This method was restricted to data from Canada and assumed that the epidemic there was relatively advanced in that the trend data for cases and hospitalisations were suggestive of a peak in early June with a subsequent waning of the epidemic in the following three weeks [17]. To calculate the CFR, we assumed that the epidemic in Canada was half complete in terms of cumulative deaths (with n=21 deaths confirmed as of 26 June [17]), which is possibly a conservative assumption given the low level of new hospitalisations in late June. We also assumed that the cumulative total of symptomatic cases would ultimately reach between 5% of the total population (which is within the range of seasonal influenza) and around 30% (which is approximately the value predicted by

modelling for a pandemic with an RO value of 1.5 [18] as estimated for the current pandemic using the Mexican data [1]).

Results

The four different methods produced a wide range of estimates for the CFR in developed countries, from 0.0004% to 0.06%, a range of 150-fold (Table 2). The ranges for each model overlapped with at least one other model. When these CFR estimates were applied to a country with a population of 10 million, that ultimately experienced a cumulative incidence of symptomatic infection with the pandemic strain of 30%, the total number of deaths would range from 12 to 1,800 (Table 2).

Discussion

All these estimated CFRs are substantially lower than the previously published estimate (0.4% for Mexico). They also differ markedly from the simplistic estimate that would be derived from using surveillance data available only for confirmed cases reported to WHO (i.e. of CFR = 0.29%, based on 110 deaths in 38,409 cases for the 29 OECD countries used in this analysis [7]). A low CFR would be consistent with the mild first wave seen in previous pandemics which caused widespread infection but low mortality [19]. It could also be related to the relatively young age of the

TABLE 1

Estimates of annual seasonal influenza-associated deaths in the <65 year-old population with average results for the 1976-7 season through to the 2002-3 season* and calculated case fatality ratios

Model	Number of deaths	CFR (5% AIR)*	CFR (10% AIR)*
Summer season rate difference model (10% threshold)	6,574	0.060%	0.030%
Summer season rate difference model (15% threshold)	4,509	0.041%	0.021%
Peri-season rate difference model (10% threshold)	3,819	0.035%	0.018%
Serfling-Poisson regression model	2,680	0.025%	0.012%
Peri-season rate difference model (15% threshold)	2,507	0.023%	0.012%
Serfling least squares cyclical regression model	1,475	0.014%	0.007%
Autoregressive integrated moving average (ARIMA) model	809	0.007%	0.004%

AIR: annual incidence rates, CFR: case fatality ratio.

Bold figures represent the extremes of the range and are the values used in our calculations for the range of CFRs in Table 2.

* Data from: Thompson et al. [15]

** CFR calculated using the 1990 census data for the US population (n=217,468,042 under the age of 65 years [16]), and assuming 5% and 10% AIR for infection resulting in symptomatic illness.

TABLE 2

Case fatality ratio for symptomatic infection with influenza A(H1N1)v pandemic strain in developed countries, estimated by four different methods

Method used	Estimated range of CFR	Projected number of deaths in a developed country with 10 million inhabitants where 30% experience symptomatic infection with the pandemic strain*
Extrapolating from seasonal influenza mortality method (US data for <65 year age group)	0.004% – 0.06%	120 – 1,800
Multiplier method (10x to 30x WHO-reported cases)	0.01% – 0.03%	300 – 900
Community survey method (New York City data)	0.002% – 0.003%	60 – 90
Extrapolating from a "mature" epidemic method (Canadian data)	0.0004% – 0.003%	12 – 90

CFR: case fatality ratio.

* Initial estimates suggested the pandemic virus has a reproductive number of around 1.5 [1], so it could be expected to infect around 40% of the population [18] and to cause symptomatic illness in about 30% of people.

majority of cases and the use of highly effective modern treatment for those who are seriously ill.

Although based on the most current data possible, all the methods used still have substantial limitations. The multiplier method merely relied on the judgement (from other experts as well as ours) of widespread and relatively mild disease that is not being reported. Nevertheless, the suggestion of widespread community spread in the US is broadly consistent with the community survey in New York City and another community survey in the US with around 6% cumulative incidence of ILI [14].

The New York City survey was limited by asking only about ILI that occurred during a 20-day period in May and by ignoring illness in April even though there were hospitalisations in New York City in that month. Therefore the method using this survey could have overestimated the CFR, although the opposite could have occurred if some of the reported ILI symptoms were due to other respiratory infections and allergic conditions such as hay fever.

The method that extrapolated from seasonal influenza mortality data in under 65 year-olds was limited in that it effectively considered no aspects of the epidemiology of the new pandemic influenza virus other than the age distribution, i.e. that it seems to affect younger age groups more than older age groups. Yet there is little information comparing the current pandemic strain with seasonal influenza strains in terms of mortality risk in this younger age group. Furthermore, the data from which the estimated range was derived may be outdated in that modern medical care has progressed since the early part of the period used in the particular US study [15] that the estimates were based on.

Although the Canadian epidemic appears to be waning, the method using the crude extrapolation of the course of this epidemic was very simplistic. Indeed, rather than being half complete, this epidemic wave could continue throughout the northern hemisphere summer and beyond.

These methods tended to focus on correcting for under-ascertainment of the denominator, yet there is also a potential bias from under-ascertainment of the numerator of the CFR. Particularly in the early stages of an epidemic there will be a lag in reported deaths and other severe outcomes. Sophisticated statistical methods have been proposed for obtaining adjusted CFR estimates using data from the early phase of an epidemic [20], and these result in adjustment for various time lags and an upward shift of the CFR. However, such adjustments would probably have little effect on the estimates presented in this article which are based on data from country epidemics which have progressed well beyond their early stages (e.g. the Canadian data). There is also the potential for under-recognition of deaths attributable to influenza in those with serious co-morbidities, but this can only be addressed by careful research studies and post-epidemic modelling to determine total excess deaths. Nevertheless, this bias might be relatively smaller in this pandemic where more deaths involve young people. Also, once the new influenza A(H1N1)v strain was recognised there is likely to have been increased sensitivity for diagnosing influenza-related deaths (at least in developed countries where hospitalisation is likely to precede influenza-related death).

All of the presented methods have limitations and could be refined using additional data to provide more robust estimates.

Ultimately, such estimates require enhanced surveillance, outbreak investigations in a range of settings, and carefully designed population studies, ideally with serological testing [21]. Additionally, the ranges of CFRs for disadvantaged populations in developed countries and for most of the population in developing countries are likely to be much higher than those estimated here, given likely differences in disease transmission, co-morbidity, access to antivirals and standards of medical care.

Conclusion

We present several methods for provisionally estimating the plausible range for the CFR of the emerging influenza pandemic in developed countries. All methods used have significant limitations, but they collectively suggest that infection with this particular pandemic strain is likely to cause illness with a relatively low CFR compared to an earlier estimate and also to historical standards. A further reason for presenting this range of methods is to encourage data collection that can start to reduce the uncertainty around this important pandemic parameter.

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MODELLING OF THE INFLUENZA A(H1N1)V OUTBREAK IN MEXICO CITY, APRIL-MAY 2009, WITH CONTROL SANITARY MEASURES

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We use a time dependent modification of the Kermack and McKendrick model to study the evolution of the influenza A(H1N1)v epidemic reported in the Mexico City area under the control measures used during April and May 2009. The model illustrates how the sanitary measures postponed the peak of the epidemic and decreased its intensity. It provides quantitative predictions on the effect of relaxing the sanitary measures after a period of control. We show how the sanitary measures reduced the maximal prevalence of the infected population from 10% to less than 6% of the total population. We also show how the model predicts the time of maximal prevalence and explains the effect of the control measures.

Introduction

In this work we present an analysis based on theoretical considerations, with the aim of understanding quantitatively the effects of the sanitary controls and their relaxation on the evolution of the influenza A(H1N1)v outbreak in Mexico City in the period from April to May 2009. Since the only controllable parameter during an outbreak of this infectious disease is the contact rate, the World Health Organization (WHO) recommends reducing it by avoiding gatherings, closing schools, restaurants, cinemas, etc. These actions result in decreasing the maximum number of infected individuals, and the delay of the epidemic peak. We show that these sanitary measures, followed by a period with measures such as frequent hand washing and other prophylactic measures, can control the outbreak. Using this regime, our model is consistent with the currently available data. Finally, we present a less positive scenario which shows a second peak of the incidence curve after the return to school on 11 May, which might be seen in the real data, once the complete information on incident cases becomes available.

Methods

We used a simple model in terms of the number of parameters, the Kermack and McKendrick model [1,2]. The purpose of using such a simple model was to have a small number of parameters, first to give a rough estimate of the time of maximal prevalence, and second, to analyse the behaviour of the contact rate under

the sanitary measures recommended by the WHO. It is generally accepted that the influenza A(H1N1) virus is transmitted by direct contact. There is no evidence that vaccination for seasonal influenza creates cross-immunity to influenza A(H1N1)v virus. Moreover, once the outbreak started there was some evidence of spatial homogeneity in the Mexico City area with cases being reported in different parts of the city. For these reasons, it was possible to use the Kermack and McKendrick model, without considering vaccination, in terms of the proportions

$$s(t)=S(t)/N, \quad i(t)=I(t)/N, \quad \text{and} \quad r(t)=R(t)/N$$

of the total number of susceptible $S(t)$, infected $I(t)$, and removed $R(t)$ individuals, where the total population N was assumed constant.

The equations for the time evolution of the epidemic outbreak take the form:

$$\begin{aligned} ds/dt &= -\beta N s i, \\ di/dt &= \beta N s i - a i, \\ dr/dt &= a i. \end{aligned}$$

Here, $1/a$ was the expected infectious period with an estimated value of 3 days, and βN was the contact rate which in this case controlled the reproduction number R_0 . The initial conditions and the initial time for the applicability of the model were determined from the data on the onset of the epidemic (between 10 and 20 April) available from the Mexican Secretariat of Health (Secretaría de Salud de México) [3]. The control measures established on 23 April, changed the contact rate and their effects were modelled using a time-dependent contact rate. We calculated the prevalence and incidence curves integrating numerically these equations. The results were then used to assess the effect of the sanitary measures on the evolution of the epidemic. Finally, we comment that the delay due to the incubation period was not included because according to the Mexican Secretariat of Health, infected individuals become contagious soon after their infection, even before presenting symptoms.

Results

The basic reproductive number $R_0 = \beta N/a$ was estimated at the beginning of the outbreak using the force of infection and an exponential fitting of the data from the Mexican Secretariat of Health. We assume $i(t) = \exp(\lambda t)$ at the onset of the epidemic, and substitute this expression in the equation for the infected proportion to obtain the relation $R_0 = 1 + \lambda/a$, where λ is estimated fitting the data by least squares method. We used this approach to obtain $R_0 = 1.72$ for the outbreak in Mexico City. For the La Gloria community in the state of Veracruz, this same approach yielded an R_0 of 1.716, which to two decimal places is the same as the R_0 for Mexico City. This estimate is in good agreement with the results of Fraser et al. [4]. From this expression for R_0 and from $a = 0.333$, we obtained $\beta N = 0.57$. This fit in addition gave the interval from 10 to 20 April as the possible time of onset. Moreover, assuming a population of 8×10^6 individuals, we obtained from the fitting the estimate of 730 actually infected individuals for each reported case. Finally, using the estimated parameters, we calculated the numerical solution of the model and compared it with the observational data reported at the National System of Epidemic Surveillance of the Mexican Secretariat of Health [3].

In curve a) of Figure 1, we show the solution of the model starting at $t = P_0$, which coincided well with the data from before the controls were started. When the control measures were implemented on 24 April, the Mexican Secretariat of Health reported that R_0 was approximately equal to 1.3 [3]. With this value we estimated a contact rate βN of 0.44. Assuming this decay of the contact rate, curve b) shows the evolution of the epidemic as calculated from the model. We observed a substantial reduction of the maximal prevalence, at the expense of a delay of the maximum.

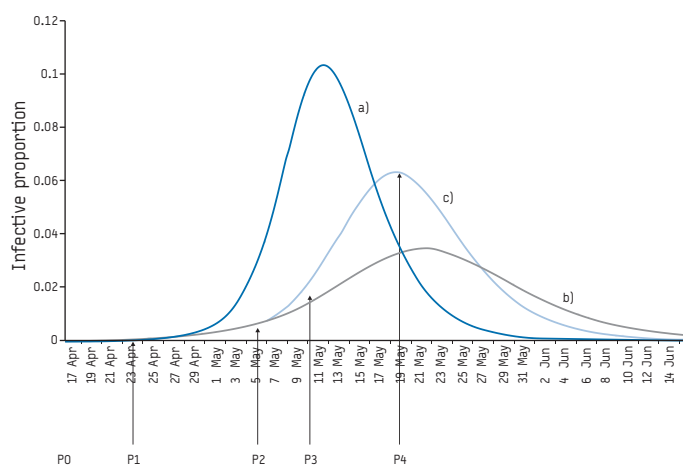
In order to have a preliminary estimate of the effect of the relaxation of the controls, we calculated the prevalence curve i

(t). According to the model, a natural time to partially relax the controls would be close to the inflection point P2 of curve a), which corresponds to 6 May. Indeed, the health authorities announced relaxation of the measures near that date, on 1 May. At this date, the contact rate βN increased due to the continuation of normal activities. We assume that it increased from 0.44 to 0.5. We calculated the evolution of the epidemic shown in P3 of curve c). We observed an increase in the maximal prevalence, but no substantial change of the time of arrival of the peak compared to curve b). This calculation predicted the maximum prevalence at P4 on 20 May, which is the maximum of curve c) and corresponds to zero incidence. We remark that these calculations were available on 30 April and we assumed an instantaneous response of the contact rate for these preliminary estimations. Next, we examined in detail with the new available data how a more precise fitting of the model explains in simple terms the observed evolution of the epidemic.

To fit the evolution of the incidence we considered the data shown in Figure 2, and used the probable cases to determine the time evolution of the contact rate as a result of the controls. We start by remarking that when this work was under revision, the Mexican Secretariat of Health reported on 2 June 126 new cases in Mexico City without giving the dates of their occurrence; these cases were therefore not included in the calculations in the paper. Looking at the incidence data for the whole country for 26 May and 2 June, it is obvious that some cases take up to 30 days to be reported [3].

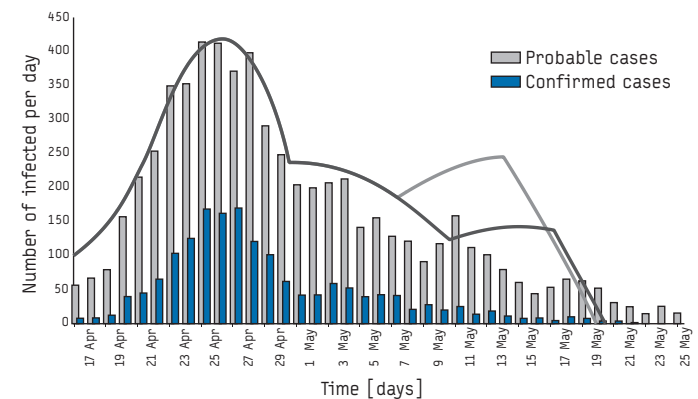
There is a clinical estimate of about five days as the relaxation time of the contact rate βN after sanitary measures are taken. We noticed that a better fit of the incidence data was obtained when a relaxation time of six days was used. We assumed a linear decrease of the contact rate βN between 24 and 30 April, from its original value 0.57 to 0.42. The latter value gave an R_0 of 1.27 which was

FIGURE 1
Modelling the evolution of the influenza A(H1N1)v outbreak in the metropolitan area of Mexico City, 17 April - 17 June 2009



P0=17 April, P1=24 April, P2=6 May, P3=11 May, P4=20 May.
a) The evolution of the outbreak with no control starting at April 17.
b) The evolution of the outbreak with control measures starting on April 24.
c) The evolution of the outbreak with the measures relaxed on May 6. Note the peak of the epidemic at P4 on 20 May.

FIGURE 2
Incidence curve of the influenza A(H1N1)v outbreak in Mexico City, 17 April - 26 May 2009 (n = 6,114 probable cases and 1,752 confirmed cases)



The bars indicate the incidence in Mexico City. The light gray curve gives the results of the model for a recovery of the contact rate to 0.46 starting on 7 May. The dark gray curve gives the results of the model for a recovery of the contact rate to 0.46 starting on 10 May.

slightly below the value $R_0=1.3$ given by the Mexican Secretariat of Health. The contact rate $\beta N=0.42$ was kept constant for the rest of the period under sanitary measures. With these values, we obtained a good fit to the actual evolution of the epidemic up to 10 May. On 6 and 7 May, universities and senior high schools reopened in Mexico City. Elementary schools and junior high schools reopened on 11 May, but on 10 May was Mother's Day and there was much activity in the city.

The data for May is still incomplete, therefore we present two possible scenarios. In Figure 2, the dark gray curve shows a linear increase of the contact rate βN for six days, starting on 7 May, increasing to the value 0.46 and keeping this constant value until the incidence curve reaches zero on 20 May. The light gray curve shows a linear increase of the contact rate for six days starting on 10 May, increasing to the value 0.46 and keeping this constant value until 20 May. The available data seem to indicate that the increase of the contact rate did not start until 10 May, suggesting that the reopening of universities and senior high schools in Mexico City did not have a big impact on the contact rate. However, as we remarked above, the data for this period are incomplete and therefore, we will only be able to see which scenario is more likely to have occurred once these data become available.

Finally, we note that the curves in the final phase are similar to straight lines and indicate 20 May as the time of zero incidence which corresponds to maximal prevalence. The straight line behaviour is due to the short duration of the peak as seen in the prevalence curves in Figure 1. We therefore propose a closer examination of the data, when available, to understand the duration of the peak in detail.

Figure 3 shows the reproductive ratio $R(t)$ computed with the data from the Mexican Secretariat of Health shown in Figure 2 and using the method of Wallinga and Lipsitch [5] and the mean and standard deviation for the distribution intervals from Carrat et al. and Boëlle et al. [6,7]. This ratio determines the current growth rate relative to its weighted average in the past. It reaches one at the maximum incidence.

The reproductive ratio $R(t)$ was >1 at the onset of the outbreak and decreased slowly until 7 May, crossing the value 1 on 25 April. This behaviour is consistent with the results shown in Figure 2, where the maximum incidence occurred on 26 April, which was the

same day when $R(t)$ was 1. After 26 April, both curves descended until 7 May. After this, $R(t)$ showed larger oscillations, which are another indication of a change in the progression of the epidemic due to the relaxation of the sanitary measures. This is the region for which we give two possible scenarios. We observed that both methods complement very well each other.

Discussion

We have shown how a time dependent modification of a classical model can be used to make reliable predictions on the evolution of the influenza A(H1N1)v epidemic, using only preliminary estimates of the life time of the virus and the initial growth of the incidence curve at the onset of the outbreak. Usually, these are the only available data when an outbreak of a new virus starts. The effect of the sanitary measures was studied modelling the decrease and increase of the contact rate using linear functions of time. The fitting shows a time of relaxation of the contact rate of around six days. The model shows that the sanitary measures had a long lasting effect in that it kept the contact rate low in the period when these measures were in place. Once the sanitary measures were lifted, the contact rate remained much lower than at the onset of the outbreak. The use of antivirals as a prophylactic measure requires an independent study. However antiviral drugs were not used in Mexico during the outbreak.

The time scale of the response to controls and their relaxation show that the present model together with real-time monitoring of the incidence curve can provide reliable forecasts of the evolution of the outbreak, providing another tool for a decision regarding the epidemic alert level during a future outbreak.

Acknowledgements

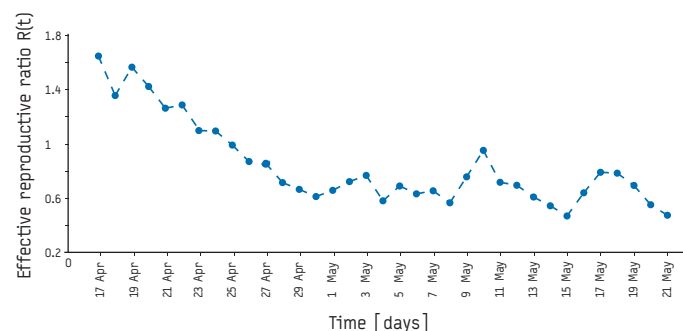
The authors are grateful to Ana Cecilia Pérez and Ramiro Chávez for technical support. G. Cruz-Pacheco and L. Esteva were supported by grant IN108607-3 of PAPIIT-UNAM.

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FIGURE 3

Effective reproductive ratio $R(t)$, influenza A(H1N1)v outbreak in Mexico City, 17 April – 21 May 2009



OUTBREAK OF INFLUENZA A(H1N1)V WITHOUT TRAVEL HISTORY IN A SCHOOL IN THE TOULOUSE DISTRICT, FRANCE, JUNE 2009

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In June 2009, for the first time in France, a confirmed outbreak of influenza A(H1N1)v without history of travel occurred in a secondary school in Toulouse district. A total of 15 cases were confirmed among students of which three were asymptomatic. This report describes the outbreak and its public health implications.

Background

In France, in order to detect early influenza A(H1N1)v virus circulation [1], reporting of clusters of at least three cases of respiratory tract infections occurring within one week in a small community without other identified aetiology has been set up [2]. In the early phase of the pandemic, this surveillance was complementary to the national active surveillance of recent travellers from affected areas [3].

On 12 June 2009, the headmaster of a secondary school in the suburb of Toulouse, South Western France, notified 11 absentees among sixth-grade students in the same class that had reported fever and respiratory symptoms. The regional unit of the Institut de Veille Sanitaire and the local health authority requested nasal and throat specimens for viral testing of the three most recent and severe cases among the 11 sick children. On 13 June, two cases were confirmed with influenza A(H1N1)v virus infection.

An investigation was conducted to describe the outbreak and to identify the source of transmission.

Methods

A retrospective cohort study was conducted among all students and staff members of the class in which the first cases were reported. The following case definitions of suspected and confirmed cases were used:

- A **possible case** of influenza A(H1N1)v virus infection was defined as a person with high fever ($\geq 38^{\circ}\text{C}$) or asthenia or myalgia and at least one acute respiratory symptom (cough or dyspnoea);
- A **probable case** was defined as a possible case with a history of close contact to a probable or confirmed case during 24h and until the seven days after the onset of those cases' symptoms;
- A **confirmed case** was defined as a person confirmed by real-time PCR specific for influenza A(H1N1)v virus.

Subsequently, active case finding was initiated among contacts (close family members and social contacts) of all cases (possible, probable or confirmed) of sick pupils of the class. Passive case-finding was also conducted in the whole school by means of posters.

Nasal and throat swabs were taken from all children and staff members of the class: at the school infirmary for asymptomatic children and at the Toulouse regional hospital for symptomatic children. All possible or probable cases identified through subsequent case finding were also investigated at the hospital.

Staff and school children were interviewed face-to-face using a standardised questionnaire. Information on demographics (sex, age), potential exposure to influenza A(H1N1)v virus since 1 June 2009 (personal or close family, travel history, infection in a relative, social gathering) and medical data for symptomatic cases (fever, cough, asthenia, dyspnoea etc.) were collected. The outbreak was described by time and person, and exposure factors were analysed.

Results

The class included 30 students at the age of 11 to 12 years, and 18 staff members had been in contact with the pupils. All students and eight staff members were investigated. We found 20 cases (18 students and two staff members) corresponding to the case definition (five probable cases and 15 confirmed cases). The attack rate was 60% among children and 25% among staff members. Three cases were asymptomatic.

The reported symptoms were headache (94%), cough (88%), fever (76%), asthenia (53%), sore throat (41%) and rhinorrhoea (35%). No complications were reported and no death occurred.

The onset of the outbreak (Figure) among the 17 symptomatic cases was abrupt (10 and 11 June) which could indicate a common exposure to an unrecognised case and secondary transmission from person to person in the following days (12 to 14 June).

12 out of 17 (71%) cases corresponded to the definition of a possible case (Table).

Assuming that a positive real-time PCR was the gold standard, we estimated the sensitivity of the definition of a possible case at

47%, its specificity at 78%, its positive predictive value at 58% and its negative predictive value at 69% among all students and staff members of the class.

In the course of subsequent case finding, nine symptomatic contacts were investigated and only one of them, a student of another class of the school, was confirmed. No case was found among about 120 close family contacts that were traced and among social contacts reported to have had extracurricular activities together with the cases.

None of the students or staff had a history of travelling after 1 June to countries affected by influenza A(H1N1)v or had been in contact with someone symptomatic. However, several children's relatives worked in sectors related to travel (international firms, airplane construction or air travel staff).

Actions taken

All symptomatic cases were admitted to hospital, examined and treated with antiviral curative treatment (oseltamivir). All close contacts were quarantined and received prophylactic treatment (120 relatives and other social contacts). Each family of a student of the class was interviewed and followed up. The family was asked to call the emergency mobile medical service (Centre 15) if a family member became symptomatic.

On 15 June, the school was closed for one week. The school was reopened on 22 June, since no secondary case had been observed seven days after the last reported case (14 June).

Discussion

This is the first confirmed outbreak of pandemic influenza A(H1N1)v infection reported in France without a well identified

chain of transmission. Our investigation could not find any history of travel nor any contact with a previously identified imported case among the children and staff members of this class.

The high attack rate in a single school class, as well as the abrupt onset of the epidemic curve suggests that the children could have shared a strong common exposure. Cases that occurred from 12 to 14 June were probably due to secondary transmission from earlier cases. The fact that no secondary case was observed outside the school after its closure, isolation of cases and prophylaxis of contacts, suggests that these complementary measures were effective to limit transmission to the community.

The source of the outbreak remains unknown. A contact with a previously undiagnosed case could have occurred without being reported. This contact may have occurred within a family, since many parents had occupations related with international travels. Contact with Spanish residents in the area is also possible, related or unrelated with the parents' occupation. Trade and travels to Spain are frequent in this area of France and the incidence of A(H1N1)v influenza was higher in Spain than in France at the time of the outbreak.

The investigation of the whole school class identified three asymptomatic cases with confirmed influenza A(H1N1)v virus infection. Underreporting of symptoms is unlikely in the context of this intense investigation. Asymptomatic influenza infection is known to occur among about 33% of cases in the seasonal influenza [4]. In a population of 20 cases, we could expect between 12% and 54% of asymptomatic cases, which correspond to our observation (3 of 20 cases).

The low sensitivity (47%) of the French definition of a possible case means that many children had indeed several other symptoms (headache, sore throat, rhinorrhoea, vomiting etc.) than those included in the influenza-like syndrome. This may be due to the high variability of symptoms in children and suggests that this definition was not appropriate for children. In addition, this definition could also be inadequate for adults because the clinical presentation of this new virus was not well-known at the beginning of the outbreak.

Several public health implications arise from this outbreak. After the experience of this cluster, systematic hospitalisation of cases was stopped. Many people in the general population of Toulouse attended newly opened dedicated influenza A(H1N1) consultations, even if they didn't fulfil the case definition. They were evaluated and none of them was laboratory-confirmed.

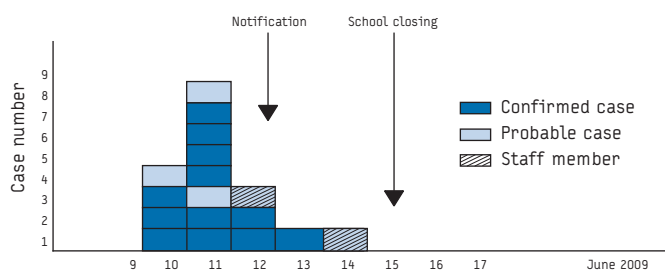
This outbreak was an important event that allowed adjusting the surveillance of influenza A(H1N1)v in the early phase that focussed mainly on imported cases. Surveillance is now moving to wide community surveillance through sentinel networks, surveillance of hospitalised severe cases and reporting of clusters.

Acknowledgements

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FIGURE
Epidemic curve for influenza A(H1N1)v school outbreak, Toulouse district, France, June 2009 (n=17)*



* For three additional asymptomatic confirmed cases the date of onset was not known.

TABLE
Distribution of possible influenza A(H1N1)v cases among students and staff members according to laboratory results, Toulouse district, France, June 2009 (n=38)

		Confirmed cases of influenza A(H1N1)v		Total
		Yes	No	
Possible case of influenza A(H1N1)v	Yes	7	5	12
	No	8	18	26
Total		15	23	38

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PRELIMINARY DESCRIPTIVE EPIDEMIOLOGY OF A LARGE SCHOOL OUTBREAK OF INFLUENZA A(H1N1)v IN THE WEST MIDLANDS, UNITED KINGDOM, MAY 2009

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This report describes the preliminary results from the investigation of a large school outbreak of influenza A(H1N1)v in Birmingham, United Kingdom in May 2009, when influenza A(H1N1)v was confirmed in 64 of 175 (36%) symptomatic pupils and members of staff. Initial findings in this study suggest that the symptoms were mild and similar to those of seasonal influenza, with an illness attack rate of nearly one third.

Introduction

On 27 April 2009, the first two confirmed cases of the pandemic influenza A(H1N1)v in the United Kingdom (UK) were reported in Scotland. As of 2 July 2009 there have been 7,447 cases reported in the UK [1]. During the early phase of the outbreak, the majority of the cases were amongst travellers, initially those returning from Mexico and then also those returning from the United States (US). The first indigenously acquired case was reported on 1 May 2009 and since then an increasing number of indigenous cases have been reported [2].

Since the outbreak in the UK began, transmission has occurred in a number of school settings [3]. We present the results of a preliminary epidemiological investigation on an influenza A(H1N1)v outbreak that began in mid May in a primary school in Birmingham, West Midlands, England.

Epidemiological description of the outbreak

On 18 May 2009, the Health Protection Agency (HPA) was informed of an increased rate of absenteeism in a primary school in Birmingham, West Midlands. The school has 419 pupils in the primary school and 60 in a nursery and is located in inner city Birmingham, in the West Midlands region, England. Symptoms reported included fever, respiratory and gastrointestinal symptoms. None of the symptomatic pupils had a history of school absence for holiday travel in the seven days before onset of symptoms. On 19 May 2009, given that some symptoms described were influenza-like, nose and throat swabs were arranged for a small number of symptomatic pupils. One specimen was confirmed on 21 May by real-time PCR specific for influenza A(H1N1)v.

On 21 May, the school closed for seven days; this period coincided with a scheduled school holiday of one week. Between Saturday, 23 May and Monday, 25 May, the investigation team attempted to contact, by telephone, parents of pupils as well

as members of staff on lists provided by the school in order to administer a brief questionnaire. Information collected included: demographic details, symptoms, recent travel history and details of out-of-school activities. Information about household and close social contacts was also recorded.

Upon conclusion of the telephone interview parents of all asymptomatic children were advised that their children should start a prophylactic course of antiviral medicine being distributed at the school on 23 and 24 May. A total of 304 asymptomatic children were prescribed prophylaxis. Parents of children who were symptomatic at the time of interview or who had been symptomatic in the previous seven days were asked to stay at home so that specimens (nose and throat swabs) could be collected from their child(ren). At the time of swabbing, all symptomatic children were provided with a treatment course of oseltamivir. Contact tracing was carried out to identify household contacts and close social contacts. The contacts were then followed up by an out-of-hours general practitioner (GP) service and provided with antiviral prophylaxis.

All pupils and staff attending the primary school were contacted. Of 563 pupils/members of staff, 175 (31%) were symptomatic and required testing. Of those 175, 64 (37%) were found to be positive for influenza A(H1N1)v. A further 139 symptomatic household contacts were tested out of 664 identified. Household contacts are

FIGURE 1
Confirmed cases of influenza A(H1N1)v among pupils and staff by date of illness onset, school outbreak West Midlands, May 2009 (n=64)

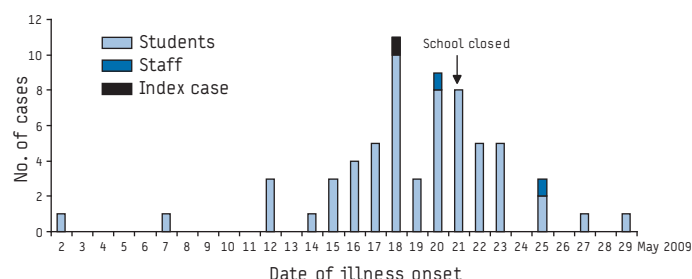


TABLE 1

Symptoms reported by influenza A(H1N1)v cases among pupils and staff, school outbreak West Midlands, May 2009 (n=64 confirmed cases*)

Symptoms	Cases (percentage)
Fever	54 (84%)
Nasal congestion	45 (70%)
Sore throat	38 (59%)
Nausea/vomiting	26 (41%)
Muscle/joint pain	23 (36%)
Diarrhoea	14 (22%)
Headache	21 (33%)
Respiratory symptoms	20 (31%)
Additional free text reports**	
Cough	12 (19%)
Eye problems	1 (1.6%)
Dizziness	1 (1.6%)

* A person could report more than one symptom.
 ** These symptoms were not included in the questionnaire but were reported by respondents.

excluded from the data analysis, and analysis is restricted to only laboratory confirmed cases.

Figure 1 shows the date of symptom onset for cases of influenza A(H1N1)v in the school. Of the 64 cases, 31 (48%) reported symptom onset between 18 and 21 May. At the time of interview and before treatment had started, symptoms reported by the 64 confirmed cases included: subjective fever (54, [84%]); nasal congestion (45 [70%]) and sore throat (38 [59%]) (Table 1). No cases were hospitalised and the duration of illness was not recorded.

Table 2 shows the attack rate by school year group. The index case was confirmed on 21 May, but the earliest reported date of onset was 2 May (see Figure 2) in a year 4 pupil (aged nine years). The next date of onset was 7 May in a year 5 pupil (aged 11 years). Neither of these early cases had a travel history or history of contact with a confirmed case. Fifty-three percent of cases were female and the highest attack rate was seen in pupils in year group 5 (23%). Excluding two members of staff, cases ranged in age from 4 to 12 years, with a mean of 8.5 years and a median of 9 years. None of the cases had a recent history of travel outside the UK.

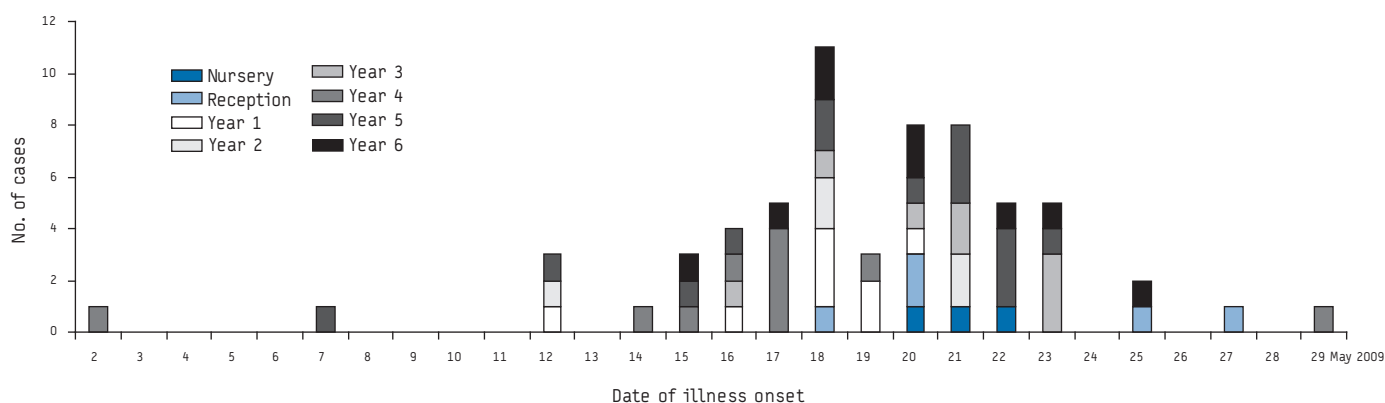
TABLE 2

Proportion of influenza A(H1N1)v cases among pupils in each school year and attack rate by year group school outbreak West Midlands, May 2009 (n=62 confirmed cases)

Class (age-range in years)	Number of pupils in class	Laboratory-confirmed cases	Attack rate for pupils
Nursery (4)	58	3	(3/58) 5.2%
Reception (5-6)	61	5	(5/61) 8.2%
Year 1 (6-7)	60	8	(8/60)13%
Year 2 (7-8)	59	5	(5/59) 8.5%
Year 3 (8-9)	59	8	(8/59)14%
Year 4 (9-10)	62	10	(10/62)16%
Year 5 (10-11)	60	14	(14/60)23%
Year 6 (11-12)	60	9	(9/60) 15%
Total	479	62	(62/479) 13%

FIGURE 2

Date of illness onset for confirmed cases of influenza A(H1N1)v among pupils, by school year, school outbreak West Midlands, May 2009 (n=62)



Discussion and conclusion

A total of 64 confirmed cases of influenza A(H1N1)v have been identified in pupils and members of staff in a school in the Midlands, UK. This large primary school outbreak resulted in an overall clinical attack rate of 30% and a microbiologically confirmed attack rate of nearly 13%. The clinical attack rate in this single school is higher than the average attack rate of 24% reported for outbreaks of seasonal influenza in UK schools during the 2005-6 influenza season [4].

Feedback from interviewees and the GP out-of-hours service suggested that symptoms were generally mild in children, predominantly fever, nasal congestion and sore throat consistent with other case series from the UK reported thus far [3]. No children were hospitalised and no data were available on the duration of illness or on underlying disease in the cases. Most cases reported date of onset of symptoms between 18 and 21 May, suggesting that the rate of transmission may have been highest during the period immediately prior to the school closing, when high absenteeism had been reported. The latest date of onset was 29th May, and most cases were asymptomatic by the time the school re-opened after the holidays on 1 June.

Subsequent to this incident, there have been no further cases in the school. However, cases continue to be identified in the local area with an increasing number of local schools reporting high absenteeism and confirmed cases. Cases occurring outside schools suggest ongoing and widespread community transmission in the area.

Further investigation of this school incident includes sequential swabbing of a subset of families with confirmed cases and presentation of data on those pupils who were symptomatic but were not laboratory-confirmed cases. These analyses will be presented at a later date.

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AN OUTBREAK OF INFLUENZA A(H1N1)V IN A BOARDING SCHOOL IN SOUTH EAST ENGLAND, MAY-JUNE 2009

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An outbreak of influenza A(H1N1)v was confirmed in May and June 2009 in a boarding school in South East England involving 102 symptomatic cases with influenza-like illness. Influenza A(H1N1)v infection was laboratory-confirmed by PCR in 62 pupils and one member of staff. Control measures were implemented as soon as a case was confirmed and included school closure, active case finding and treatment as well as post-exposure prophylaxis offered to the entire school population. Had the outbreak had been detected earlier, the school closed earlier and prophylaxis commenced after the initial cases were detected, we may have seen lower levels of transmission.

Background

The first case of influenza A(H1N1)v in the United Kingdom (UK) was reported by the Health Protection Agency (HPA) on 27 April 2009 [1]. Following this initial report, the number of confirmed cases has risen steadily.

On 27 May 2009, a case of influenza A(H1N1)v was confirmed in a 14 year-old pupil at a boarding school in South East England. The case did not meet the HPA's algorithm for testing at the time. The algorithm for testing of influenza A(H1N1)v at the time included travel to the United States or Mexico or contact with a probable or confirmed case. While this patient had influenza-like symptoms, there was no history of travel to an affected area or relevant contact. Swabs were taken from this pupil under the auspices of a private medical care service for independent schools. It subsequently became obvious that a significant outbreak was in progress in the school.

This paper describes the epidemiology and public health response to this outbreak. This is the first published report of an outbreak of influenza A(H1N1)v in a boarding school.

The index case and initial investigation

The index case became symptomatic on 24 May 2009, swabs were taken on 26 May and a positive result by PCR with primers specific for influenza A(H1N1)v [2] was received on 27 May. The positive result was notified to the local Health Protection Unit (HPU) on the evening of the same day, 27 May. The school was scheduled to close on the next day, 28 May, for a planned break during term time.

The initial risk assessment suggested that the index case had very limited contact with other pupils while symptomatic. His close

contacts were identified as 15 other pupils who were also boarders at the school. All 15 close contacts were assessed for influenza-like illness (ILI), and offered post-exposure prophylaxis with oseltamivir, in accordance with HPA guidance at the time.

Following the identification of the first positive case, further enquiries were undertaken at the school by the HPA. It became apparent that there had been an ongoing outbreak of ILI at the school which preceded the confirmed diagnosis of influenza A(H1N1)v in the index case. A total of 39 cases had reported to the school's health services with ILI prior to the identification of the index case on 27 May 2009. Following this finding, a decision was taken to extend the response beyond the initial 15 cases, to include the entire school population. Active case finding was initiated by asking all students and staff with ILI to telephone one of the nine "flu response centres" around the country for assessment. If appropriate, they were recommended testing and treatment. This was necessary as staff and students were dispersed across the country following the closure of the school for a short break. This led to the identification of further possible and probable cases associated with the school.

The HPA case definition was used: A possible case was any person meeting the clinical and epidemiological criteria; a probable case was any person meeting the clinical and epidemiological criteria and with a positive test for influenza A infection that was untypable at the local laboratories.

Descriptive epidemiology

Setting

The outbreak occurred in a boarding school in South East England with a total population of 2,132 made up of 1,307 pupils and 825 members of staff.

Case definition

Since it was obvious that there was a rise in the number of ILI cases before the index case, we considered these as "clinical" cases and included them in our description of the outbreak. We therefore categorised our cases into confirmed cases and clinical cases.

Confirmed cases were cases of influenza A(H1N1)v confirmed by laboratory testing of swabs taken while the patient is symptomatic with ILI.

Clinical cases were among pupils documented as attending a healthcare facility at the school with ILI from 1 May 2009 to the confirmation of the first case on 27 May 2009.

Outbreak description

In total, there were 102 symptomatic cases with ILI. Nose and throat swabs were taken from all cases symptomatic at the time the outbreak was detected. Influenza A(H1N1)v infection was laboratory-confirmed by PCR with primers specific for influenza A(H1N1)v in 63 of the 102 cases, 62 pupils and one member of staff. The remaining 39 cases were no longer symptomatic at the time the outbreak was recognised, and it was too late to take throat swabs. These 39 were classified as cases of ILI, epidemiologically linked in time and space to the confirmed cases.

The onset of the outbreak was estimated to have been on 1 May 2009 and the end on 3 June 2009. The school was closed from 28 May to 7 June 2009, extending the scheduled break by four days. The incubation period for influenza A(H1N1)v is unknown but estimated to be between one and seven days [3], therefore cases presenting with symptoms after 3 June 2009 were considered to have resulted from secondary transmission outside the school setting.

Potential source of exposure

There were two potential points of contact between pupils from this boarding school and other schools (schools A and B in Figure 1) that had already had confirmed cases of influenza A(H1N1)v. No confirmed cases of influenza A(H1N1)v or clinical ILI cases were seen in the specific students who reported contact with students from school A during a social function. The second point of contact was with a group of students who visited school B for a tennis match on May 9. One of the students in contact with school B developed symptoms on 24 May 2009 and tested positive for influenza A(H1N1)v. Contact during this event may represent the source of the outbreak assuming that the ILI cases that occurred before this

event may not have been due to influenza A(H1N1)v. School B had been closed due to an outbreak of influenza A(H1N1)v between 11 and 18 May 2009 in six members of staff and students.

The first confirmed case of influenza A(H1N1)v at the boarding school developed symptoms on 20 May 2009, pre-dating the onset of symptoms in the index case (27 May) by seven days (Figure 1). The incubation period for influenza A(H1N1)v is estimated to be between one and seven days indicating that there may have been ongoing transmission in the school from as early as 13 May 2009.

Attack rates by house of residence and school year group

All school years and all houses of residence were affected by the outbreak. Taking the entire school population (pupils and staff), there was a clinical attack rate of 5% (102/2,132). However, given that the living circumstances of the students were significantly distinct from those of members of staff, the student population was considered as the affected cohort. Among the students, the clinical attack rate was 8% (101/1,307). The attack rates among the pupils were also calculated by house of residence as well as by school year (Figure 2). These attack rates varied by house, ranging from 1.8% (1/55) to 18.9% (10/53), as well as by school year, ranging from 5.4% (14/258) to 11.9% (32/268). The school year with pupils aged between 16 and 17 years had the highest attack rate of 11.9%.

Clinical epidemiology

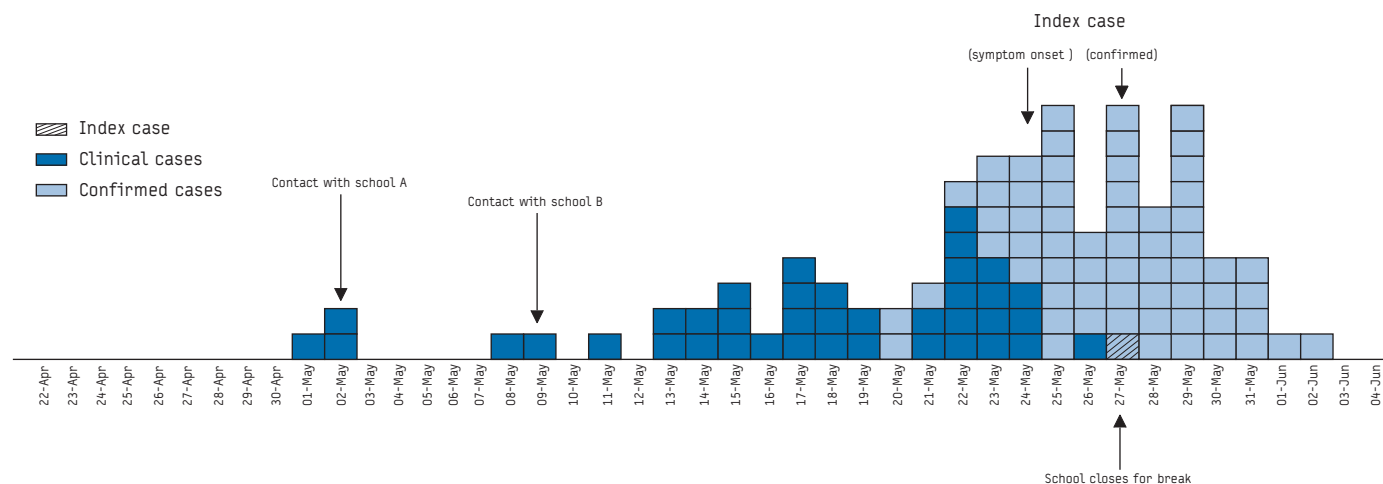
The distribution of symptoms among the cases is illustrated in Figure 3. These were typical of influenza-like illnesses. There were no hospitalised cases. Information on the duration of symptoms was not available.

The public health response

School closure

The school closed to all pupils from 27 May until 7 June 2009. The advice to close for seven days according to HPA guidance at

FIGURE 1
Confirmed influenza A(H1N1)v and clinical ILI in pupils, boarding school South East England, May-June 2009 (n=102)



ILI: influenza-like illness
Date of onset is shown for confirmed cases. For clinical cases, the date that medical treatment was sought was used as a proxy measure for date of onset.

the time became redundant as the school was already closed for a scheduled break for four days, and this break was extended by a further seven days as the school preferred to open on a Sunday. Those without symptoms of ILI who had their state exams scheduled for Monday, 1 June 2009, were permitted to return on 31 May, while the rest of the school remained closed. These pupils were assessed for symptoms, and if symptomatic, were offered anti-viral medicines and testing. They were permitted to take their exams under special conditions to minimise the risk of transmission.

Antiviral prophylaxis

Following the identification of additional probable and possible cases associated with the school, the HPA's advice of prophylaxis was extended beyond the initial group of close contacts to all staff (n=825) and students (n=1,307) attending the affected school. Despite the HPA's advice, the estimated uptake of antiviral prophylaxis among those for whom it was recommended was only 48%. We do not know whether cases occurred in those who took the oseltamivir and do not have information on why the uptake

of prophylaxis was not higher. These issues will be explored in a subsequent study.

Information to parents

Parents were informed by letter that the school had a confirmed case of influenza A(H1N1)v and that the school would close until 7 June 2009. A second letter was subsequently issued detailing advice to offer antiviral prophylaxis to all the pupils and staff at the school.

Clinic at school

An assessment and collection point was established at the college to offer assessment and treatment to returning students, staff members and families of resident staff.

Discussion and conclusion

This outbreak represents the first in a boarding school. The index case had no associated travel history or clear contact with a confirmed or probable case. The other school outbreak described in the literature [4], in New York, United States, involved 45 confirmed cases.

The initial risk assessment following the identification of the index case indicated there were few close contacts, and therefore post-exposure prophylaxis was limited to this group. It became evident during the investigation that the school had had an ongoing outbreak of ILI in the weeks prior to the identification of the index case. It is likely that many of these cases of ILI were due to influenza A(H1N1)v. Swabs taken from some of these cases who were still symptomatic identified a further three confirmed cases. Influenza A(H1N1)v could not be confirmed in most of the earlier cases of ILI as they were no longer symptomatic at the time the outbreak was detected. The source of the outbreak in this school was probably contact with pupils in another school with confirmed cases. This outbreak will add evidence to the hypothesis that the number of confirmed cases of influenza A(H1N1)v underestimates the burden of disease as has been reported previously [5].

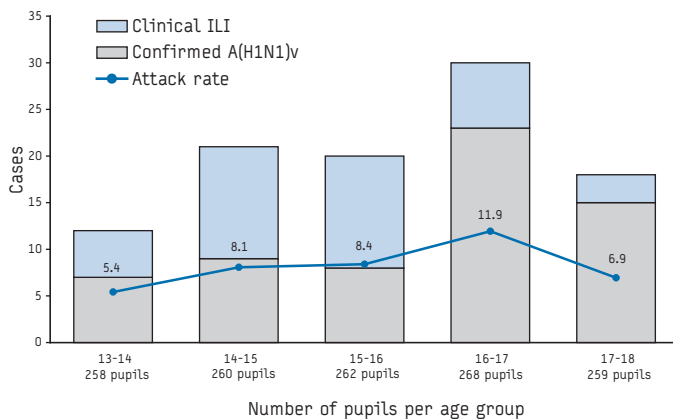
It has been evident from previous reports (including unpublished data) that schools represent an important location for transmission [1]. The reported symptoms suggest an illness of no worse severity than seasonal influenza. None of the cases were hospitalised. While all school years and houses were affected, there was considerable variation in the attack rates between boarding houses. Further insight into this variation will depend largely on gaining some understanding of the transmission dynamics following the first case in the school and the extracurricular and social activities the pupils participated in while exposed to symptomatic cases.

Control measures were implemented as soon as the index case was confirmed. The school closed on 27 May 2009 and post-exposure prophylaxis was offered to the whole school from 31 May 2009. Had the outbreak had been detected earlier, the school closed earlier and prophylaxis commenced after the initial cases were detected according to the HPA's guidance at the time, we may have seen lower levels of transmission within the school.

Acknowledgements

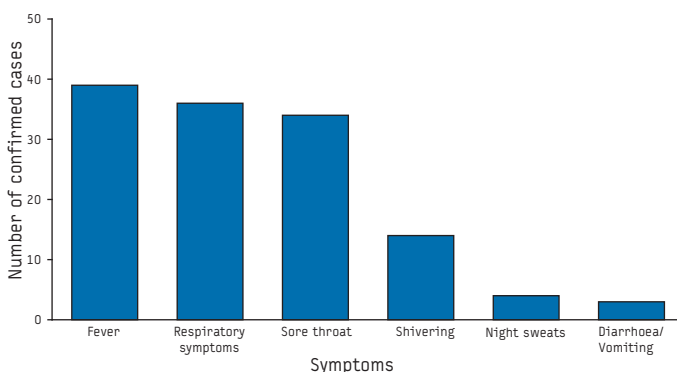
We will like to acknowledge the contribution of Gail Fairbairn for diligently supporting the data management for this report, and all our colleagues in the Flu Response Centres across England who rose to the challenge at very short to offer treatment and prophylaxis to the school population

FIGURE 2
Cases of clinical ILI and influenza A(H1N1)v by age group, boarding school South East England, 1 May-3 June 2009 (n=102)



ILI: influenza-like illness

FIGURE 3
Symptoms reported by confirmed cases of influenza A(H1N1)v by age group, boarding school South East England, May-June 2009 (n=63)



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Rapid communications

ENHANCED EPIDEMIOLOGICAL SURVEILLANCE OF INFLUENZA A(H1N1)v IN ITALY

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As of 7 July 2009, a total of 158 laboratory-confirmed cases of influenza A(H1N1)v were reported in Italy, from half of the 21 Italian regions. To date all cases have had symptoms consistent with seasonal influenza and no severe or fatal cases have been reported. An active surveillance of cases has been set up in Italy in order to undertake appropriate measures to slow down the spread of the new virus. This report describes the routine and enhanced surveillance currently ongoing in Italy.

Background

Following the recent emergence in late April of a new influenza A(H1N1)v virus in the United States and Mexico [1], the same strain has been detected in an increasing number of countries [2,3], and on 11 June the World Health Organization (WHO) officially declared the influenza pandemic. In response to this situation the WHO has recommended enhancing the collection of information on the chain of transmission of the first identified cases in order to timely identify groups of population at higher risk and to guide preventive actions. The information to be gathered is also crucial for validation and refinement of the parameters used in mathematical models to estimate the potential impact of the pandemic. In Italy,

the health authorities have developed specific recommendations for epidemiological and virological surveillance [4] based on the WHO and the European Centre for Disease Prevention and Control recommendations [5,6].

The first confirmed cases of influenza A(H1N1)v in Italy were reported in travellers. The preliminary virological findings have previously been described [7]. This report provides the first description of Italian response and main epidemiological findings of the new influenza A (H1N1)v virus infections in Italy.

Methods

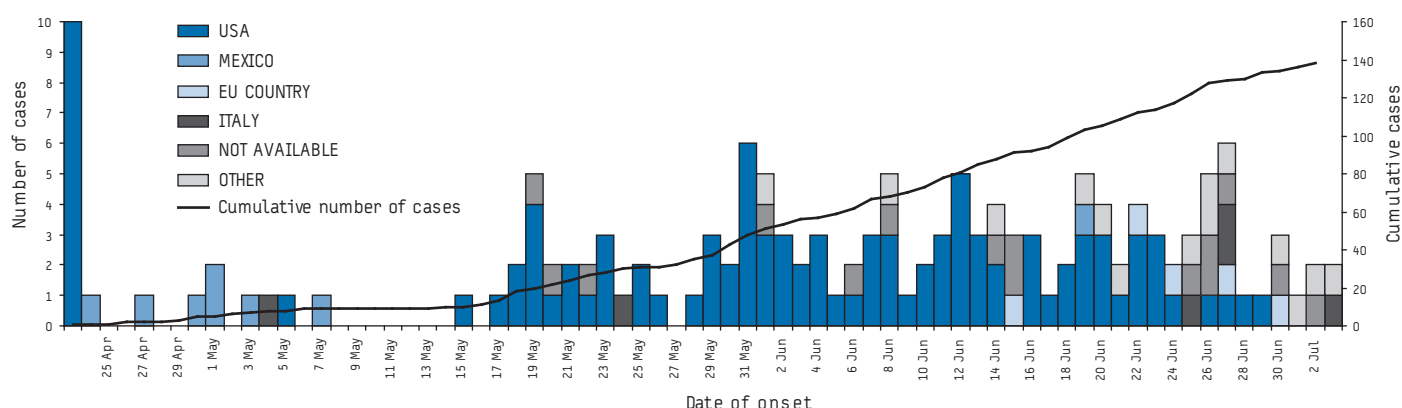
A(H1N1)v surveillance

Since 26 April, suspected, probable and confirmed cases of influenza A(H1N1)v virus are to be reported to the Italian Ministry of Health according to the specific European Union case definition [8].

A suspected case is any person meeting the clinical and epidemiological criteria, a probable case is any person meeting the clinical and epidemiological criteria and with a positive laboratory

FIGURE 1

Distribution of travel-related and locally transmitted confirmed cases of influenza A(H1N1)v virus infection in Italy, by date of onset and place of travel, and cumulative number of cases, as of 7 July 2009 (n=138*)



Note: Of the total number of 158 confirmed cases reported by 6 July 2009, 20 cases are excluded from this Figure because of missing information on the date of onset.

result showing influenza A infection of an unsubtypeable type, a confirmed case is any person meeting the laboratory criteria for confirmation [4].

In order to control the spread of the disease, an active surveillance system of individuals presenting with influenza-like illness and recent history of travel to the affected areas has been set up. All individuals coming from affected areas receive specific medical advice through the health authorities at the airports and seaports, in order to refer to the hospital in case of symptoms. Information about demographic data, illness (e.g. date of onset), and type of travel (e.g. flight number or type of cruise ship) has to be collected. Moreover, specific distancing measures (early isolation of cases and precautionary school closure) and antiviral prophylaxis of close contacts of cases have been set up, in order to contain the spread of A(H1N1)v virus in the country. Any person who has been in close contact with a confirmed case is asked to remain at home for 7-10 days avoiding contacts with others.

Local health authorities should notify any suspected, probable or confirmed cases within 12 hours of symptoms onset, to the Ministry of Health (MoH) and to the National Centre for Epidemiology and Health Promotion (CNESPS) at the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) [4].

In Italy, influenza surveillance is routinely based on a nationwide sentinel surveillance network together with a structured virological surveillance (INFLUNET). The system is based on general practitioners and paediatricians with the aim of monitoring the incidence of influenza-like illness, identifying the extent of the seasonal epidemics and collecting information on circulating strains. Web-based electronic forms are used for data reporting.

Epidemiological investigation of confirmed cases and close contacts

In order to facilitate standardised and timely reporting and updating, the CNESPS in collaboration with the MoH, has developed specific forms for epidemiological investigation of confirmed cases [4] to be recorded on-line. These forms are available at a secure website (<https://www.iss.it/Site/FLUFF100/login.aspx>). This tool is based on the United Kingdom Avian Influenza Management System (AIMS), which was designed to record, organise and

analyse the epidemiological, clinical and personal data for human cases of avian influenza [9], and to facilitate the fulfilment of the International Health Regulations (IHR) requirements.

The information must be collected and entered into the website by the local health authorities within 12 hours after case confirmation. This includes demographic data and details of clinical illness (e.g. date of onset, signs and symptoms, severity, outcome). Data on contacts include exposure data (e.g. relationship to case, type/date of contact, household information) and subsequent development of illness and/or asymptomatic infection. Follow-up information is requested after 15 days from the first epidemiological investigation.

Results

Data from A(H1N1)v surveillance

As of 7 July 2009, a total of 995 suspected cases have been reported to the Italian surveillance system of influenza A(H1N1)v. Of those, 439 (44%) cases were laboratory-tested as negative (excluded), 158 (16%) cases were confirmed and 398 (40%) cases are still under investigation. Of the cases still under investigation 347 had symptoms onset more than one week before 7 July. This indicates that probably only 51 cases can be defined as being still under investigation.

Almost all confirmed cases (n=152) were travel-related, the remaining six cases who acquired the infection in Italy were close contacts of a confirmed travel-associated case. Among the 152 A(H1N1)v cases who had travelled out of the country, 137 (87%) had available data regarding the travel during the week before the date of onset. Of these, 100 (73%) had returned from the United States (US), 8 (6%) had travelled from Mexico, 9 (7%) had been in another European Union Member State, and 14 (10%) had travelled to other countries (Argentina, Canada, Peru, Philippines, and Singapore) (Figure 1). All cases returning from Mexico were reported in the first two weeks of surveillance (24 April - 8 May), and to date, the majority of confirmed cases were travellers to the US.

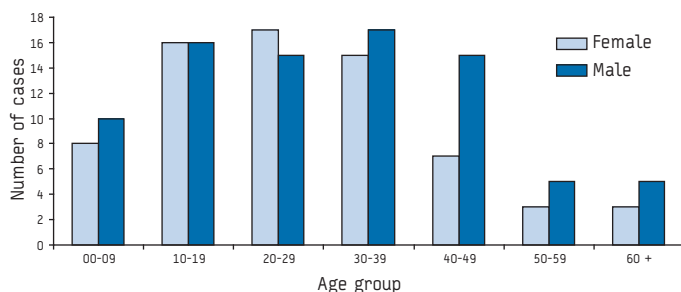
For the 148 (94%) influenza A(H1N1)v cases with available information on age, the median age was 28 years (range 0-69 years) and 83 (56%) were male. Cases younger than 19 years of age constituted 34% of the cases, 59% were aged between 20 and 49 years, and only 7% of cases were 50 years or older (Figure 2).

To date, there have not been significant signals of increased influenza activity through the INFLUNET system. Outputs from this system are published on a weekly basis (available in Italian at the website: <http://www.iss.it/iflu/>).

Data from epidemiological investigation of confirmed cases

Results of the epidemiological investigations of confirmed cases are available for 86 cases. Among these cases, 22 (26%) have been admitted to hospital. It is important to note that some hospitalisations were due to isolation purposes, and therefore the proportion of patients admitted to hospital is not an indicator of the severity of disease. The mean length of stay in hospital was 3.4 days (range 0-7 days). Time elapsed from disease onset to laboratory confirmation was 3.1 day (range 0-12 days). The list of symptoms and the proportion of confirmed cases reporting specific symptoms are given in the Table. Most of the symptoms were reported at disease onset. The most frequent symptoms reported were fever and/or respiratory symptoms, and the least frequent were the gastrointestinal symptoms.

FIGURE 2
Distribution by age group and sex of cases of influenza A(H1N1)v virus infection reported in Italy, as of 7 July 2009 (n=148*)



Note: Of the total number of 158 confirmed cases reported by 6 July 2009, 10 cases are excluded from this Figure because of unavailable data on age.

Of the 86 confirmed cases investigated two were healthcare workers. One had travelled abroad, the other one had acquired the infection in Italy due to contact with a confirmed case in hospital setting. Further five confirmed cases were tourists (not Italian residents) travelling on a cruise ship.

Of the 86 confirmed cases investigated, all received antiviral treatment, once diagnosed, and 90% were treated within 48 hours of symptom onset. Overall 371 close contacts have been identified and put under surveillance, and the average number of contacts for every confirmed case was 5.2 (range 1-39 contacts). Information on prophylaxis of close contacts was available for 319 individuals, 125 of these (39%) received antiviral drugs (114 took oseltamivir, six got zanamivir, and five did not specify the drug taken). Of reported close contacts, 14 (4%) were infected and confirmed as cases, including four who had not received prophylaxis (one because of underlying medical conditions). In 39% of close contacts, antiviral prophylaxis was administered more than 48 hours after symptoms onset of the confirmed case they had been in contact with.

The information on the vaccination status for seasonal influenza in the previous season was available for 73 confirmed cases. The number of persons reported to have been vaccinated during the 2007-8 and 2008-9 seasons was 9 and 2, respectively.

Among 80 confirmed cases for whom information on pre-existing conditions was available, nine persons reported chronic pre-existing conditions (such as cancer, diabetes, heart disease, immunodeficiency conditions). In addition, one case of otitis media in a seven-month-old child and pneumonia in two adults (30 years of age) were reported after the 15 days requested follow-up of cases.

Discussion

The results presented provide some general information on demographic characteristics (age, sex), travel history, clinical

presentation, treatment and prophylaxis of patients infected by influenza A(H1N1)v in Italy.

To date, no local sustained transmission has been reported in Italy. Our results should nevertheless be cautiously interpreted, as approximately all confirmed cases were imported from affected areas. Moreover, since 14 May 2009 the number of confirmed cases has been increasing most probably due to the application of specific RRT-PCR test from the US CDC [7] and due to the increasing number of cases worldwide. In particular, in the last week (30 June - 7 July) the number of reported confirmed cases increased from 100 to 158 and the number of close contacts that had been infected and confirmed as cases increased from 4 to 14.

This preliminary description of the current Italian situation highlights that surveillance activities in Italy are effective at this stage of the outbreak for containment purposes. In fact, 90% of confirmed cases received treatment within 48 hours after symptoms onset. However, it should be noted that only 39% of close contacts received prophylaxis. This is probably due to heterogeneity of the use of antiviral prophylaxis because no specific national guidelines are available. No sustained local transmission has been reported to date in Italy (7 July 2009), except for 14 secondary cases.

Epidemiological investigation with the web-based reporting system is crucial in order to gain specific information on pre-existing chronic conditions and complications among hospitalised cases. This data will help to build a comprehensive database in order to better monitor the epidemic in Italy, in particular to identify risk groups and factors contributing to the development of the epidemic. Moreover, this could represent an important opportunity to share data within EU countries using similar approaches [9].

It is clear that this kind of epidemiological investigation cannot be maintained during the epidemic peak when the number of cases

TABLE

Number and proportion of confirmed cases of influenza A(H1N1)v in Italy reporting specific symptoms, in general and at disease onset, (n=86 cases for whom this information was available)

Symptoms	Number (%) of cases reporting the symptom	Number of cases reporting the symptom at disease onset
Fever non specified	3 (3%)	2
Fever $\geq 38^{\circ}\text{C}$	58 (67%)	42
Fever $< 38^{\circ}\text{C}$	11 (13%)	7
Headache	36 (42%)	24
Muscle pain	37 (43%)	28
Joint pain	22 (26%)	15
Dry cough	35 (41%)	26
Productive cough	7 (8%)	4
Cough not specified	18 (21%)	12
Sore throat	35 (41%)	26
Runny nose	39 (45%)	25
Shortness of breath	8 (9%)	5
Diarrhoea	8 (9%)	2
Vomiting	6 (7%)	4
Nausea	6 (7%)	3
Conjunctivitis	10 (12%)	8
Asthenia	38 (44%)	31
Other (various)	2 (2%)	1

becomes too high. However, collecting information on the first few cases, especially those locally transmitted, could be crucial in order to describe the mechanisms of transmission and biological parameters to fill the existing epidemiological gaps.

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EPIDEMIOLOGY AND CONTROL OF INFLUENZA A(H1N1)V IN THE NETHERLANDS: THE FIRST 115 CASES

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Introductions of the new influenza A(H1N1) variant virus in the Netherlands led to enhanced surveillance and infection control. By 24 June 2009, 115 cases were reported, of whom 44% were indigenously acquired. Severity of disease is similar to reports elsewhere. Our point estimate of the effective reproductive number (Re) for the initial phase of the influenza A(H1N1)v epidemic in the Netherlands was below one. Given that the Re estimate is based on a small number of indigenous cases and a limited time period, it needs to be interpreted cautiously.

Introduction

The first human infections with the new influenza A(H1N1) variant virus [A(H1N1)v], a novel triple reassortant swine influenza virus, were diagnosed in two patients in the United States on 14 and 17 April 2009 [1]. Subsequently, this virus was identified as the cause of a large, ongoing epidemic of respiratory disease in Mexico [2]. Following the report of community transmission in more than two regions, the World Health Organization (WHO) declared on 11 June 2009 the outbreak of influenza A(H1N1)v to be a pandemic [3]. In this short report we summarise the infection control and surveillance activities undertaken in the Netherlands in response to the emergence of influenza A(H1N1)v, as well as the epidemiological characteristics of the first 115 laboratory confirmed cases.

Infection control and case finding

In response to the emergence of the new, potentially pandemic, A(H1N1)v strain of influenza virus, the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (RIVM) in the Netherlands advised on 25 April that individuals who developed fever within seven days after returning from Mexico should consult their general practitioner (GP) by telephone. On 29 April, new influenza A(H1N1)v virus infection was upgraded to a Category A notifiable disease, requiring doctors and laboratories to report the name of the patient to the Municipal Health Service when the disease was suspected or identified. Notifications are entered by Municipal Health Services into a national anonymous web-based database, including information on travel history, contact with symptomatic cases and clinical symptoms. Enhanced surveillance was carried out for clusters and for suspected patient-to-healthcare worker transmissions.

The case definitions (Table) were based on the European Union case definitions [4].

Indigenous cases were defined as cases with no history of travel abroad during the incubation period. In this report we only include laboratory-confirmed cases. Case finding was carried out by Municipal Health Services, who set out to offer laboratory testing to all reported possible cases of A(H1N1)v from 29 April onwards. Case finding was enhanced by testing all household and other close contacts of confirmed cases. From 28 May travellers with fever within seven days of arriving from the United States were also advised to consult their GP. As of 23 June, contacts (even if symptomatic) are no longer required to be tested for A(H1N1)v, unless this is indicated for their clinical management.

To control the spread of infection and attenuate disease in those infected, oseltamivir treatment was recommended from 30 April onwards for all possible, probable and confirmed cases, and for their contacts, irrespective of symptoms. This included airplane passengers seated in the same row as the index case as well as those in the two rows in front and behind. Infected individuals were advised to stay indoors for at least 10 days after the date of onset or shorter if laboratory testing turned negative after day five. The national pandemic influenza preparedness plan includes detailed instructions for protective equipment for health care workers [5]. Entry screening at airports, school closure and hospitalisation for infection control purposes have not been employed.

As of 23 June, asymptomatic contacts of confirmed cases are no longer recommended to receive oseltamivir. However, symptomatic contacts of laboratory-confirmed cases are still recommended to be treated with oseltamivir, and they continue to be notifiable.

Laboratory methods

Laboratory testing is carried out by the National Influenza Centre in the Netherlands (represented by Erasmus Medical Centre, Rotterdam and RIVM, Bilthoven) using general influenza A and A(H1N1)v specific real-time RT-PCR, initially with confirmation by sequence analysis [6]. Results of laboratory testing have been available within 32 hours after sampling to allow timely oseltamivir treatment and prophylaxis.

Methods to estimate key epidemiological parameters

For all indigenous cases we tried to identify a most probable source by examining the patients' contact history reported by Municipal Health Services who interviewed cases. For all epidemiologically linked cases, we subsequently estimated the generation interval as the average number of days between the

dates of symptom onset in the source case and in the secondary case.

To estimate the effective reproduction number (R_e), we divided the epidemiological curve in windows of duration equal to the estimated generation interval. For each pair of successive windows in the period from 30 May to 18 June we calculated the ratio

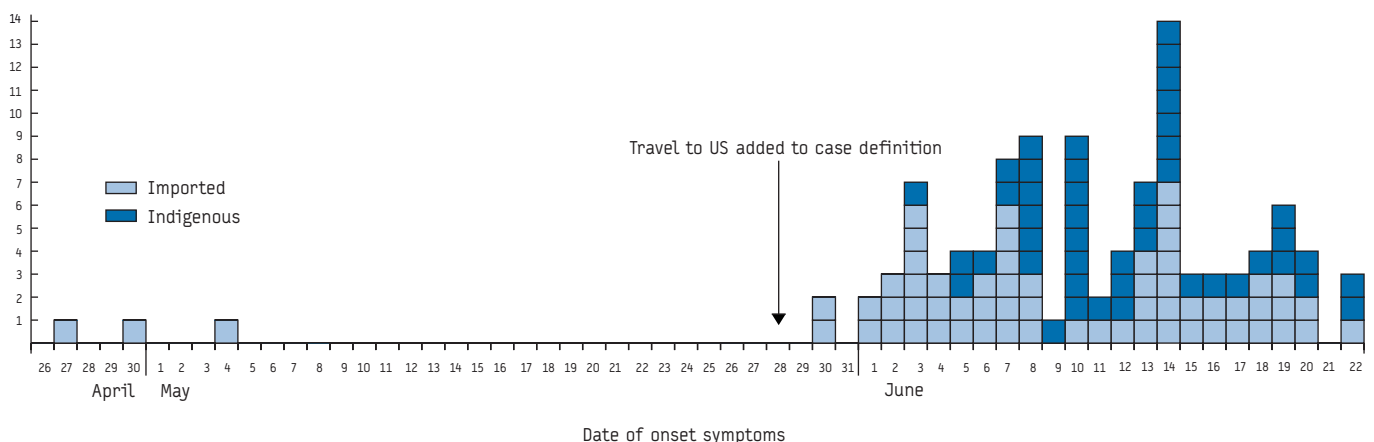
TABLE

Case definitions for new influenza A(H1N1)v [4]

Clinical criteria
Any person with one of the following three:
• fever > 38 °C AND signs and symptoms of acute respiratory infection,
• pneumonia (severe respiratory illness),
• death from an unexplained acute respiratory illness.
Laboratory criteria
At least one of the following tests:
• RT-PCR,
• viral culture (requiring BSL 3 facilities),
• four-fold rise in novel influenza virus A(H1N1) specific neutralising antibodies (implies the need for paired sera, from acute phase illness and then at convalescent stage 10-14 days later minimum).
Epidemiological criteria
At least one of the following three in the seven days before disease onset:
• a person who was a close contact to a confirmed case of novel influenza A(H1N1) virus infection while the case was ill,
• a person who has travelled to an area where sustained human-to-human transmission of novel influenza A(H1N1) is documented,
• a person working in a laboratory where samples of the novel influenza A(H1N1) virus are tested.
Case classification
A. Case under investigation
Any person meeting the clinical and epidemiological criteria.
B. Probable case
Any person meeting the clinical AND epidemiological criteria AND with a laboratory result showing positive influenza A infection of an unsubtypable type.
C. Confirmed case
Any person meeting the laboratory criteria for confirmation.

FIGURE 1

Cases of laboratory-confirmed influenza A(H1N1)v virus infection by day of symptom onset and import status, the Netherlands, reported between 29 April and 24 June 2009 (n=108, further seven asymptomatic cases, of which one was imported, are not included)



between the number of indigenous cases in one window and the total number of cases in the previous window. Re was then estimated by the average of this ratio.

Results

Incidence and travel history

On 30 April the first laboratory-confirmed case of A(H1N1)v in the Netherlands was reported in a three-year-old girl who on 27 April returned with her parents from a family visit in Mexico. By 24 June, 115 confirmed cases were reported, of whom 64 (56%) were most likely imported and 51 (44%) were indigenously acquired (Figure 1). Three of the indigenous cases were in individuals who

FIGURE 2

Cases of laboratory-confirmed influenza A(H1N1)v by age group and import status, the Netherlands, 29 April – 24 June 2009 (n=115)

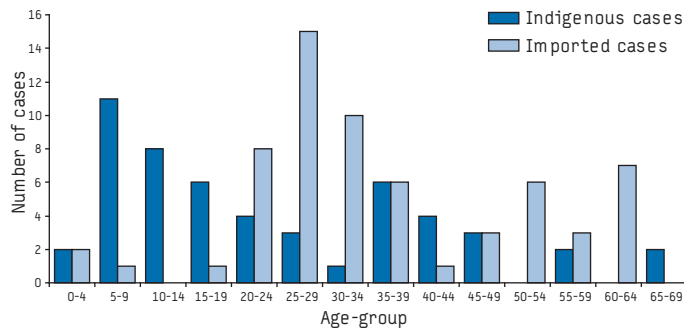
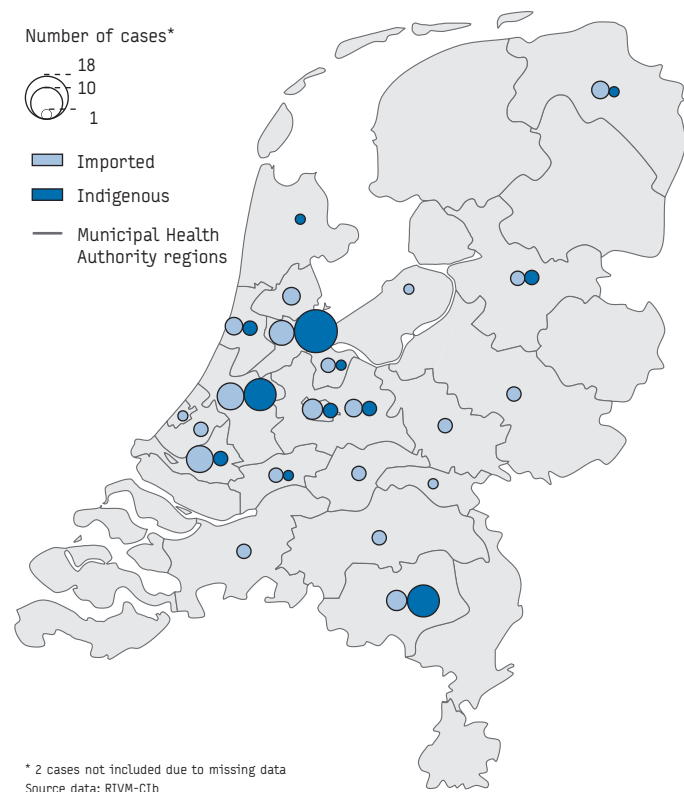


FIGURE 3

Cases of laboratory-confirmed influenza A(H1N1)v by Municipal Health Service region, the Netherlands, 29 April – 24 June 2009 (n=115)



had not been in contact with any known case or cluster. These sporadic cases were tested for the new influenza A(H1N1)v virus because they presented with influenza-like illness (n=2) or viral pneumonia (n=1). So far, no cases of influenza A(H1N1)v have been detected in the sentinel influenza surveillance.

Clinical picture and vaccination status

None of the 115 reported confirmed cases has died. Two (2%) have been admitted to hospital, including a previously physically fit man who required admission to an intensive care department with severe viral pneumonia. He was tested for influenza A(H1N1)v after presenting with respiratory failure. He had not been in contact with any known cases, and had not travelled during the incubation period. The other hospital admission concerned a tourist with asthma visiting the Netherlands. She presented with influenza-like symptoms, and did not have pneumonia. She was admitted for social indications, and was discharged after less than 24 hours. One further case had clinically diagnosed pneumonia but was not admitted to hospital. Of all cases for whom information was available (n=46), three (7%) had underlying chronic illnesses. No cases in pregnant women have been reported.

Of the 48 indigenous, non-sporadic cases, six (13%) were asymptomatic at the time of sampling. It is yet unknown, however, whether they became symptomatic after sampling. Symptoms reported by laboratory-confirmed, symptomatic cases for whom this information was available included: sore throat, cough and/or coryza (93 cases, 90%), fever $\geq 38^{\circ}\text{C}$ (76 cases, 88%), myalgia (54 cases, 52%) and diarrhoea (9 cases, 9%).

Of 111 cases for whom the seasonal influenza vaccination status for 2008-9 was known, 17 (15%, 95% CI 9-23%) reported to have been vaccinated. In 2007, an estimated 10% of the practice populations of less than 65 years of age of GPs participating to a research network (LINH, the National Information Network of General Practice) were vaccinated, whilst 15% were targeted for vaccination [7]. In our case-series, 7% of cases below 65 years of age were in the target group for seasonal influenza vaccination due to underlying illnesses (see above), and only two cases were 65 years or older. The relatively high vaccine coverage among cases compared to the coverage among the general population is consistent with a lack of effectiveness of the 2008-9 seasonal influenza vaccine against the new influenza A(H1N1)v [8].

Epidemiological characteristics

Indigenous cases were younger than imported cases, with a median age of 18 and 31 years, respectively ($p < 0.05$, Figure 2). Cases occurred in most Municipal Health Service regions, with three main clusters of indigenous transmission (Figure 3).

Of the 51 indigenous cases, 36 cases could be epidemiologically linked to an index case, 12 cases could be linked to a cluster and three cases were sporadic. Of four indigenous cases in healthcare workers who did not report contact with a case outside of work, one was considered as resulting from patient to healthcare worker transmission.

In total, nine clusters of more than one case were identified, including three larger clusters with 19, 12 and 9 cases, respectively. The mean generation (or serial) interval for these clusters was 2.5 days (standard deviation (SD) 0.9 days, cluster of 19 cases, n=13), 3.1 days (SD 1.1 days, cluster of 12 cases, n=8) and 2.8 days (SD

1.7 days, cluster of 9 cases, n=5). Overall, the generation interval was 2.7 days (SD 1.1, N=32).

Based on this, we applied a generation interval of three days as moving average window to the epidemic curve. The mean ratio of the number of indigenous cases in one window to the total number of cases in the previous window (the effective reproductive number R_e) was 0.5 between 30 May and 18 June. We did not include cases with a date of onset after 18 June and due to the reporting delay we may have missed cases in this period, which would have resulted in an underestimation of R_e . We observed that no epidemiological links could be traced back to the seven asymptomatic cases, suggesting a very low R_e for asymptomatic cases. However, due to the small number of indigenous cases, the confidence bounds on these estimates of R_e can be considered to be very wide. The implicitly assumed delta distribution gives an upward bias in the point estimate of R_e . However, as the SD of the generation interval was small relative to the doubling time of the epidemic, this bias is negligible [9].

Conclusions

Despite repeated introductions of the new influenza A(H1N1)v into the Netherlands, our enhanced surveillance results suggest that indigenous transmission of this virus has remained relatively limited. A large proportion of cases were imported, and only 15% of these caused secondary cases. Moreover, only three clusters of more than four cases were detected, all relatively limited in size. This suggests that the R_e was below one, consistent with our estimate of R_e based on the epidemiological curve. Our point estimate of R_e for the influenza A(H1N1)v epidemic in the Netherlands was lower than the R_0 estimated for Mexico or the US [10]. However, as the number of indigenous cases was low, this point estimate needs to be considered cautiously. The estimated R_e was based on observations in the period 30 May and 18 June, and is likely to change in future months. Explanations for the relatively low R_e estimate may include the rigorous case-finding and infection control implemented in the Netherlands following the introductions of the influenza A(H1N1)v virus. However, our data do not allow drawing conclusions on the effectiveness of this policy. Our observations are consistent with an absence of effectiveness of the 2008-9 seasonal influenza vaccine against the current pandemic strain.

The incidence of reported cases of influenza A(H1N1)v in the Netherlands is much lower than in the United Kingdom [11]. This may reflect the phase of epidemic; the epidemic in the UK could be more advanced due to earlier and more frequent introductions, especially from the US. It may also reflect chance effects early on in the epidemic, where introductions into schools are likely to lead to intense transmission.

The clinical picture and severity of disease among our cases is similar to what was reported elsewhere [12]. However, due to the limited time of follow-up, we may have somewhat underestimated the severity in our report.

The occurrence of a new strain of influenza virus coupled with intense efforts to control it offer a unique opportunity to document its key epidemiological, virological and pathogenetic properties. This information is crucial for modeling aiming to predict the future burden of disease and to design strategies for most effective control of this pandemic. However, changes to the strain's properties, including emergence of resistance, would render these predictions invalid. Continued surveillance is therefore of key importance.

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INFLUENZA A(H1N1)v VIRUS INFECTIONS IN BELGIUM, MAY-JUNE 2009

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In response to the ongoing influenza A(H1N1)v pandemic, first detected in North America in April 2009, Belgium has set up an active surveillance system for influenza-like illness among travellers returning from affected areas. This communication describes the clinical and epidemiological features of the first 43 laboratory-confirmed cases in Belgium.

Introduction

On 25 April 2009, the World Health Organization (WHO) declared an outbreak of A(H1N1)v influenza, first reported by the United States (US) [1] and Mexico, a 'Public Health Event of International Concern' (PHEIC) under the International Health Regulations [2]. The WHO Director-General raised the pandemic alert phase to the maximum level (phase 6) on 11 June 2009 [3]. As of 14 July 2009, 30 of 31 European Union (EU) and European Free Trade Association (EFTA) countries have reported cases of influenza A(H1N1)v [4].

On 12 May 2009, the Belgian National Reference Laboratory for Influenza confirmed the first case of influenza A(H1N1)v in a person returning to Belgium from the US. A total of 130 confirmed cases have been detected in Belgium as of 14 July 2009.

An active surveillance system was implemented, following a delaying strategy. It aimed at detecting cases of A(H1N1)v influenza in travellers returning from affected areas [5] and in their contacts for the purpose of taking control measures to delay the spread of the virus.

Methods

Table 1 shows the case definitions developed for the investigation and the case classification used.

The Interministerial Influenza Coordination Committee disseminated protocols for case and contact management regarding notification, sampling, prophylaxis, treatment and isolation. The involved physicians, mostly general practitioners (GPs), were required to contact the Community Health Inspectorate when finding a possible or suspected case. Physicians took samples and sent them on the same day to the National Reference Laboratory for Influenza. Samples were treated under biosafety level 3 (BSL3) conditions and tested by realtime reverse transcription PCR (RT-PCR) using primers directed against A and B influenza virus, and in case of a positive result for A influenza also with primers against A(H1) and A(H3); from 3 May 2009 we also used primers specific

for A(H1N1)v influenza virus, sent from the Centers for Disease Control and Prevention (CDC).

All involved public health authorities scaled up their response service to operate around the clock. A duty service with epidemiologists was available for Health Inspectorates and involved physicians through a restricted access telephone hotline in order to support them with case definitions and the organisation of sampling.

Hospitalisation was recommended for the first 25 confirmed cases for the purpose of isolation. From 2 June 2009 onwards, the recommendation was for patients to stay at home for seven days after onset of symptoms and to hospitalise severe cases only. Confirmed cases were treated with neuraminidase inhibitors.

Provincial health inspectorates performed contact tracing. Close contacts of confirmed cases should take a neuraminidase inhibitor

TABLE 1

Case definition and case classification for A(H1N1)v influenza, Belgium, May-June 2009

Case definition for investigation		
Possible case	A person with: <i>all three</i> clinical criteria <i>and</i> <i>at least one</i> epidemiological criterion during the seven days prior to onset of symptoms	Clinical criteria: • Fever (>38°C) • One respiratory symptom (cough, dyspnoea) • General discomfort Epidemiological criteria: • History of travel to affected areas • History of close contact (<1 metre) with a confirmed or symptomatic probable case
Suspected case	A person fulfilling the epidemiological criteria for influenza A(H1N1)v infection, but not all clinical criteria for a possible case	
Case classification		
Confirmed case*	A person with laboratory-confirmed A(H1N1)v influenza	
Non-case	A person with a negative test for influenza A(H1N1)v	

* Until 3 May 2009, real-time reverse transcription PCR (RT-PCR) for influenza A(H1N1)v virus was not available and cases were tested for influenza A and B, and subtyped for seasonal influenza A(H1) and A(H3). A person with a positive test for influenza A, untypable for seasonal strains, would have been considered as a probable case.

as prophylaxis and were requested to stay at home for seven days after the latest contact and to avoid unnecessary further contacts as a quarantine measure. Close and other contacts were advised to seek immediate medical advice if they noticed fever or respiratory symptoms.

Cases were notified to the WHO and through the Early Warning and Response System (EWRS) to the European Centre for Disease Prevention and Control (ECDC) by the Belgian Federal Public Service for Public Health (FPS).

Results

As of 14 July, 633 people have been tested in Belgium and 130 cases of influenza A(H1N1)v have been confirmed. Two of the possible cases were not tested because they were close contacts of confirmed cases and under antiviral prophylaxis when they developed influenza symptoms.

We analysed the first 43 laboratory-confirmed cases. Infection was acquired abroad by 35 cases, of which 18 had a travel history to the US, nine had returned from the Dominican Republic and three from the United Kingdom (UK). The other imported cases had returned from Argentina (n=1), Australia (n=1), Canada (n=1), Chile (n=1) and Costa Rica (n=1). The first eight imported cases had come back from the US. Seven imported cases declared onset of symptoms prior to their return. According to information available for 26 of 28 cases, disease onset occurred up to five days after arrival (mean 1.6 days, median 2 days).

All indigenous cases (n=8) were close contacts to previously confirmed cases. Figure 1 shows the evolution of the cases by date of symptom onset and by import status.

Table 2 shows the geographic distribution of the cases by province. On 28 June 2009, eight of 11 provinces in Belgium were affected. One third of the cases were residents in the province of Antwerp. One case who had been in transit at Brussels airport was counted in the province of Flemish Brabant.

The female to male ratio was 1.05 (22 women and 21 men). The age range was from eight months to 51 years (median: 28 years, mean: 29 years). Seven cases were younger than 20 years. The most affected age group were the 20-29 year-olds with 16 cases.

Information about symptoms was available for 42 cases. The most commonly reported symptoms were cough in 40 cases

followed by general discomfort in 38 cases and fever or history of fever in 36 cases. Dyspnoea was reported by 12 cases and diarrhoea by five cases; nausea was reported by two cases and vomiting, sore throat and headache were reported by one case each.

No complications have been detected so far. One confirmed case, already under treatment with oseltamivir, was hospitalised because influenza symptoms persisted and the patient had asthma as underlying condition. Respiratory samples from this patient are currently being cultured and tested for resistance against oseltamivir. One pregnant woman was confirmed to be infected with influenza A(H1N1)v. Information on underlying factors for the other 41 patients was not available.

Discussion

When Belgium detected the first confirmed case of influenza A(H1N1)v, many neighbouring countries had already notified cases. We assume that the number of Belgian travellers to Mexico is small compared to that of more populated European countries and that the number of Belgian travellers returning from the US is larger than the amount of those returning from Mexico. This may explain why Belgium started detecting imported cases when sustained community transmission happened in the US.

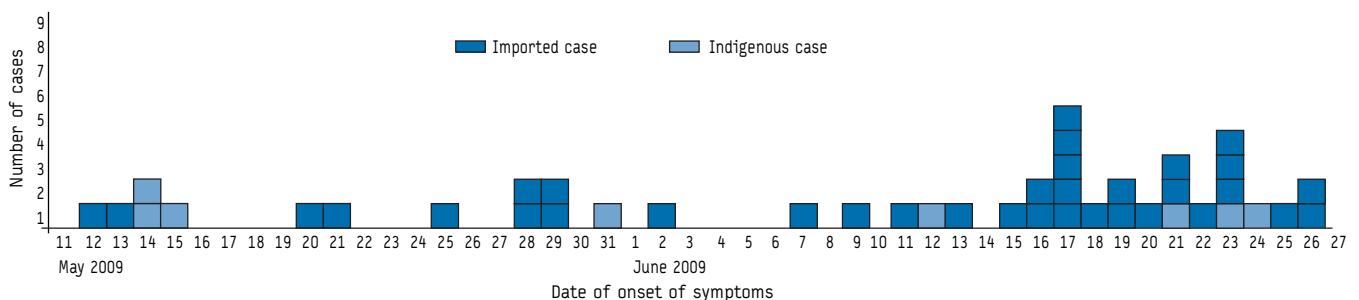
Continuous monitoring of affected areas worldwide and consequent updating of the case definition allowed the detection of cases returning from countries with a low number of cases but with evidence of community transmission like Costa Rica or the Dominican Republic.

The age distribution of the cases may reflect the age of the people that travel and is not representative of the Belgian population. Children of school age were only sporadically affected until 11 July 2009, and this may have played an important role in the disease not spreading in the community. Secondary cases occurred in the same age groups as imported ones, reflecting the importance of contact patterns. However, an outbreak in a summer language school that has affected 14 people between 10 and 18 years-old, is currently under investigation.

This preliminary analysis of the 43 first confirmed cases of influenza A(H1N1)v in Belgium suggests that the clinical manifestation resembles that of seasonal influenza. This is consistent with an analysis by the ECDC on aggregated data of European cases of influenza A(H1N1)v [6].

FIGURE 1

Distribution of laboratory-confirmed cases of influenza A(H1N1)v by date of onset and by import status, Belgium, 12 May-28 June 2009 (n=43)



Currently, mitigation strategies are being adopted by countries in the southern hemisphere that are facing the influenza season, such as Chile, New Zealand and Australia, but also by European countries where sustained community transmission has been declared, like the UK [7]. In Belgium, the Interministerial Influenza Coordination Committee announced the switch to a mitigation strategy on 13 July 2009. This will require appropriate surveillance of influenza-like illness. A GP-based sentinel surveillance network for seasonal influenza is being reinforced in Belgium and from 14 July 2009 onwards has taken over the enhanced system put in place from the beginning of the pandemic. This network aims at characterising the circulating influenza viruses, seasonal or pandemic strain, as well as estimating the burden of disease at community level. The Belgian system for the monitoring of mortality will contribute to observing the situation.

Conclusions

The introduction of influenza A(H1N1)v virus in Belgium happened in the same way as in other EU/EFTA countries, causing a small but increasing number of cases. Given the uncertainty of the evolution of the current influenza A(H1N1) pandemic, and the emergence of complications in a small proportion of the cases, the Belgian health authorities continue to closely monitor the severity and the spread of the disease in order to provide an adequate response during the coming months.

Working group:

The Belgian working group on influenza A(H1N1)v is formed by the Flemish Community, the French Community, the Brussels Region, the Hospital Saint-Pierre in Brussels, the Federal Public Service for Public Health and the Belgian Scientific Institute of Public Health, under the coordination of the Interministerial Influenza Coordination Committee. The corresponding author is S.Quoïlin, IPH (s.quoilin@iph.fgov.be).

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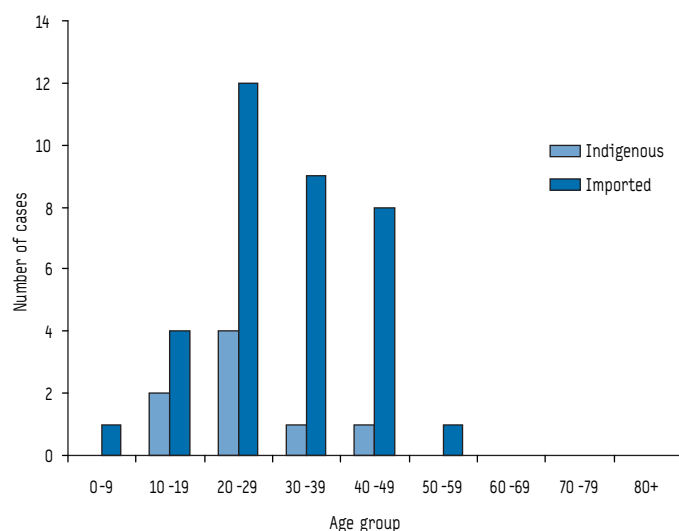
TABLE 2

Distribution of laboratory-confirmed cases of influenza A(H1N1)v by province of residence, Belgium, 12 May-28 June 2009 (n=43)

Province	Frequency	Percentage
Antwerp	14	32.6
Brussels	4	9.3
East Flanders	7	16.3
Flemish Brabant	10	23.3
Hainaut	2	4.7
Liege	0	0
Limburg	2	4.7
Luxembourg	0	0
Namur	2	4.7
Walloon Brabant	2	4.7
West Flanders	0	0
Total	43	100

FIGURE 2

Distribution of cases of influenza A (H1N1)v by age group and import status, Belgium, 12 May-28 June 2009 (n=43)



EUROPE'S INITIAL EXPERIENCE WITH PANDEMIC (H1N1) 2009 - MITIGATION AND DELAYING POLICIES AND PRACTICES

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Europe has experienced more than two months of the first transmissions and outbreak of the 2009 pandemic of A(H1N1)v. This article summarises some of the experience to date and looks towards the expected autumn increases of influenza activity that will affect every country. To date the distribution of transmission has been highly heterogenous between and within countries, with one country the United Kingdom (UK) experiencing the most cases and the highest transmission rates. Most infections are mild but there are steadily increasing numbers of people needing hospital care and more deaths are being reported. An initial difference in practice between Europe and North America was over case-finding and treatment with some authorities in Europe using active case-finding, contact tracing and treatment/prophylaxis with antivirals to try and delay transmission. This article details the history of this practice in the past two months and explains how and why countries are moving to mitigation, especially treating with antivirals those at higher risk of experiencing severe disease.

The current situation in the United States and Europe

In the three months since its first recognition the pandemic strain of influenza A(H1N1)v virus has spread to all six continents [1]. So many people are being infected that the World Health Organization (WHO) considers counting cases of little value in the more affected countries and hence it has advised to stop testing and reporting individual cases and to move on to other surveillance strategies [2]. In the temperate areas of the southern hemisphere, where it is winter, the first pandemic wave is in progress. In the northern hemisphere most countries are in the initiation phase (Figure).

The United States Centers for Disease Control and Prevention (CDC) broadly estimates that at least a million people have been infected with the pandemic virus in the United States, a large figure, but representing only 0.3% of the US population compared to the 20-30% that is anticipated to be affected in the first wave in the winter season [3]. The picture is also heterogeneous geographically as is often the case with both seasonal and pandemic influenza. Up to 7% of the population may have been infected in New York city in May, while other places are reporting only a few infections [4,5]. CDC expects the virus to keep spreading in the US through the summer and then transmission to accelerate in the autumn [6].

In the European Union all countries have now reported cases and the picture is even more heterogeneous than in the US [1].

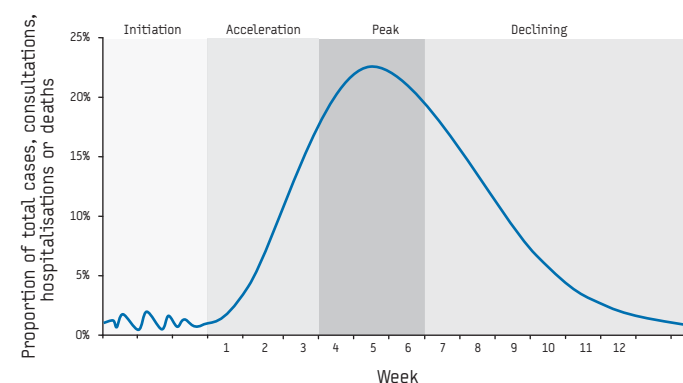
Two countries, Spain and the UK account for more than four fifths of the reported cases and France and Germany have recently also reported significant numbers [1,7]. Hospitalisations and deaths are mounting up and the most affected country (UK) has revised its planning assumptions for a major first wave in the light of its particular experience (Table 1) [8].

Reported case numbers will become increasingly meaningless as countries abandon trying to test all cases and stop being able to count cases. However the initial analyses give important information. Initially case reports in Europe were dominated by imported (travel-related) cases [9]. These now represent ever decreasing proportions. In the latest cumulative analysis they accounted for only 13% (1,946 of 14,146) reported cases and the countries that have reported substantial numbers have all observed a strong trend of predominating domestically-acquired infections [7].

The most affected country is the UK and its experience gives useful indications of what is to come. Again the picture is one of heterogeneity with some parts of the UK experiencing intense

FIGURE

Idealised national curve for planning, Europe 2009 (reality is never so smooth and simple)



Single-wave profile showing the proportion of new clinical cases, consultations, hospitalisations or deaths by week. Based on influenza pandemic in London in 1918, second wave.

transmission indicating the start of an acceleration phase with numbers of primary care consultations several times higher than those experienced at the peak of last winter (when seasonal influenza was the worst in some years) [10]. However other parts are relatively unaffected [10]. The most recent numbers (as of 23 July) are available at the website of the Health Protection Agency: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1247816558780?p=1231252394302

Overall the modelled estimated rate of new infections for the week of 23 July of 0.2% (100,000 in the week) in the UK is still somewhat down the acceleration phase but according to the UK's planning assumptions it might be expected to peak at about 6.5% or around 800,000 clinical infections per week (Table 1) [8].

Severity of the disease and risk groups

It remains the case that most people who are infected in Europe experience a mild illness that does not require treatment. However this in itself is making surveillance more difficult since most people will not need to seek medical attention when infected [11]. For example in a New York city survey very few of the people reporting illness thought it was sufficiently serious to seek medical care (I Weisfuse, personal communication). Certainly many cases are also not coming to the attention of surveillance in Europe.

TABLE 1
United Kingdom revised planning assumptions for the pandemic – first wave A(H1N1) 2009

Clinical attack rate	30%
Peak clinical attack rate	6.5% (local planning assumption 4.5% to 8%) per week
Complication rate	15% of clinical cases
Hospitalisation rate	2% of clinical cases
Case fatality rate	0.1-0.35% of clinical cases
Peak absence rate	12% of workforce

Source: United Kingdom Department of Health: http://www.dh.gov.uk/en/Publicationsandstatistics/publications/PublicationsPolicyAndGuidance/DH_102892

TABLE 2
Risk groups for the pandemic (H1N1) 2009

<p>The following groups are considered more at risk of experiencing severe disease than the general population should they become infected with the pandemic A(H1N1)v virus 2009:</p> <p>People with chronic conditions in the following categories:</p> <ul style="list-style-type: none"> • chronic respiratory diseases; • chronic cardiovascular diseases (though not isolated mild hypertension); • chronic metabolic disorders (notably diabetes); • chronic renal and hepatic diseases; • persons with deficient immunity (congenital or acquired); • chronic neurological or neuromuscular conditions; and • any other condition that impairs a person's immunity or prejudices their respiratory (breathing) function, including severe or morbid obesity. <p><i>Note: These categories will be subject to amendment and development as more data become available. These are very similar underlying conditions that serve as risk factors for seasonal influenza. What is especially different from seasonal influenza is that the older age groups (over the age of 60 years) without underlying conditions are relatively unaffected by the pandemic strain.</i></p> <p>Pregnant women</p> <p>Young children (especially those under two years)</p>
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Crucial information is being published on the *higher risk groups* (those who are more likely to experience severe disease). The conclusions are still preliminary but the initial data from North America and Europe on who is affected by severe symptoms indicate risk groups similar to those for seasonal influenza, though with some important differences, notably the relative absence of cases in older people [12] (Table 2).

Expectations for the autumn in Europe

The European Centre for Disease Prevention and Control (ECDC) expects that in autumn European countries will experience a major first wave well beyond anything that has been experienced to date in this pandemic (Figure) [11]. However it is not possible to predict exactly what percentage of the population will be infected in the autumn wave and when it will come for individual countries. It is unlikely to occur at once and there will be heterogeneity within countries. Even if the experience of the UK is that the first acceleration phase of the pandemic truncates in the summer (perhaps as schools close), ECDC considers it important to prepare for an earlier start in autumn than the time when seasonal influenza usually takes off. Based on the initial surveillance results the UK has revised its planning assumptions for up to 30% of the population to be affected in the first wave [8] (Note: It is important here to distinguish between planning assumptions and predictions. Planning assumptions represent the reasonable worst case scenario for a first major pandemic wave).

Hence Europe should be prepared to experience a very large number of cases in the coming months with inevitable strain on the health services because of a proportion of cases requiring primary or secondary care [11,13-15] (Table 1). A new approach to surveillance, building on what is already there will be needed and that is being developed by ECDC with Member States and WHO.

Initial differences in practices between North America and Europe

An area of differing practice or even policy between countries has been how to manage the initial cases and transmissions of influenza A(H1N1)v virus. In North America the approach from the start was of mitigation, essentially following WHO's early advice (Table 3) [16]. This includes applying standard guidance on the management of influenza cases and outbreaks similar to those for seasonal influenza, not treating the majority of cases who experience a mild self-limiting illness but offering antivirals to those who are considered at higher risk of experiencing severe disease [17,18]. Prophylaxis is being reserved for these groups when they are thought to have been exposed.

In Europe the initial approach was different from North America with some countries starting by attempting *containment* (trying to stop influenza spread beyond initial outbreaks) with energetic case-finding, treatment, contact-tracing and chemoprophylaxis of contacts (Table 3). Cases were isolated in hospital and quarantine was practised. A country that typified this approach was the UK which practised active finding and treatment of cases and contacts in schools and families, although not isolation in hospital or quarantine [19]. Though the word containment was used this was better described as *delaying* (Table 3). Despite great efforts in May and June daily reports of new laboratory confirmed cases rose to over 500 a day in late June. Hence, the UK found it difficult to sustain the intensive case-finding and contact-tracing strategy and on 2 July announced it was moving to a mitigation strategy

which it called a *treatment* approach [20]. The principle is to make antivirals available for all, but focusing especially on the early treatment of those in risk groups and to limit the use of prophylaxis to protect those at higher risk of severe disease [20]. Some other European countries have also treated all cases and contacts [21] but as their numbers of detected cases are small they were initially able to manage this more readily.

The question therefore was which practise should all European countries follow when they are inevitably affected, either over the summer or sometime in the autumn? Following a request from EU member states for guidance, in June ECDC published the arguments for and against these approaches, which this article will now summarise [22,23].

WHO's position on containment

When announcing pandemic phase 4, WHO indicated that the epidemic had already started to spread beyond a level justifying attempts at containment and a mitigation approach was recommended [16]. Two days later, on 29 April, WHO escalated to phase 5 and then on 11 June to phase 6. According to WHO guidance, under phases 5 and 6, measures differ between affected and not yet affected countries but containment attempts are no longer recommended, the guidance advises member states to implement a mitigation strategy, including considering measures for reducing the spread of infection [16,24]. This includes applying standard guidance on the management of influenza cases and

outbreaks similar to those for seasonal influenza (Table 3). This entails not treating the majority of cases who experience a mild self-limiting illness but offering antivirals to those who are considered at higher risk of experiencing severe disease [16-18]. Neither ECDC nor WHO recommend the use of the word 'containment' for influenza outside of the theoretical context of place and time where a pandemic strain first emerges somewhere in the world [25]. Previous modelling work has suggested that containment will be both impractical and unsuccessful once there is extensive community transmission and certainly once the pandemic has entered its acceleration phase [26]. Apart from some very isolated settings, history dictates that European communities will not be able to contain the pandemic strain or isolate themselves from it [27].

The experience with delaying and containment

The 'delaying' strategy was certainly legitimate to attempt, especially in the EU where the initiation phase started at the very end of the seasonal influenza period when influenza transmission would be expected to be low. The delaying strategy is therefore appealing when a pandemic starts in the spring or early summer. The rationale is that an aggressive approach could decrease the effective reproduction number (R) and delay the inevitable acceleration of the pandemic until autumn allowing more time for preparations and for vaccines to be developed and licensed. Besides, identifying the first cases and documenting their clinical presentation has proven to be important at the early stages of a pandemic to gather information needed for the *early assessment* to steer the strategy for response [14,15,28].

Operational aspects

The main issues around the debate on mitigation versus delaying are operational and concern the *opportunity costs* of aggressive case-finding, contact tracing and management (Table 3). The question is whether there are staff available who can deliver the necessary response seven days a week and what else cannot be done because the human and other resources are fully engaged on case-finding, contact-tracing, testing and treating. In the UK delivering the delaying strategy was initially possible because the Health Protection Agency and Health Protection Scotland led the work and combined effectively with local public health and primary care staff to focus massive effort on the initially affected communities. At the same time central authorities concentrated on making final preparations especially readying the health services for the autumn wave. Even so the intense work involving many schools and families was unsustainable. This has demonstrated that where there is active influenza transmission the strain on the work-force from attempting delaying is considerable. Probably only countries with national public health workforces who can be moved around the country could implement such a policy at the population level during initiation. Once into the acceleration phase in the autumn the task will be impossible in any country given what is known now about the effective reproductive number [29]. Australia and New Zealand are unusual in having formal containment phases in their pandemic plans. Their current experience is telling for what Europe could expect in the autumn. Both these countries moved through and beyond containment rapidly into mitigation [30,31].

Communication challenges

Besides burden on staff there are major communication challenges from an initial delaying approach. These arise from starting on a delaying tactic and treating everyone with what may seem a very mild disease, plus their contacts. Then having to move

TABLE 3

Mitigation, containment and delaying – the definitions

<p>Mitigation is a collective term recommended by WHO for actions in affected countries in phases 5 and 6 of pandemic alert, essentially reducing the impact of a pandemic.</p> <p>In the health sector, the aims of mitigation include:</p> <ul style="list-style-type: none"> • reducing the overall number of people affected; • reducing transmission; • ensuring healthcare for those who may be infected; • maximising care for those with disease; • protecting the most vulnerable; and • more general interventions.
<p>Containment</p> <p>Containment means preventing spread of a infection in a defined areas or areas by:</p> <ul style="list-style-type: none"> • case-finding: detecting imported infections and first generation transmissions; and • taking actions to prevent their turning into chains of transmission and outbreaks, notably through vigorous contact tracing, treatment and/or quarantine of contacts. <p>The objective is to stop as many transmissions as possible and eventually the outbreak 'burns out'.</p> <p>The term 'containment' is not recommended in this context by WHO or ECDC as it raises expectations that a pandemic virus can be contained once it has got beyond the initial outbreak, as was the case with the 2009 virus because, when it was discovered, transmission was already well beyond a delimited area.</p>
<p>Delaying is a less complete form of containment where the aim is not to contain the pandemic but rather to simply slow down transmission.</p>
<p>Differences</p> <p>It is important to note that many of the actions and messages being undertaken or promulgated are the same for delaying and mitigation strategies.</p> <p>What is different between the two is that in delaying there is special emphasis put on:</p> <ol style="list-style-type: none"> 1. Vigorous case-finding and tracing of contact-persons and giving antivirals or alerting them to watch for symptoms; 2. Putting contact-persons or even all travellers from areas with community transmission under quarantine.

back to mitigation with only offering antivirals to those in the risk groups [8,10]. Explaining this to professionals and the public may not be easy. It is also not clear how it is possible to get patients, especially children to take antivirals and complete course when they are only experiencing mild disease or are contacts of cases [32].

Differences between mitigation and containment

It should be appreciated that looked at overall mitigation and delaying strategies have a lot in common. They only differ in the emphasis in delaying on finding as many infectious cases as possible and treating them and their contacts (Table 3) However that difference is very important as the UK found the work is very demanding on human resources in the field and in the laboratory. This is especially so with using antivirals because of the evidence that to be effective treatment has to be given early, within 48 hours of symptoms starting [33,34].

Exit strategies

If a country decides to adopt delaying it needs to have a very clear exit strategy and triggers for giving up. ECDC does not recommend delaying but if a country does adopt the policy then it could consider the ECDC criteria for being 'affected' as the sign it is time to change to mitigation in all parts of the country [35]. Once policy makers adopt delaying or containment as a formal policy rather than an operational practice it can be especially difficult to change policy in a timely manner and so it is best to keep decisions at the technical level. An additional factor influencing the choice of strategy is that if a number of countries in Europe started on delaying or containment then others might have felt they had to follow. Unlike in the United States and Canada there are no cross-European agreed recommendations on the use of antivirals (although there is an ECDC guidance) [34]. It is therefore difficult to explain why delaying is being done in one country and not in others and this problem will arise again (i.e. in the autumn). Some solution was offered by meetings that took place in early July where experts met to discuss this topic and advised ministers at an informal EU Health Council to allow a degree of coordination. There was also broad agreement based on the UK example that mitigation should be adopted either in the initiation phase or when acceleration starts (Figure) in individual countries [36,37].

Has delaying been effective?

Have attempts at case-finding, contact tracing and treatment of all cases and contacts been effective in Europe so far? The answer depends on whether effectiveness is considered at the individual or population level. For those infected and treated within 24 to 48 hours the answer is almost certainly 'yes'. Trials of both the neuraminidase inhibitors, oseltamivir and zanamivir against seasonal influenza have shown benefit in otherwise healthy adults [33,34] although it must be appreciated that antivirals are not 'magic bullets'. Even if given in time they only shorten the illness by one or two days and do not stop a person being infectious [33,34]. There may be more benefit when antivirals are given to those developing severe illness [34]. There are no such data for the pandemic strain as yet but since only a handful of viruses have shown genetic markers of resistance to either drug (they do have markers of resistance to the adamantanes) a reasonable default assumption is that they should be effective for treatment of infected individual [34,40] The arguments around prophylaxis are more complicated. Certainly many episodes of illnesses will have been prevented but we do not know how successful prophylaxis is in preventing actual infection rather than just preventing the onset of symptoms. A sophisticated view, not supported by ECDC, recalls the accounts of the 1918-19 pandemic, which was also the last A(H1N1)-based pandemic. Then a lower pathogenicity wave in the spring in Europe was followed by a much higher pathogenicity wave in the autumn [41]. So the logic goes it may be better to be infected now by this mild A(H1N1)v virus rather than later by one causing more severe disease.

At a population level it is harder to determine the success of the delaying tactic. Delaying can appear to work by chance alone. Pandemics of influenza, like seasonal influenza each autumn, take an uncertain time to move from initiation to acceleration (contrary to popular belief influenza is only 'infectious' not 'highly infectious' (Table 4)) Considering the United States since April the heterogeneity of transmission has been striking [5]. If relatively pandemic-spared cities like those on the West Coast had attempted delaying they might now be congratulating themselves while cities like Chicago and New York would be wondering what they did wrong. It is highly possible that the efforts made by the UK and other European countries delayed the progression of transmission in May and June. Indeed given the scale of the effort in the UK it seems hard to imagine there has not been some benefit but a final verdict on how much delaying was achieved will have to await the results of considered evaluations which will take some time.

What to do?

In conclusion, what should a European country do when confronted by first cases? It can be difficult when there are only a handful of cases to offer no treatment except to individuals in risk groups. But that may be what national policies dictate, what WHO recommends and what is being done in North America [16-18]. It would also seem to be in line with the ECDC documents [22,23].

When confronted with more cases countries should consider whether to attempt delaying at all, what the advantages are of any time it might buy and the opportunity costs from what else will not be done as a consequence. The conclusion of the Swedish Presidency meeting was that countries should move to mitigation [36,37], and at least two more countries report having taken this decision [38,39].

TABLE 4

Infectiousness of some communicable diseases

Infection	Effective (R) or basic reproductive rate (Ro)	Notes
Seasonal influenza	R around 1.1 - 1.2	Higher in crowded communities
Pandemic influenzas	R = 1.5 to 2.5	Higher in crowded communities
Pandemic (H1N1) 2009	R = 1.5 to 2	Presumed higher in crowded communities
Measles	Ro > 10	
Mumps	Ro 4 to 7	

R = effective reproductive rate = the average actual number of people that are observed to be infected by one infected person
 Ro = basic reproductive rate = a theoretical concept of the average number of people that one person infects in a wholly susceptible population

However that does not mean that the first cases and transmissions in a country do not deserve special attention. There are very legitimate reasons for undertaking enhanced surveillance and working closely with those first affected to determine some of the *known unknowns* of the pandemic – for example: what proportions of people in a family are affected, are most older people really immune, how long are people infectious, do those who choose to take antivirals stop excreting virus and do they develop immunity [14,15,40-45] A number of countries are undertaking such work in Europe and ECDC and WHO are working with them to ensure the rapid sharing of protocols and data.

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CLINICAL FEATURES OF CASES OF INFLUENZA A (H1N1)v IN OSAKA PREFECTURE, JAPAN, MAY 2009

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This report describes the clinical characteristics of influenza A(H1N1)v virus infection in Osaka. By the end of May, 171 cases had been reported in Osaka. Most patients were from one school. No patient had a serious underlying medical condition. Clinical symptoms were mild and resembled those of seasonal influenza. The sensitivity of the rapid antigen test was 77%. Antivirals were given to the majority of the cases. Early antiviral treatment may have shortened the duration of fever.

Background

In Japan, the first case of influenza A (H1N1)v was found at Narita International Airport quarantine station on 9 May. The patient was a high school student who had traveled to Canada [1]. The first non-travel case was detected on 16 May in Kobe. On the same day, subsequent cases were found in Osaka prefecture, about 30 km from Kobe [2]. In the beginning, the authorities decided to hospitalise all patients for the purpose of isolation, based on the infection control law [3,4]; consequently 18 patients were hospitalised in Osaka. On 18 May, Osaka prefecture revised its hospitalisation policy based on clinical severity because of the rapid increase of the number of cases. Patients with mild symptoms were treated as outpatients and placed under medical observation at home. By 20 July, 847 cases had been reported in Osaka. Among them, 171 cases had been reported by the end of May. Most patients were adolescents. Of the 171 cases (including 13 who resided in other prefectures) 105 were from one school. This paper summarises the clinical characteristics of influenza A(H1N1)v cases reported in Osaka by the end of May.

Investigation in Osaka

The National Institute of Infectious Diseases (NIID) in Japan started an investigation on 17 May. By then, two clusters had been found in Osaka. One was the previously mentioned school and the other was a nearby elementary school. Although the numbers of cases were increasing day by day, most cases were linked to these two clusters. We focused the NIID investigation on these clusters; the remaining cases were investigated by the local health center.

Case definition

A case of influenza A (H1N1)v is defined as a person with influenza A(H1N1)v virus infection confirmed by real-time RT-PCR.

Cluster 1

- Secondary school: 1,934 students and 143 employees.

- Study population: 105 cases (103 students, 2 teachers), male: 83, female: 22
- Median age: 16 years (range: 13 to 53 years)
- One patient had mild asthma. No patient had a serious underlying medical condition.

Data collection

Direct face-to-face interviews were carried out by the NIID with 17 hospitalised patients, and telephone interviews were performed with 88 home-quarantined patients by school teachers with our technical assistance.

Cluster 2

- Elementary school: 624 pupils (no information on employees).
- Study population: 7 cases (pupils only), male: 2, female: 5
- Median age: 11 years. (range: 9 to 12 years)
- One patient had asthma. No patient had a serious underlying medical condition.

Data collection

Direct face-to-face interviews with the patients and their parents were conducted by the NIID or the local health center.

Other cases

- Study population: 59 cases (31 secondary school students, 7 elementary school pupils, 21 other), male: 33, female: 33
- Median age: 15 years (range: 6 to 48 years)
- No patient had a serious underlying medical condition.

Data collection

Direct face-to-face interviews with the patients (or their parents) were conducted by the NIID or the local health center.

Clinical findings

Symptoms and laboratory data

Fever, cough and sore throat were most frequently observed (Table 1, 2). Most of the cases had clinical features similar to seasonal influenza [5]. 19.8% of cluster 1 and 14% of cluster 2 cases had diarrhoea, while usually fewer (approximately 10%) patients have diarrhoea with seasonal influenza in Japan [6]. Standard blood test results of 12 hospitalised patients showed no results specific to this virus. Cluster 2 included the first cases of the outbreak of influenza A (H1N1)v in children in Japan. No

significant differences were found between age groups in symptoms or severity of illness.

Rapid antigen test

Rapid antigen tests were conducted in the majority of cases. However, information on when this was performed was available for

35 cases only. The sensitivity of the rapid antigen test depended on when the kit was used; it was highest on day 1 (82.4%) and was relatively low on days 0 (75%) and 2 (60%) (Table 3). It is difficult to determine the accuracy of the rapid antigen test kit from the data presented here because of insufficient information (e.g. type of kit used). However, we conclude that the rapid antigen test cannot be used to rule out the possibility of influenza A(H1N1)v virus infections.

TABLE 1

Clinical symptoms of cases of influenza A(H1N1)v in cluster 1 (secondary school n=105), Osaka, Japan, May 2009

Symptom	Number of cases	Proportion of cases (%)
High fever of or above 38°C	94/105	89.5%
Cough	86/104	82.7%
Low grade fever below 38°C, feverish, chills	66/99	66.7%
Sore throat	68/104	65.4%
Nasal discharge, nasal congestion	62/104	59.6%
General fatigue	56/97	57.7%
Headache	50/96	52.1%
Joint pain	32/94	34.0%
Muscle pain	19/96	19.8%
Diarrhoea	19/96	19.8%
Conjunctivitis	6/94	6.4%
Vomiting	5/94	5.3%

TABLE 2

Clinical symptoms of cases of influenza A(H1N1)v in cluster 2 (elementary school, all ≤12 years old, n=7), Osaka, Japan, May 2009

Symptom	Number of cases	Proportion of cases (%)
High fever of or above 38°C	7/7	100%
Cough	7/7	100%
Nasal discharge, nasal congestion	6/7	86%
General fatigue	5/6	83%
Headache	5/6	83%
Sore throat	5/7	71%
Low grade fever below 38°C, feverish, chills	5/7	71%
Joint pain	3/5	60%
Muscle pain	3/5	60%
Diarrhoea	1/7	14%
Conjunctivitis	0/5	0%
Vomiting	0/5	0%

TABLE 3

Rapid kit test results of RT-PCR positive cases of influenza A(H1N1)v in Osaka, Japan, May 2009 (n=35)

Result of rapid test	Number of days from onset				Total
	Day 0	Day 1	Day 2	Day 3	
Positive	9	14	3	1	27
Negative	3	3	2	0	8
Positive rate (%)	75.0	82.4	60.0	100	77.0

Treatment

Among 171 cases in Osaka, antivirals were given to 165 (96%); oseltamivir to 95 (56%) and zanamivir to 68 (40%) of the cases. Further two cases took zanamivir at first, and then switched to oseltamivir. Information on the duration of symptoms under treatment was available for 90 cases. Of these 90 cases, 44 received oseltamivir, 45 zanamivir and one switched from zanamivir to oseltamivir in the middle of clinical course. There was no significant difference in the duration of fever between two medications (oseltamivir 2.32 days, zanamivir 2.36 days, P=0.88, t test). Nevertheless, the results indicated that earlier administration of antivirals contributed to a reduction in the duration of fever (Table 4). However, this result is not enough to completely evaluate the effectiveness of antivirals, because we could not compare these groups to a group without prescriptions. Also, we could not assess whether antivirals reduced severity of illness, since the symptoms of all cases were mild.

Outcome

A few patients had underlying medical conditions, such as asthma. All these cases had a relatively quick and uneventful recovery. Because of the infection control law, 18 patients were hospitalised but all had mild symptoms and had no clinical indication for admission.

Conclusions

In Osaka, the majority of influenza A (H1N1)v cases occurred among healthy children and adolescents. The proportion of patients who had diarrhoea was slightly higher compared to that observed in seasonal influenza patients, but other clinical symptoms resembled those of seasonal influenza. No severe cases occurred. The results of the rapid antigen test were not sufficient to diagnose influenza A (H1N1)v virus infections. Antivirals were given to the majority of the cases. The analysis showed that early antiviral treatment shortened the duration of fever. One limitation of our study was that the methods of collection of clinical information were not standardised. Further studies are necessary to determine the accuracy of rapid antigen tests and the effectiveness of antivirals.

TABLE 4

Prescription day and duration of fever in confirmed cases of influenza A(H1N1)v in Osaka, Japan, May 2009 (n=90)

Prescription day from onset of fever*	Number of cases	Average duration of fever	Standard deviation (SD)	P-value**
Day 0	39	1.90 days	0.821	P < 0.001
Day 1	39	2.51 days	0.970	
Day 2-5	12	3.42 days	1.379	

* Fever ≥ 38°C

** One-way ANOVA

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ENHANCED SURVEILLANCE OF INFLUENZA A(H1N1)V IN GREECE DURING THE CONTAINMENT PHASE

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Following the emergence of a novel influenza virus (influenza A(H1N1)v) with pandemic potential in late April 2009, public health measures were put in place in an effort to contain disease spread in Greece. These included enhanced surveillance of infections due to influenza A(H1N1)v virus, in order to continuously ascertain the situation and guide further public health action. On 15 July, Greece moved to mitigation phase. This report summarises surveillance findings in Greece during the delaying (or “containment”) phase, from 30 April to 14 July 2009.

Introduction

In late April, a number of human cases of influenza due to a novel swine-origin virus strain were identified in Mexico and the United States. This prompted the World Health Organization to declare a “public health emergency of international concern” [1], advising national public health authorities to enhance surveillance activities for influenza. As community transmission of influenza A(H1N1)v virus began to be established around the world, a phase 6 pandemic was declared on 11 June 2009 [2]. As of 19 July the number of confirmed cases worldwide was 137,232 with 779 deaths [3]. On 15 July, Greece moved to mitigation phase. We herein report surveillance findings for cases reported until 14 July.

Public health measures

In Greece, an enhanced surveillance system for influenza A(H1N1)v was set up by 30 April 2009. The main target was travellers coming back from affected areas and their contacts. Information was disseminated to the public through the media, the internet, and by posters and leaflets distributed at international points of entry. Thermal imaging cameras were installed at airports in order to screen incoming travellers for fever. A telephone hotline was used to provide information and guidance to the public, advise health professionals, and guide cases under investigation for influenza A(H1N1)v to designated reference hospitals for clinical evaluation and nasopharyngeal swab collection. Specimens were sent to one of two reference laboratories, one in Athens (Hellenic Pasteur Institute) covering southern Greece and one in Thessaloniki (Aristotle University of Thessaloniki, Second Microbiology Laboratory) covering northern Greece. The diagnosis was confirmed with real-time PCR. In early July a third laboratory

was introduced into the system (University of Athens School of Medicine, Department of Microbiology).

All cases under investigation for influenza A(H1N1)v were managed in the reference hospitals; they were referred there by primary care physicians, from non-reference hospitals, from other healthcare facilities such as airport medical offices, or they could present to the emergency department of a reference hospital on their own. This applied to both Greek and foreign citizens, regardless of insurance status.

Guidelines for case and contact management and for infection control were prepared by the Hellenic Centre for Disease Control and Prevention (KEELPNO). These were sent to hospitals and published on the KEELPNO website (<http://www.keelpno.gr/articles/topic/?id=994>).

Methods

A case definition was adopted, which closely matches the case definition that was agreed upon on the European level [4]. A “case under investigation” was defined as a person meeting clinical criteria (fever >38°C plus symptoms of acute respiratory infection such as cough, dyspnoea, sore throat, etc.) and epidemiological criteria (in the week before onset of symptoms: history of travel to an affected area or history of close contact with a confirmed case during his/her infectious period). A “probable case” was defined as a person meeting clinical and epidemiological criteria plus a positive laboratory result for influenza A of an unsubtypable type. A “confirmed case” was defined as a person tested positive for influenza A(H1N1)v.

However, due to the rapidly changing nature of the pandemic, clinicians were allowed at their discretion to submit samples from patients not fitting the case definition, particularly in regard to the affected areas which were no longer easy to define as more and more countries reported community transmission.

All cases investigated for influenza A(H1N1)v were notified directly to KEELPNO on an individual basis, both by hospital clinicians and by the reference laboratories.

Results

On 18 May, the first case of influenza A(H1N1)v was detected in a 19-year-old male, who had returned from New York city two days earlier. On 26 and 27 May the second and third cases were detected in two students returning from the United Kingdom. These were the first cases imported from another European Union country [5].

By Tuesday 14 July 2009, 1,258 cases had been investigated and a total of 312 (25%) laboratory-confirmed cases had been reported, of whom 208 (66.6%) described a history of recent travel abroad. Of the remaining, i.e. domestically-acquired cases, 23 (7.4%) had been in direct contact with a traveller, 53 (17.0%) had no well-defined epidemiological link to another case, 25 (8.0%) were linked to other non-traveller cases, and for three (1.0%) the mode of transmission could not be ascertained. Figure 1 shows the epidemic curve. A definite increase in the numbers of reported cases with symptom onset from 30 June onwards was observed. Before this date 23% of cases (25 out of 107) were domestic; from 30 June onwards 37% (73 out of 196) were domestic including 23% (46 out of 196) for whom no epidemiological link to another case could be identified.

The mean time from symptom onset to diagnosis of influenza A(H1N1)v infection was 2.8 days (SD 1.6 days). The most frequent countries of travel for travel-associated cases were the United States, the United Kingdom and Australia (in descending order). This probably reflects the high number of people travelling to and from these countries, mainly foreign tourists and Greeks living abroad.

The age distribution was not significantly different between travel-associated and domestically-acquired cases. The mean age was 23.6 years (SD 14.0) and 26.4 years (SD 13.6) respectively. No significant differences were identified between sexes; of the total 312 cases reported, 170 were male (54.5%) and 142 were female (45.5%).

The clinical features of the described influenza A(H1N1)v cases were very similar to those observed in seasonal influenza patients. In the vast majority of cases the illness was mild, and the most prevalent symptoms were fever and a dry cough reported by more than 80% of cases. Sore throat, rhinorrhoea, muscle pain and headache were each reported by about half of the cases. The frequency of diarrhoea and vomiting was low, under 10% of cases, contrary to some reports [6], but consistent with the epidemiological picture across Europe [7]. Hospitalisation is not representative of disease severity, because initially it was used as a means of isolation. No deaths were reported.

Of those reporting fever, 30% had a temperature lower than or equal to 38°C. Thus we estimate that only about 60% of our cases initially fulfilled the clinical criterion of fever >38°C specified in the case definition.

A number of clusters were identified. These included a cluster of five Americans and an Italian guide from a group of tourists visiting Athens in mid-June, and a cluster of 14 American students who fell ill while on a visit in Thessaloniki in early July. There were also clusters of domestic transmission, for example a woman returning from the US who transmitted the virus to her family (four cases)

FIGURE 1

Cases of laboratory-confirmed influenza A(H1N1)v reported in Greece until 14 July 2009, by day of symptom onset and type of transmission, (n=300, missing data for 12 cases)

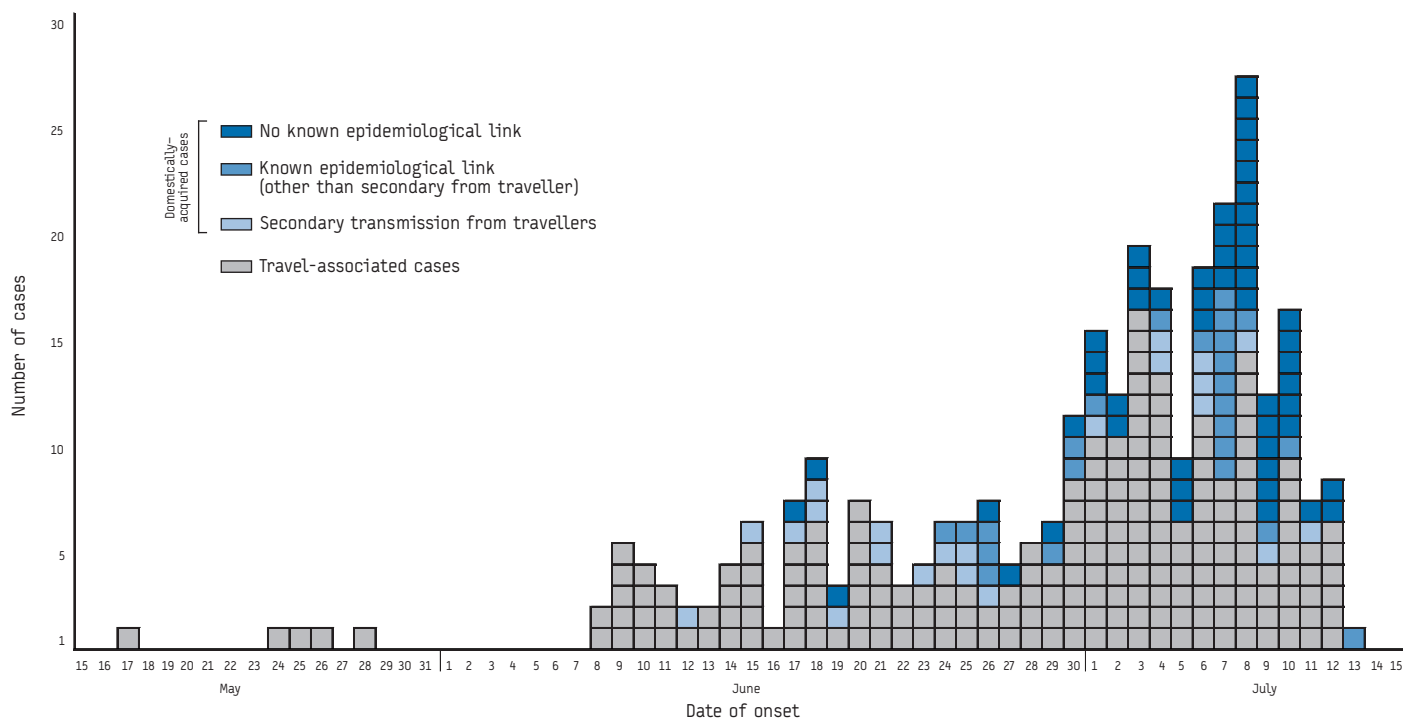


FIGURE 2

Travel-associated influenza A(H1N1)v cases reported in Greece until 14 July 2009, by country of travel (n=206)

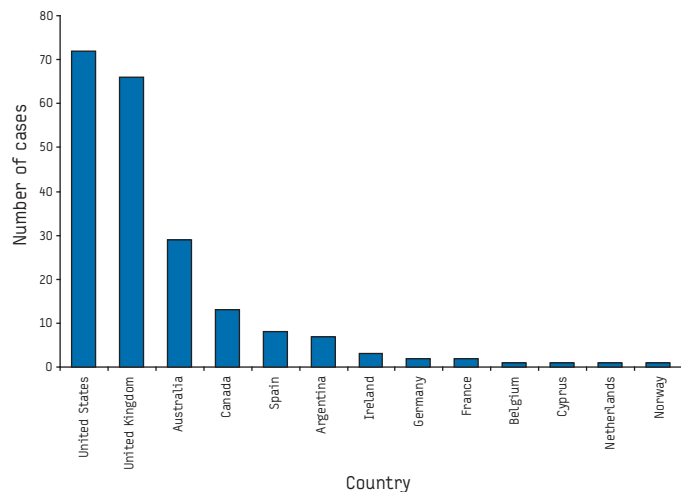
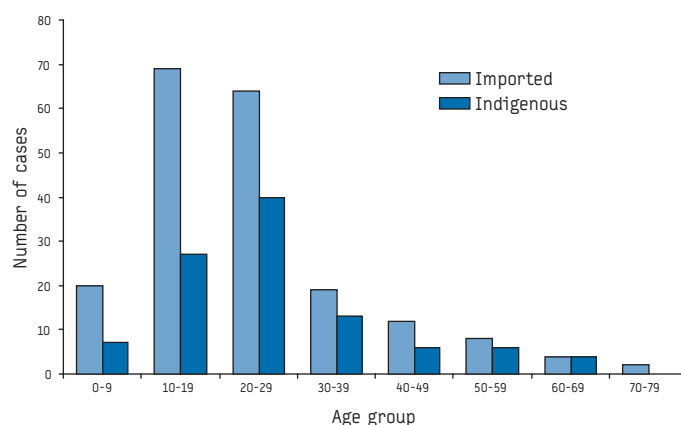


FIGURE 3

Age distribution of influenza A(H1N1)v cases reported in Greece until 14 July 2009, by type of transmission (n=301)



TABLE

Clinical features of laboratory-confirmed influenza A(H1N1)v cases in Greece, reported by 14 July 2009

Symptom	Cases with symptom / Cases for whom information was available	Percentage
Fever	235 / 277	85%
Cough	224 / 274	82%
Myalgia	137 / 262	52%
Headache	136 / 266	51%
Rhinorrhoea	134 / 270	50%
Sore throat	110 / 269	41%
Diarrohea	20 / 266	8%
Vomiting	14 / 263	5%
Dyspnoea	8 / 267	3%
Pneumonia	2 / 269	1%

and a hospital employee with no known exposure to an infectious case who transmitted the virus to his family and one colleague (five cases). Also, a complex cluster of seven cases was detected, starting from an 18-year-old male who had returned from London (Figure 4). One case highly publicised by the media was that of a South American footballer, who plays for a Greek superleague team. He and his family (four cases) fell ill shortly after returning to Greece.

As already mentioned, of the 101 domestically-acquired cases of influenza A(H1N1)v, 53 had no well-defined epidemiological link to another probable or confirmed case. Of these, 13 were airport employees, two were hospital employees, seven worked in bars or restaurants in tourist areas, three worked in tourist-related occupations (a travel agent, a bus driver and a tour guide) and one was a taxi driver. This highlights the rapid spread of the virus and points to occupational exposure by specific risk groups.

However, no influenza A(H1N1)v cases have been identified from sentinel surveillance to date, indicating that overall the circulation of the A(H1N1)v virus in Greece is still limited.

Discussion

These results support the importance of surveillance activities in order to monitor the epidemic and guide public health action by collecting data on epidemiological parameters and mechanisms of transmission in the community.

Several cases were identified during the first two and a half months of enhanced surveillance of A(H1N1)v influenza in Greece. Most of the identified cases concerned travellers from affected countries, especially those with community-wide sustained transmission, and about one in ten cases were secondary cases directly related to travellers. Furthermore, half of the cases without well-identified epidemiological link to another probable or confirmed case were persons related to the tourist industry in Greece. As the number of cases increased, we noticed a gradual increase in secondary and tertiary cases and eventually we identified domestic confirmed cases where no traceable link to a confirmed case was established. The increase in the number of reported cases observed

FIGURE 4

Example cluster of in-country transmission (n=7). The age, sex and date of symptom onset are shown



from 30 June onwards might in part reflect the increased frequency of tourist visits to Greece in this period. This was accompanied by a high number of cases infected in the community during the same period.

A number of conclusions can be drawn from the surveillance results in Greece:

1. Many of the samples collected from clinicians did not fit the definition for “cases under investigation”, either in terms of clinical parameters or in terms of epidemiological criteria. Particularly the “affected areas” proved to be a fast-moving target, as cases were becoming identified from an ever increasing number of countries not previously declared as affected, and cases were tested and identified on the basis of clinical judgement exercised by astute clinicians. Ironically, the fact that clinicians did not abide by the case definition agreed at European and national level allowed us to have a better picture of the evolving epidemic, enabling the detection of the first cases imported from an EU country [5], as well as community-acquired cases.

2. Given the above mentioned shortcomings of the case definition, which tends to systematically ignore patients with local transmission unless contact with a probable or confirmed case can be documented, the actual proportion of domestic cases might be underestimated in our findings.

3. During the summer, a peak influx of tourists is anticipated from countries with higher prevalence of influenza A(H1N1)v to Greece and other southern European countries. Greece is expected to host 13-14 million tourists this year, which is more than the national population of 11 million. This is expected to introduce a large number of infected subjects, and might account for an earlier start of the next influenza season. Furthermore, the advice against travel when a person is ill is apparently not adhered to by the general public. For example, media reported of several tourists who having spent a significant amount on travel expenses were unwilling to delay or postpone their trip and travelled while symptomatic.

4. The continuation of enhanced surveillance of influenza A(H1N1)v, including contact tracing around cases, would be inadvisable as case counts increase. Under such circumstances it is exceedingly difficult to maintain this practice, and its public health benefit is doubtful [8].

In conclusion, we report the cases of influenza A(H1N1)v recorded in Greece during the containment phase, from 30 April to 14 July. In an effort to contain disease spread and in order to continuously ascertain the situation and guide further public health action several measures were taken. However, our results illustrate that the spread of this disease is rapid, transmission in the community could not be prevented, and we anticipate there may be evidence of wider community transmission in our country soon and out of season. In this evolving situation, healthcare and public health resources need to be managed efficiently and sparingly.

As a result, a decision was announced on 15 July to move public health measures in Greece to a mitigation phase, which was communicated as “patient protection phase”. In this phase, contact tracing was discontinued and the recommendation for chemoprophylaxis of all close contacts was withdrawn; chemoprophylaxis is now recommended for particularly vulnerable contacts, at the physician’s discretion. Criteria for testing mainly include severe cases requiring hospitalisation, and selected

cases from clusters of influenza-like illness; testing can be also carried out in special situations according to clinical judgment. Treatment with antivirals is now recommended for cases with severe symptoms or belonging to high-risk groups. Surveillance shifted to: a) notification of laboratory-confirmed severe cases who are hospitalised, b) laboratory reporting of influenza A(H1N1)v cases, c) sentinel surveillance of influenza-like illness, including a clinical and a laboratory component. Surveillance can contribute in an important way to public health decisions.

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Rapid communications

MODIFIED SURVEILLANCE OF INFLUENZA A(H1N1)v VIRUS INFECTIONS IN FRANCE

Influenza A(H1N1)v investigation teams^{1,2}

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Up to early July 2009, surveillance of H1N1 cases in France was based on the identification of all possible cases in order to implement, around each of them, control measures aimed at delaying the spread of the virus. The global dissemination of the virus and the starting community transmission in France led us to shift to a population-based surveillance relying mainly on the identification and investigation of clusters of influenza-like illness, on the identification and individual follow-up of confirmed hospitalised cases as well as on the monitoring, through various sentinel systems, of the use of ambulatory and hospital care for influenza-like symptoms.

Introduction

As soon as the first human cases due to infection with the novel influenza A(H1N1)v virus had been reported to the international community at the end of April, the influenza surveillance in France was adapted in order to actively detect cases. The main objectives of this strengthened surveillance and of the accompanying control measures were to delay the spread of the virus in the country. The first cases were identified in France on 1 May in two travellers returning from Mexico. As of 6 July, 358 cases have been notified. This article describes the clinical and epidemiological characteristics of those cases and the recent changes in the surveillance system made on the basis of this analysis.

Methods

In the initial phase, the surveillance aimed at identifying cases in travellers returning from affected areas in order to promptly implement control measures around each case and to contain the virus spread. A case definition and recommendations for management of the cases and their close contacts were released as early as 26 April and described in a previous paper [1]. Briefly, a possible case was defined as a person with an acute respiratory illness and a history, in the seven days preceding the onset of symptoms, of either travel in an affected area or contact with a possible, probable or confirmed case. In order to capture cases from previously undetected chains of transmission, clusters of acute respiratory illnesses defined as at least three cases in less than a week in close communities were also to be notified.

All symptomatic persons returning from affected areas were advised to call the local hospital-based emergency unit (Centre 15). If the patient was assessed as fulfilling the case definition, the Centre 15 had to call the National Institute for Public Health Surveillance (Institut de veille sanitaire, InVS) for case validation,

which triggered the implementation of the specific A(H1N1)v case management protocol (nasal sampling of the case, systematic hospital-based isolation, antiviral treatment by a neuraminidase inhibitor). Antiviral prophylaxis was recommended for close contacts of probable or confirmed cases, which were asked to observe a home quarantine. Nasal samples had to be sent to one of the 24 and then 31 laboratories which had been authorised by the Ministry of Health to run, in a bio safety level 3 environment, the A(H1N1)v RT-PCR developed by the two National Influenza Reference Centres (CNR). Positive samples were sent to the CNR for confirmation and further investigations.

This case management protocol has evolved over time. Since 26 June, only severe cases, based on the judgment of the treating physician, have to be hospitalised. The antiviral indications have been restricted to severe cases or to cases with an underlying condition that could increase their risk of complication and, as prophylaxis, recommended for their household contacts with an underlying condition. The indications for sampling of possible cases have also been restricted to severe cases, to patients under antiviral

FIGURE 1
Geographical distribution of confirmed cases of influenza A(H1N1)v, France, 26 April – 6 July 2009 (n=358)



treatment whose condition is not improving, to contacts under antiviral prophylaxis developing an influenza-like illness, to cases returning from the southern hemisphere and to at least three cases in each suspected A(H1N1)v cluster.

Case-based epidemiological and virological data have been collected by InVS and its regional epidemiological units (CIRE) through an interactive application (adapted from Voozano®, Epiconcept®), allowing real time exchange of information between InVS, the 16 CIRE, the CNR and the local public health offices in charge of the case management [2]. A clinical follow-up of the confirmed cases has been set up in collaboration with the clinicians in charge of the cases. Daily feedbacks have been posted on the InVS website (<http://www.invs.sante.fr>) since the 26 April. Several

syntheses of the influenza A(H1N1)v epidemiological situation in France have already been published [3,4].

Results

As of 6 July, InVS received 4,867 notifications of possible cases, of whom 4,744 were from mainland France, 66 from the French Caribbean islands, 13 from French Guiana, 22 from the Reunion Island, one from Mayotte, 16 from New Caledonia and five from French Polynesia. All these possible cases were tested and 358 cases were confirmed as due to the A(H1N1)v virus. Twenty six cases were diagnosed as infected by a seasonal influenza virus (12 with H1N1, 14 with H3N2), one as co-infected with (H1N1) and (H1N1)v.

FIGURE 2

Distribution of confirmed cases of influenza A(H1N1)v, by date of onset of symptoms and travel history, France, 26 April – 6 July 2009 (data available for 315 cases)

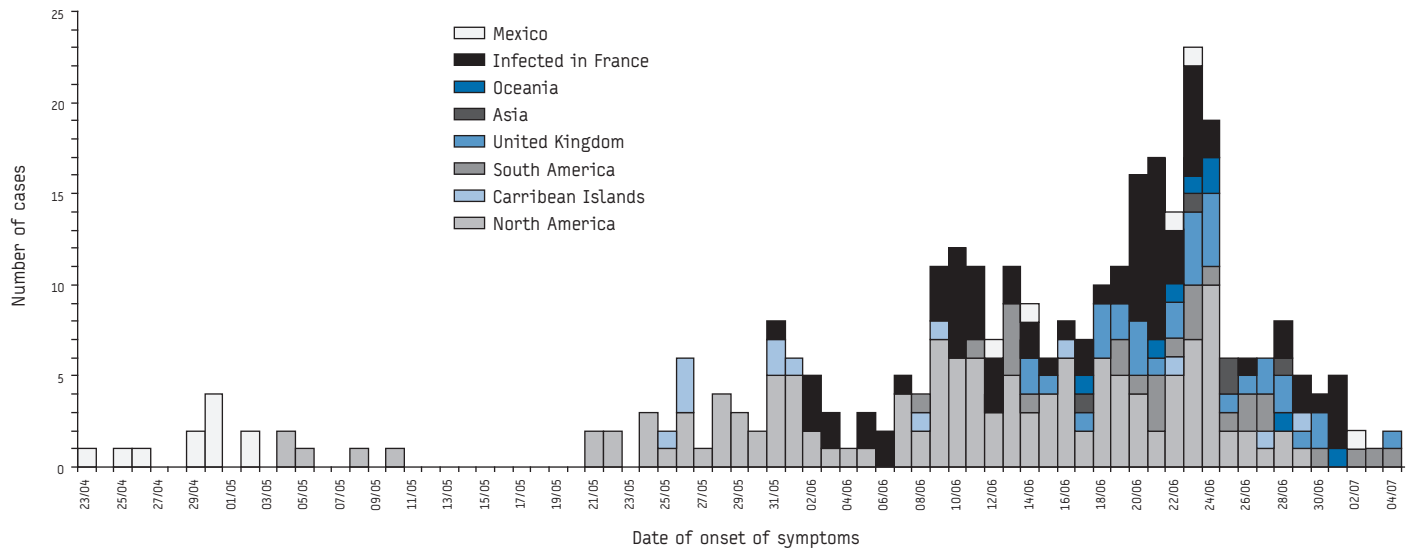
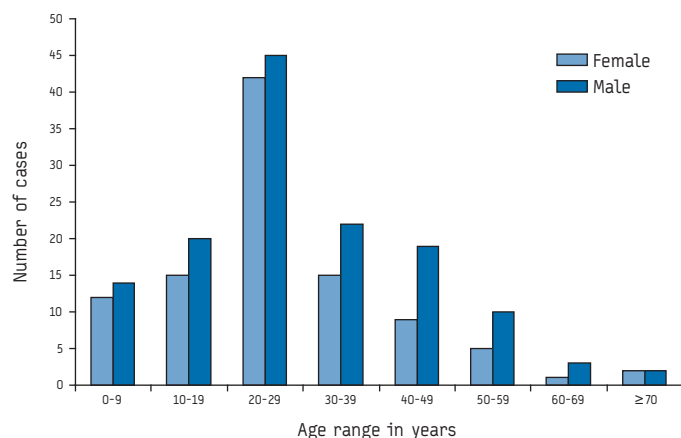


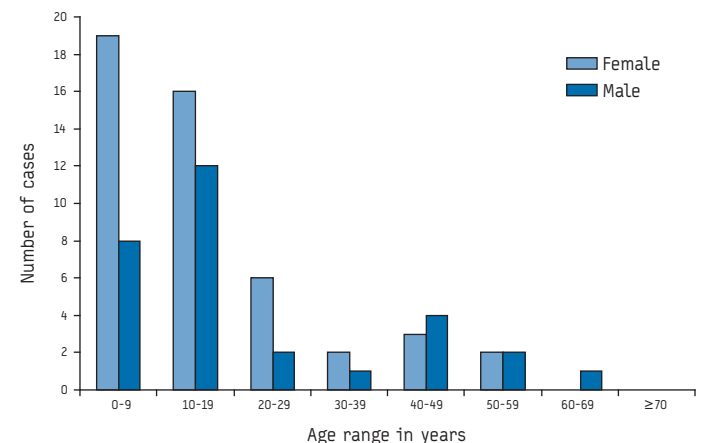
FIGURE 3

Distribution of confirmed cases of influenza A(H1N1)v, by age, sex and travel history, France, 26 April – 6 July 2009 (data available for 335 cases)

3a. Imported cases (n=245)



3b. Indigenous cases (n=90)



Geographical distribution

Of the 358 confirmed cases, 40% came from the Ile-de-France region which includes Paris. Twenty seven cases were from the French overseas territories (Figure 1).

Imported and indigenous cases

The first cases were detected in travellers returning from Mexico, then the United States (US) and Canada (Figure 2). Among the 261 cases in travellers, 16 were from Mexico, 121 from the US, 21 from Canada, 27 from South America, 13 from the non-French Caribbean islands, five from Asia, 24 from Oceania and 33 from the United Kingdom (UK). Data on country of travel was unavailable for one case.

For 92 cases, there was no history of recent travel. For 30 among these, belonging to six clusters, no link, even indirect, to any person travelling abroad was found.

For five cases, the information about a recent travel history was missing.

Clusters

In total, 18 clusters were identified. Eight occurred in schools and eight in households. One episode of domestic transmission occurred in the working environment and one in a rugby team. The size of the clusters includes both confirmed cases and probable cases, defined as cases with an epidemiological link with a confirm case. Within the eight household clusters, two, initiated by travellers, extended to the work place. They involved respectively seven and eight cases. The number of cases in the school clusters varied from three to 67, with an average of 14 cases per cluster. Three large clusters of respectively 17, 32 and 67 cases occurred in one secondary and two primary schools. For only one of these three clusters, a link with travel abroad has been identified. In the rugby team cluster, seven out of 38 persons who had travelled from an affected area were affected.

TABLE

Clinical characteristics of the confirmed cases of influenza A(H1N1)v in France, 26 April – 6 July 2009

Symptoms	Number of cases with the symptom / number of cases with this data available	Proportion of cases (%)
Cough	294 / 336	88%
Fever ($\geq 38^{\circ}\text{C}$)	286 / 333	86%
Myalgia	158 / 330	48%
Asthenia	131 / 326	40%
Headache	86 / 223	27%
Runny nose	83 / 325	26%
Sore throat	72 / 323	22%
Shiver	57 / 319	18%
Joint pain	23 / 324	7%
Conjunctivitis	18 / 326	6%
Shortness of breath	20 / 332	6%
Vomiting	18 / 328	5%
Diarrhoea	14 / 324	4%
Nausea	11 / 326	4%

Demographic characteristics

There were 183 male and 155 female cases (data on sex was not available for 20 cases). The sex ratio male to female was 1.2. Age of the cases ranged from 7 months to 77 years, with a mean of 25 years and a median of 23 years. Domestic cases were younger (mean 17 years) than imported ones (mean 28 years) ($p < 0.0001$) (Figure 3).

Clinical characteristics

The clinical characteristics of the cases are shown in the Table. They appear to be similar to those observed in seasonal flu cases.

Two patients were admitted to hospital with bacterial pneumonia, one of them had asthma and required ventilation, but both recovered. No death due to this virus has been identified in France.

Case management

For imported cases who were not symptomatic on their return, the onset of disease occurred on average 1.4 days after their return (range 0 to 6 days). On average, these and the domestic cases notified the relevant healthcare units 1.8 days after the onset of symptoms. The length of stay in hospital for the 96 cases admitted for isolation purpose and for whom this information was available varied between 0 and 7 days (mean and median of 3 days). The two patients hospitalised for pneumonia stayed in hospital 6 and 10 days respectively.

Discussion

The intensive mobilisation of multiple public health stakeholders and health professionals made it possible to set up in a very reactive way a system of surveillance of the first influenza A(H1N1)v cases at the national level. This surveillance allowed the collection of clinical and epidemiological information on cases and the implementation, around each case, of control measures in order to slow down the spread of the virus.

It is not possible to estimate the exhaustiveness of this surveillance. It is likely that mild cases have not been systematically identified. However, the absence of large clusters, up to early July, suggests that the system was capable of preventing sustained chains of transmission from the initial imported cases.

The follow-up of imported and secondary cases and the results of the cluster investigations were essential indicators of the level of indigenous transmission, allowing the adaptation of the control measures to the evolving epidemiological situation. Similarly, the decreasing average age over time reflects the change over time of the main pattern of transmission from sporadic cases in travelling young adults to secondary transmission in families and schools

The identification, at the beginning of July, of several clusters of significant size, some of them without any identified link with a travel abroad, indicated the occurrence, at least in some French regions, of a, though still limited, transmission in the population. This, together with the global spread of the virus, which made it superfluous to update the list of affected countries, led to the decision, released on 8 July, to modify the definition of a possible case by removing any reference to a return from an affected area. At the same time the case-based surveillance was replaced by a population-based surveillance relying mainly on the identification and investigation of clusters of influenza-like illness, on the identification and individual follow-up of confirmed hospitalised

cases as well as on the monitoring, through various sentinel systems, of the use of ambulatory and hospital care for influenza-like symptoms.

Regarding the overall response to the pandemic, these important changes in surveillance methods signed the transition from a delaying to a mitigation strategy. Indeed, between 7 and 23 July, 22 new clusters were identified, including 193 cases of whom 59 were confirmed. For 16 of these 22 episodes, no link with a travel abroad has been identified.

Our data show that the spread of the virus in the community occurred later than in neighbouring countries such as Spain or the UK [4,5]. Comparative analysis of surveillance data between countries, in connection with the respective methods of case management, could help to investigate this difference.

The new surveillance procedures, which include the detection and investigation of clusters, will contribute to further characterisation of the dynamic of the virus spread in France and will be used to better describe mechanisms and parameters of transmission.

*The InVS investigating team is composed of more than 90 members of staff of the Institut de Veille Sanitaire and its regional units (Cellules Interrégionales d'Epidémiologie [CIRE]), and it was constituted to manage the response to the epidemic, to assess suspected cases and to regularly update international information.

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HOW THE MEDIA REPORTED THE FIRST DAYS OF THE PANDEMIC (H1N1) 2009: RESULTS OF EU-WIDE MEDIA ANALYSIS

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The European Centre for Disease Prevention and Control (ECDC) commissioned an in-depth review of European media coverage of the opening days of the pandemic (H1N1) 2009. A total of 3,979 articles were collected from 31 European countries in the period 27 April until 3 May 2009. National and international public health authorities were by far the leading source of information on the new virus. They were identified as the main source of information in 75% of the articles analysed. 94% of the articles were either neutral, relaying factual information (70%), or expressing support for the authorities' handling of the situation (24%). These results seem to vindicate the communication strategy adopted by the public health authorities.

Introduction

One of the key principles of the World Health Organization's (WHO) Outbreak Communication Guidelines is that public health authorities need to "announce early" – i.e. engage with the media proactively as soon as they become aware of a major public health event, such as the emergence of a new virus [1]. The rationale for this advice is that, in the modern era of 24 hour media and instant international communication, news travel fast. No major development stays secret for long. Unless the authorities rapidly establish themselves as the main source of reliable information, the media will report rumours and speculation.

On Monday 27 April the European Centre for Disease Prevention and Control (ECDC) placed an order with its media monitoring contractor to collect and analyse articles in the European media relating to the new influenza virus that had just emerged in North America. The aim of the study was to capture a Europe-wide picture of how the media reported the opening days of the new pandemic. WHO, and national public health authorities, largely acted in accordance with the Outbreak Communication Guidelines. Therefore the study can also cast light on the effectiveness of the "announce early" strategy.

Methods

Articles were collected by the contractor's offices across Europe from the top three national newspapers and the website of the main broadcaster in each country. A total of 124 sources were monitored. The 31 countries surveyed were the 27 European Union (EU) Member States plus the four European Free Trade Association (EFTA) countries (Iceland, Liechtenstein, Norway and Switzerland).

TABLE 1

Articles related to pandemic (H1N1) 2009 published from 27 April to 3 May 2009, breakdown by country (n=3,979)

Country	Number of articles
United Kingdom	1,070
Norway	234
Spain	233
Switzerland	217
Denmark	209
Germany	206
Greece	165
Ireland	143
Italy	140
Austria	129
Netherlands	118
France	117
Luxembourg	105
Portugal	104
Sweden	97
Finland	91
Lithuania	81
Belgium	73
Czech Republic	70
Poland	63
Romania	55
Hungary	53
Iceland	51
Bulgaria	50
Malta	28
Cyprus	23
Estonia	14
Liechtenstein	14
Slovakia	13
Slovenia	7
Latvia	6
Total	3,979

TV and radio were not included in the survey due to the high cost of monitoring these media.

The search was performed for media articles that either mentioned the term “swine flu” or which were about the emergence of a new type of influenza in the United States and Mexico. The articles were to be analysed in terms of the main source of information being reported in the story: was it from international or national authorities; was it from academic experts or non-governmental organisations? In addition, if the source quoted was a national authority, was it the authority of the country of the media report or another country? Which spokespeople were being most widely quoted in the media?

FIGURE 1
Articles related to pandemic (H1N1) 2009 published in 31 European countries, by date of publication from 27 April to 3 May 2009 (n=3,979)

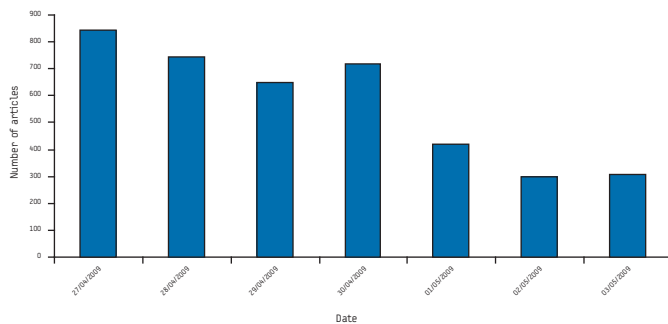
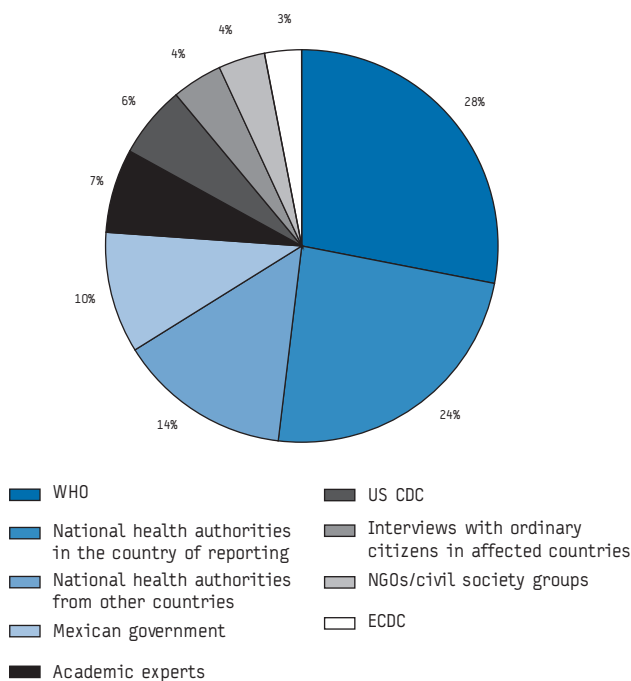


FIGURE 2
Institutions/organisations mentioned in relation to pandemic (H1N1) 2009, articles published in 31 European countries, 27 April to 3 May 2009



The messages featured in the story were also evaluated to see whether articles were supportive, critical or neutral concerning the actions of the authorities.

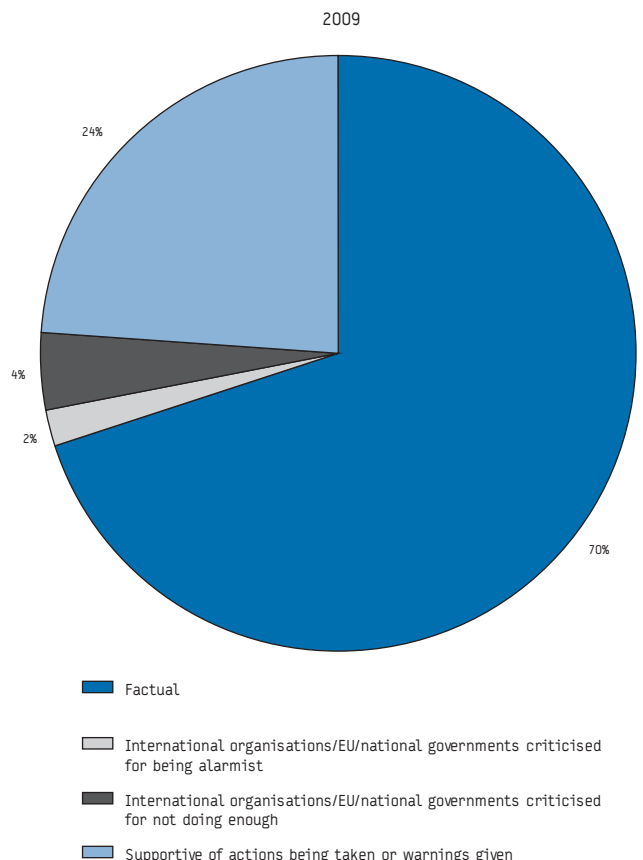
The contractor used was an international media monitoring company. The same company has been conducting Europe-wide monitoring and analysis of the impact of ECDC’s media activities since 2006, so their analysts have some familiarity with infectious disease issues.

In early 2009 ECDC used this contractor to conduct an analysis of all health-related stories published in the media of 33 European countries (27 EU Member States plus Croatia, Former Yugoslav Republic of Macedonia, Iceland, Liechtenstein, Norway and Turkey) between 15 January and 15 February. Some of the data from this study is used for comparative purposes in this article.

Results

For the week 27 April – 3 May 2009, a total of 3,979 articles that mentioned the new influenza A(H1N1)v virus were identified (Table 1). Of these articles, 3,463 were from media in the EU 27 countries. To put this figure in perspective, an earlier survey of all health-related stories found a total of 2,824 articles in the EU 27 media during a period of one month (15 January – 15 February 2009).

FIGURE 3
Tone of coverage related to pandemic (H1N1) 2009, articles published in 31 European countries, 27 April to 3 May 2009



The highest number of articles (842) was recorded on 27 April, the day WHO raised the level of influenza pandemic alert to phase 4 (Figure 1). There was a smaller, though still large, peak of the number of media articles on 30 April (717 articles). This appears to be linked to WHO's announcement of pandemic alert phase 5 at 22:00 Central European Time on 29 April: many of the European media reports about this were published on 30 April. Media interest dropped considerably after 30 April.

National and international public health authorities were by far the leading source of information on the new virus. They were identified as the main source of information in 75% of the articles analysed (Figure 2). WHO was the main source of information in nearly a third of articles (28%).

70% of the articles surveyed were found to be factual accounts of the situation. A further 24% of the articles were supportive of the actions taken by the authorities (Figure 3).

During the week surveyed, the most widely quoted spokesperson in the European media was the Mexican Minister of Health, José Ángel Córdoba (Table).

Discussion

The dominance of public health authorities as sources of information (75% of articles) appears to vindicate the strategy of announcing early. The fact that 70% of articles were factual would seem to show that if the media are provided with authoritative and reliable information they will report it in a balanced way. And, indeed, they will give it greater prominence than rumours or speculation.

The low number of articles critical of the authorities (6%) seems to indicate that they succeeded in establishing a relationship of trust with the media. The fact that the critical articles were almost evenly split between commentators saying the authorities were not doing enough, and commentators saying they were doing too much may be an indication that they got the response about right.

It is interesting to note the high prominence of the Mexican and United States health authorities as sources of information in Europe during the period surveyed (10% and 6% of articles (Figure 2).

This emphasises the international nature of news relating to the pandemic. Comments made by spokespeople from WHO and by the European Commissioner for Health, Androulla Vassiliou, were also widely reported.

Many more articles were found in the United Kingdom than in other countries, although the number of sources analysed was equal. This is consistent with the findings of the earlier study of 15 January – 15 February which showed greater interest by the main United Kingdom national media in health-related stories than national media in other countries.

Conclusion

Proactive engagement with the media by international and national public health authorities resulted in factual, non-alarmist reporting of the first stages of the pandemic (H1N1) 2009.

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TABLE 2

Prominent spokespeople mentioned in articles on pandemic (H1N1) 2009, published in 31 European countries, 27 April to 3 May 2009

Spokesperson	Number of articles
José Angel Córdoba, Minister of Health, Mexico	281
Keiji Fukuda, World Health Organization	152
Barack Obama, President of the United States	135
Androulla Vassiliou, European Union Commissioner for Health	133
Margaret Chan, Director-General of the World Health Organization	131
Nicola Sturgeon, Scottish Deputy First Minister and Cabinet Secretary for Health and Wellbeing	97
Richard Besser, United States Centers for Disease Control and Prevention	92
Trinidad Jiménez, Minister of Health and Social Policies of Spain	78
Alan Johnson, United Kingdom Secretary of State for Health	76
Felipe de Jesús Calderón Hinojosa, President of Mexico	65

Rapid communications

EPIDEMIOLOGIC ANALYSIS OF THE LABORATORY-CONFIRMED CASES OF INFLUENZA A(H1N1)v IN COLOMBIA

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From 2 May to 16 July 2009, a total of 183 laboratory-confirmed cases of influenza A(H1N1)v were reported in Colombia, 117 (63.9%) of these had travelled outside the country. Hospital admission was necessary in 26 (14.21%) cases and seven patients died (fatality-case ratio: 3.8%). The infection affected younger age-groups and the symptoms most frequently reported were cough, fever and sore throat. Our findings are consistent with recent reports from other countries.

Background

Since the first human cases of influenza A(H1N1)v were identified in Mexico and the United States, a rapid spread of this infection has been observed across the world [1,2]. On 11 June 2009, the World Health Organization declared influenza pandemic [3]. On 24 April 2009, the Colombian public health authorities implemented the National Plan for Prevention and Control of Pandemic Influenza and they reported the first cases in travellers including a group of athletes returning from a sporting event in Orlando, United States. This paper describes the main demographic and clinical characteristics of the first cases of influenza A(H1N1)v in Colombia reported during the period from 2 May to 16 July, 2009.

Methods

A suspected case was initially defined as a patient with acute respiratory symptoms and a history of travel to Mexico, United States or any other affected country within seven days before the onset of symptoms or a history of close contact with a confirmed or probable case. However, this definition has been updated due to the rapid spread of infection and the presence of laboratory-confirmed cases in patients who had not travelled outside the country. The current definition of suspected case includes history of travel in any affected country or acute respiratory illness requiring hospitalisation. A probable case is defined as an individual with an acute febrile respiratory illness who is positive for influenza A but classified as undetermined for the new virus by using a specific Real Time-PCR (rRT-PCR) from CDC (protocol reference: I-007-005). A confirmed case is defined as a patient with acute respiratory symptoms who tested positive for influenza A(H1N1)v using the specific rRT-PCR. In a few patients, the presence of the virus was confirmed by gene sequencing [4,5].

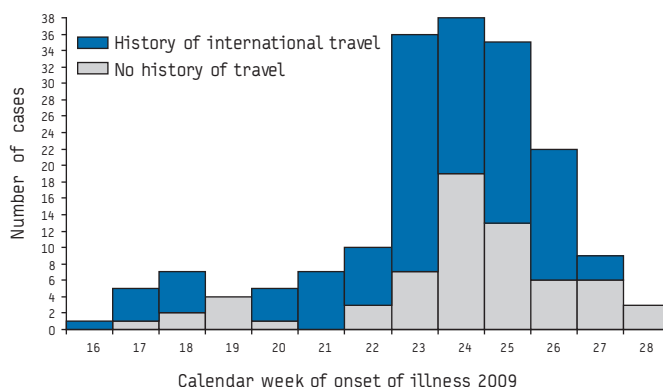
Demographic, clinical, and epidemiologic data of patients meeting these criteria for surveillance were sent to the National System of Public Health Surveillance (SIVIGILA) by public and private

hospitals. This information was validated using photocopies of the clinical records if they were available and face-to-face or telephone interviews of the patients (or their families) who were diagnosed as having the infection. Respiratory samples by throat swabs from patients with respiratory symptoms who had been defined as suspected cases of this virus were tested by rRT-PCR. In some of the patients who died, tissue samples (lung, trachea and bronchia) were also collected and analysed. Additionally, in a few patients, direct immunofluorescence (DIF) test has also been used in order to evaluate concomitant infection of other respiratory viruses such as seasonal influenza A or B virus, respiratory syncytial virus, parainfluenza virus (1, 2 and 3) and adenoviruses.

Categorical variables were presented as percentages and Pearson's or Fisher's exact tests were employed to compare groups. Quantitative variables were statistically tested for the normality of distribution by using the Shapiro-Wilk test. A non-normal quantitative variable was summarised as median and interquartile range (IQR) and two medians were compared using the Wilcoxon rank-sum test. P-values

FIGURE 1

Number of laboratory-confirmed cases of influenza A(H1N1)v by week of onset and history of travel, Colombia, reported 2 May - 16 July 2009 (n=182*)



Note: The first patient was a woman returning from Mexico whose onset of symptoms was on 14 April (week 16).
*One patient (in week 23) was excluded because of unknown history of travel.

less than 0.05 were considered as statistically significant.

Results

On 2 May 2009, the first confirmed Colombian case of influenza A(H1N1)v was reported. By 16 July, 183 cases have been confirmed (including four cases confirmed by gene sequencing). Of these, 96 (52.4%) were men. The distribution of cases by week of onset of symptoms is shown in Figure 1. A history of travel outside the country was found in 117 (63.9%) patients, most of them had travelled to United States (n=71), Argentina (n=12), México (n=7) and Chile (n=7). In 65 (35.5%) confirmed cases there was no history of travel outside Colombia and for one patient this information was not available. The majority of cases were from the provinces of Bogotá, Valle, Antioquia and Atlántico.

FIGURE 2
Number of laboratory-confirmed cases of influenza A(H1N1)v by age group and history of travel, Colombia, reported 2 May - 16 July 2009 (n=182*)



*One patient who was nine years old was excluded because of unknown history of travel

TABLE

Distribution of laboratory-confirmed cases of influenza A(H1N1)v by sex and clinical manifestations, Colombia, reported May 2 - July 16 2009

Symptoms	Female		Male		Total		p-value
	Cases	%	Cases	%	Cases	%	
Fever (n=180)	75	87.2	78	82.9	153	85.0	0.427
Cough (n=181)	84	96.5	92	97.8	176	97.2	0.672*
Sore throat (n=177)	65	76.4	68	73.9	133	75.1	0.694
Headache (n=177)	67	78.8	61	66.3	128	72.3	0.063
Myalgia (n=177)	49	57.6	58	63.0	107	60.4	0.463
Shortness of breath (n=178)	44	51.1	37	40.2	81	45.5	0.175
Nasal discharge (n=176)	63	74.1	63	69.2	126	71.5	0.473
Malaise (n=173)	25	30.1	24	26.6	49	28.3	0.614
Conjunctivitis (n=176)	9	10.7	11	11.9	20	11.3	0.795
Diarrhea (n=180)	6	7.2	4	4.4	10	5.7	0.523*

Note: n indicates the number of cases who provided information on the particular symptom. Three children aged less than one year were discarded for calculating the proportion of symptoms related to pain and malaise.

*Fisher's test was used.

The median age of cases was 27 years (IQR: 17-38). Cases ranged in age from 0 to 72 years and 80% of cases were aged less than 40 years. There were no differences in the median of age of cases by sex (women: 28 years; IQR: 18-39; men: 25 years, IQR: 16.5-36.5; p=0.24). The distribution of laboratory-confirmed cases of influenza A(H1N1)v by age group and history of travel is shown in Figure 2.

The clinical manifestations are listed in the Table. Headache and shortness of breath were observed more frequently in women than in men, but these differences were not significant. The symptoms most frequently reported included fever, cough, sore throat, nasal discharge and headache (n=78; 84.8%).

Twenty six patients (14.2%) were admitted to hospital because of complications. Patients who experienced shortness of breath were more likely to be hospitalised than those without this symptom (28.4% and 2.1%, respectively; p<0.001) while patients who reported headache were less likely to be hospitalised (p=0.031). Seven patients who were hospitalised died, including five women. Only two of the fatal cases had underlying medical conditions, including obesity (n=1) and underweight (n=1). The case-fatality ratio was 3.8%.

The medical complications related to hospitalisation and deaths were acute respiratory failure, pneumonia, hypoxia, pneumothorax, acute tracheitis, tracheobronchitis and sepsis. No influenza A(H1N1)v-related deaths have been reported in pregnant women.

The analysis of the first eight cases who have also been tested for other respiratory viruses showed coinfection of influenza A(H1N1)v with parainfluenza type 1 and influenza B viruses in one patient, and with parainfluenza type 3 virus in another patient, while the remaining six were negative.

Discussion

Our results show that 35% of laboratory-confirmed cases had no history of travel outside the country which is an evidence of local transmission. Data also suggest that young people were affected more often than older people. It is very noticeable that the proportion of people younger than 40 years of age among the first 40 cases

reported was the same as in the dataset analysed here (80%) but, in the rest of the cases, the infection has expanded the age range from 40-54 to 40-72 years.

The age distribution of cases was similar to that observed by researchers in other countries [6,7]. Our number of confirmed cases is relatively low and we were unable to find any significant differences between sexes. Clinical manifestations reported by our patients were similar to those described by other authors [7,8].

The majority of fatal cases had no underlying medical conditions. Obesity has recently been considered as a possible risk factor for severe disease [9]. This condition was found in one of the fatal cases. Finally, we considered that one reason for the relatively high case-fatality ratio observed in this dataset is that we took into account only the laboratory-confirmed cases.

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PANDEMIC INFLUENZA A(H1N1)v VIRUSES CURRENTLY CIRCULATING IN NEW ZEALAND ARE SENSITIVE TO OSELTAMIVIR

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New Zealand, like other southern hemisphere countries with a temperate climate, has been in the winter period with seasonal influenza activity. New Zealand has also experienced a dramatic increase in the number of cases of pandemic influenza A(H1N1)v virus. Early reports from the northern hemisphere at the beginning of the pandemic showed that the virus was sensitive to the antiviral drug oseltamivir. In this study we report that pandemic influenza A(H1N1)v viruses currently circulating in New Zealand are sensitive to oseltamivir, but seasonal influenza A(H1N1) viruses – the co-circulating predominant seasonal strain, is resistant to oseltamivir.

Since the declaration of a pandemic by the World Health Organisation on 12 June 2009, New Zealand has seen a surge in the number of cases of pandemic influenza A(H1N1)v. As of 16 July 2009, there have been 2,107 laboratory-confirmed cases in New Zealand and 10 deaths; the actual number of infections is certainly much higher. Like other southern hemisphere countries with a temperate climate, New Zealand entered the winter period with seasonal influenza activity. The national influenza surveillance system detected co-circulation of pandemic A(H1N1)v virus and seasonal influenza strains. Infection with pandemic A(H1N1)v has rapidly outnumbered seasonal influenza viruses within just a month [1].

The current recommended antiviral drug for treatment of pandemic A(H1N1)v is the neuraminidase inhibitor oseltamivir (Tamiflu®). Oseltamivir has been used in New Zealand to limit entry and spread of the virus since an initial incursion on 26 April 2009, for the treatment of quarantined cases and as prophylaxis for close contacts during the containment phase, and now mainly for the treatment of cases during the management phase.

Surveillance for oseltamivir-resistance in pandemic A(H1N1)v viruses currently present in New Zealand was undertaken using a fluorometric neuraminidase inhibition assay on cultured viral isolates (n = 20) from MDCK and MDCK-SIAT1 cells [2,3]. This assay determines neuraminidase activity using a fluorogenic substrate in the presence of increasing concentrations of oseltamivir. The 50% inhibitory concentration (IC₅₀) is the value at which neuraminidase activity is inhibited by 50%. All pandemic A(H1N1)v viruses were identified as being susceptible to oseltamivir, with IC₅₀ values ranging from 0.183 nM to 0.745 nM (Table). Sequencing of the

neuraminidase gene of 10 viruses showed that none harboured the H275Y mutation (N1 numbering) that is known to confer oseltamivir-resistance. Sequencing of the M2 (matrix) protein from four of the cultured isolates showed that these viruses contain the S31N mutation in the M2 protein that confers resistance to the adamantane class of anti-influenza drugs. This data are in agreement with previously published findings on antiviral drug resistance for pandemic A(H1N1)v viruses [4].

In conjunction, oseltamivir-resistance in the predominant seasonal influenza A(H1N1) that is co-circulating with pandemic A(H1N1)v in 2009 was determined. Seasonal A(H1N1) viruses (n = 24) showed 100% incidence of oseltamivir-resistance with IC₅₀ values ranging from 305 nM to 7912 nM (Table). This represents a 1,400-fold increase from the mean IC₅₀ = 0.94 nM detected for previous oseltamivir-sensitive viruses in New Zealand from before 2008 (unpublished data). Sequencing of the neuraminidase gene (n = 10), and restriction fragment length polymorphism analysis [5] (n = 28) in seasonal A(H1N1) viruses revealed that viruses contain the H275Y mutation (N1 numbering) and share a high level of sequence identity with other seasonal A(H1N1) oseltamivir-resistant viruses that were first detected in Norway in January 2008 [6].

These data show that the use of oseltamivir will be effective for the treatment of pandemic A(H1N1)v infection, but will not be effective for the treatment of seasonal A(H1N1). Surveillance for oseltamivir-resistance in pandemic A(H1N1)v is important given that oseltamivir is one of the few pharmacological interventions

TABLE

Sensitivity to oseltamivir (Tamiflu) of influenza viruses isolated in New Zealand from January to July 2009

Influenza type	Seasonal A(H1N1)	Pandemic A(H1N1)v
Number of viruses	25	20
Mean IC ₅₀ (nM)	1,399	0.372
IC ₅₀ standard deviation	1,990	0.145
Minimum IC ₅₀	305	0.183
Maximum IC ₅₀	7,912	0.745

available before an effective pandemic vaccine becomes widely available. In addition, the presence of oseltamivir-resistant seasonal A(H1N1) viruses co-circulating in the community demonstrates that influenza can be resistant to neuraminidase inhibitors without any apparent compromise in fitness or transmissibility. Close monitoring of antiviral susceptibility of pandemic A(H1N1)v is of increasing importance given the three recent isolated cases from Denmark, Japan and Hong Kong which are oseltamivir-resistant [7]. Furthermore, New Zealand faces a unique challenge where the oseltamivir-resistant seasonal A(H1N1) strain and oseltamivir-sensitive pandemic A(H1N1)v are co-circulating in the community, thus having the potential for re-assortment.

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COMPLIANCE AND SIDE EFFECTS OF PROPHYLACTIC OSELTAMIVIR TREATMENT IN A SCHOOL IN SOUTH WEST ENGLAND

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School closure along with mass prophylactic oseltamivir treatment of pupils have been used in England and elsewhere to contain school outbreaks of influenza A(H1N1)v. We evaluated the protective effect, compliance with and side effects of oseltamivir chemoprophylactic treatment with a ten-day course of 1x 75mg given to 11-12-year-old pupils in one school year in a secondary school in South West England closed for ten days in response to a symptomatic laboratory-confirmed pupil. We distributed a questionnaire to pupils in the affected school year in class after the school had re-opened. Questions included symptoms of flu-like illness, compliance with chemoprophylaxis and side effects. All present on the day, 248 (93.2%) participated. Compliance with chemoprophylaxis was high, 77% took the full course, 91% took at least seven days. Fifty-one percent experienced symptoms such as feeling sick (31.2%), headaches (24.3%) and stomach ache (21.1%). Although some children were ill with flu-like symptoms, those tested did not have A(H1N1)v infection. Compliance with oseltamivir chemoprophylaxis was high, although likely side effects were common. The burden of side effects needs to be considered when deciding on mass oseltamivir chemoprophylaxis in children especially given that the symptoms of A(H1N1)v influenza are generally mild.

Introduction

Social distancing interventions such as the closing of schools has been considered as a means to slow down epidemic spread of a

novel influenza virus and models have been created which suggest that it could be effective [1,2]. In addition to school closure, the risk of transmission may be reduced further by giving prophylactic treatment with antivirals like oseltamivir that are active against influenza viruses. However, it is difficult to predict how effective these measures will be during a real outbreak and the evidence is limited [3,4]. Even though children stay away from school, they may still meet in large groups outside school and the effectiveness of antiviral prophylaxis is dependent on compliance with taking the medication. This may in turn be affected by many factors such as, the severity of the perceived threat of disease, the way the offer of treatment is presented and the anticipated and real side effects of the medication. The success of the interventions will also depend on the timing and the transmission properties of the specific virus strain. There have been many outbreaks in schools in different countries including the United States (US) [5] and the United Kingdom (UK) during the current outbreak of influenza A(H1N1)v. The initial policy in the UK has been to consider closing affected schools and to offer antiviral prophylaxis with oseltamivir [6].

On 29 April 2009 the Health Protection Agency South West received confirmation from the Health Protection Agency Centre for Infections that a child who attended a secondary comprehensive school in South West England had tested positive for A(H1N1)v after returning from Cancun in Mexico. The child had attended school while symptomatic on 22-24 April. The school was closed

TABLE 1

Sickness prevalence and absenteeism, school in South West England, May 2009 (n=248)

	Reported sickness (n=answered question)	Absent from school (data provided by school)	Number of pupils that met clinical criteria for a possible case out of those reporting sickness
Week before closure	23 (n=246)	13	5
During closure	37 (n=244)	N/A	11
Week after re-opening	20 (n=242)	11	10

Note: Some children are included in more than one week. Absent from school data calculated from attendance percentages provided by school.

and all other 266 pupils in the same school year as the affected child were offered prophylaxis with Tamiflu® 75mg once daily for 10 days starting on the day confirmation was received. Active surveillance was undertaken for all children in the same school year until seven days after the last exposure after which passive surveillance continued. Symptomatic school contacts were assessed according to the Health Protection Agency recommendations. Three school children and two teachers were identified as possible cases. They all tested negative for influenza A. One of these school children tested positive for parainfluenza virus. The school reopened on 11 May. No other cases associated with the school have been identified since then.

We undertook a survey of compliance with treatment and incidence of side effects and illness among the school children who had been given prophylactic treatment with the aim of informing future public health action in schools.

FIGURE 1
Number of days oseltamivir prophylaxis was taken among those children who did not comply with the full 10 day course, school in South West England, May 2009 (n=56)

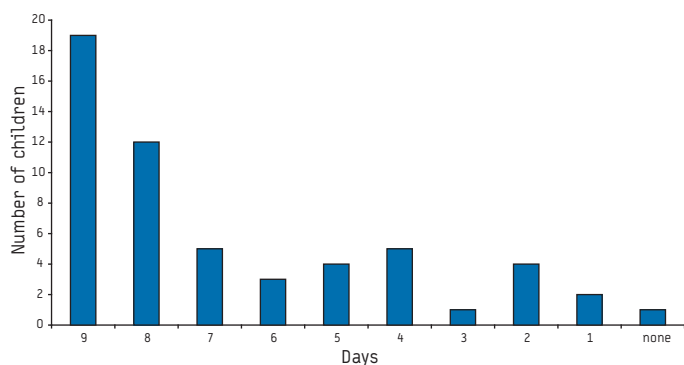
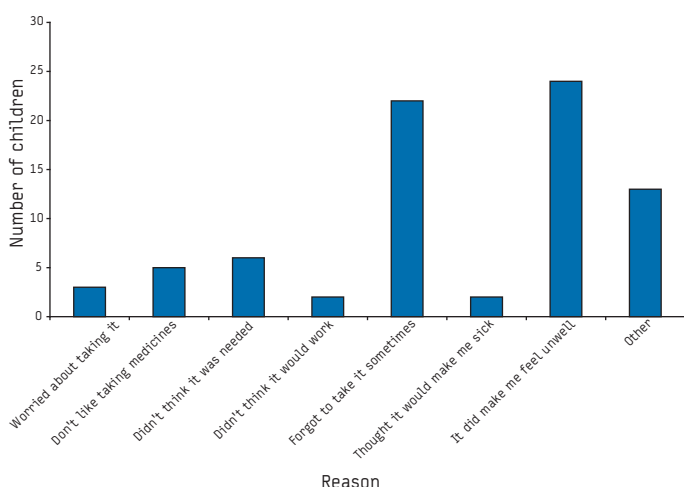


FIGURE 2
Reported reasons for non-compliance with oseltamivir prophylaxis, school in South West England, May 2009 (n=56)



Methods

An electronic anonymised questionnaire designed by the Health Protection Agency South West, with some additional questions incorporated by the school, was administered to children in the relevant year group at the school. This was undertaken on 22 May, in class under teacher supervision, using a web based questionnaire. Parents were informed about the questionnaire and given the opportunity to opt out prior to its administration.

Results

The questionnaire was offered to all year seven pupils present at school (248 children, 93.2% of all year seven pupils including 126 girls and 121 boys (one child did not provide info on sex)) on the 22 May. All children completed the questionnaire.

Sickness and absence from school

Information was obtained about the prevalence of flu-like symptoms among students in the week prior to school closure, during school closure and the week after re-opening (Table 1). Thirty-five children reported at least one flu-like symptom and of these 17 children reported symptoms that could be compatible with the Health Protection Agency's case definition of A(H1N1)v: a history of fever plus two or more other relevant symptoms and whose illness did not start before the index case [7].

The median length of illness among the children who reported symptoms and length of illness that could be compatible with the case definition for a suspected case of influenza A(H1N1)v was four days, range 2-11 days

The most commonly reported symptom was feeling feverish or having chills. Sore throat, cough, runny nose, headache and sneezing were also common. 12 of the 35 children (34.3%) reporting symptoms had a history of hay fever and 10 (28.6%) had asthma.

Compliance with prophylaxis

All children were offered the antiviral prophylaxis. Of the 246 pupils who answered this question, 190 (77.2%) reported that they had taken the full ten-day course, and 91.9% took the medication for at least seven days. Only one child did not take any doses (Figure 1). There was no difference in compliance by sex among those with known sex (n=245). Ninety-eight out of 125 girls (78%)

TABLE 2
Frequency of different side effects among children who took at least one Tamiflu® tablet, school in South West England, May 2009 (n=247)

Symptom	Number of pupils	Percentage (%)
Feeling sick	82	33.2%
Headache	60	24.3%
Tummy ache	52	21.1%
Feeling tired	42	17.0%
Vomiting	27	10.9%
Hard to concentrate	19	7.7%
Diarrhoea	17	6.9%
Skin rash	3	1.2%
Other	15	6.1%

completed the full course compared with 92 of the 120 boys (77%) who answered this question.

Of the 195 children who did not report any illness in the week before or during school closure, 156 (80%) completed the medication while of those 52 who reported having had any influenza-like symptom only 34 (65%) completed the course.

Of the 14 pupils who had disease compatible with the clinical case definition and reported being ill the week before or during school closure only 6 (43%) completed the full course.

In general, the reported reasons for non compliance were most commonly that the tablets made them feel unwell (n=24) or that they forgot to take them (n=22) (Figure 2). Six children reported more than one reason for not taking the tablets. The child who did not take any doses did not specify the reason.

Information on side effects

One hundred and twenty-six children (50.8%) reported that they felt unwell while taking oseltamivir and 125 (50.6%) reported at least one symptom compatible with side effects of oseltamivir therapy. The frequency of reported symptoms are given in Table 2. Many children reported more than one symptom.

There was little difference in compliance between those reporting possible side effects of oseltamivir medication and those who did not. Of the 125 children who reported possible side effects, 94 (75.2%) completed the course, compared with 95 completing the course among those 118 who did not report symptoms (80.5%).

School questions

The school included some questions on satisfaction with the overall management of the incident and homework undertaken during school closure. Of the 228 pupils who answered the question, 159 (69.7%) reported that they thought the swine flu incident had been handled well, 24 (10.5%) did not think so and 45 (19.7%) were undecided. 227 children answered questions on schoolwork during the school closure. Of those who answered, 105 (46.3%) reported not doing any schoolwork at all, 24 (10.6%) did some every day, 98 (43.2) only did schoolwork on some days.

Discussion

We achieved a high participation rate in this survey. All children present at school on the day it was administered completed it. The fact that it was completed in school under supervision during school time was crucial to the high response. This was possible thanks to good working relations between the local Health Protection Agency, the local National Health Service (NHS) and the school, resulting in the high level of satisfaction with the way the swine flu incident was handled.

We believe that it is unlikely that the completion of the survey in school introduced bias and affected the way the pupils answered as the questionnaire was anonymised and, for example, the questions about the amount of homework undertaken while the school was closed appear to have been honestly answered.

The survey results showed that more children reported being ill in the week when the school was closed than the week before and after, and that 17 children reported symptoms that were compatible with the HPA case definition for being a possible A(H1N1)v case.

However, attendance rates provided by the school showed that attendance was almost identical in the week before school closure and the week after reopening (95.3% vs 95.5%) and the affected school year had the highest attendance rates for both weeks. Whether or not the higher numbers of ill pupils in the week when the school was closed signified spread of A(H1N1)v or were due to other reasons is difficult to assess. Those ill may not have been true cases as the symptomatology of A(H1N1)v is not very different from respiratory illness caused by other viruses. The testing done as part of the outbreak investigation found one case of parainfluenza virus and some children reported suffering from asthma and hay fever suggesting that at least some of the reported symptoms were not due to A(H1N1)v infection. The main limitation however is that not all children who reported feeling ill had laboratory tests for influenza. All who reported compatible symptoms during the period of active surveillance (within seven days of last exposure to the case) were tested, but after this period children were advised to contact their own general practitioner (GP) if they developed symptoms. Given that all had been encouraged to seek advice and that all were aware of the outbreak, it is likely that if they presented, they were not tested because their symptoms were mild. The questionnaire did not ask for details of severity. We can not rule out that the high compliance rates with oseltamivir medication may have resulted in the milder symptomatology and negative test results in infected pupils that were tested. A serological study would help to ascertain if there was further spread of disease during school closure.

More than half of those who took the medication reported at least one possible side effect including gastrointestinal symptoms, headaches and tiredness. The reported symptoms are in line with the recognised side effects of oseltamivir prophylaxis although higher in frequency. Information from the manufacturer suggests that when used for prevention purposes 18% of people may experience headaches, 8% tiredness and 1-3% gastrointestinal symptoms [8]. The higher frequencies of reported side effects may reflect a difference between our school population and the population used for the original studies on adverse drug effects in terms of age and other factors. The mean weight of 12-year-old British children is around 40 kg [9]. For pragmatic reasons, a dose of 75mg x1 was used. This dose will have been slightly higher than what is recommended for prevention by the manufacturer for any children under 40 kg, although not higher than the total daily treatment dose. Compliance was poorer among those who reported symptoms of influenza-like illness, but not among those who reported symptoms likely to have been side effects. It may be that the children experiencing influenza-like symptoms attributed them to the medication rather than disease.

To our knowledge this is the first evaluation of oseltamivir chemoprophylaxis in school children in an outbreak of A(H1N1)v and the results can therefore only be compared with oseltamivir chemoprophylaxis during influenza outbreaks with other variants. An Israeli study evaluating the use of oseltamivir prophylaxis during an avian influenza outbreak in a poultry farm reported similarly good compliance with medication, 87.6% in poultry workers, but reported side effects were much more rare, only 1.5% [10]. Our high prevalence of perceived side effects also contrasts the findings in a Cochrane review on the use of neuraminidase inhibitors for preventing and treating influenza in children. The only side effect that was considered more common than with placebo was vomiting [11].

The results of this study suggest that high compliance with oseltamivir prophylaxis can be achieved and that the policy of school closure may be helpful in containing outbreaks of influenza if implemented early. However, the study also shows that a high proportion of school children may experience side effects of oseltamivir medication. It is possible that in some instances children may have attributed symptoms that were due to other illnesses to the use of oseltamivir, however, this is unlikely to account for all the symptoms experienced during prophylaxis. Although the severity of the perceived side effects were not assessed it is likely that most of these symptoms were relatively mild as children continued to take the medication.

The apparent success in containing the school outbreak in this instance could be linked to the absence of community transmission of the virus at the time and the high compliance with chemotherapy in this incident. The reason why compliance was high, despite the high frequency of side effects, may reflect the fact that this was the first school affected by the outbreak in the UK. There was high media attention at the time and reports coming out of Mexico suggested that this novel strain could result in serious disease [12-14].

This study shows that the compliance with prophylactic oseltamivir treatment in the first school closed due to influenza A(H1N1)v in the UK was high and that perceived side effects were common. Side effects need to be taken into consideration alongside other concerns, like the risk of resistance development, when evaluating the policy of mass prophylactic therapy for novel strains of influenza especially when symptoms are generally mild.

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OSELTAMIVIR ADHERENCE AND SIDE EFFECTS AMONG CHILDREN IN THREE LONDON SCHOOLS AFFECTED BY INFLUENZA A(H1N1)v, MAY 2009 – AN INTERNET-BASED CROSS-SECTIONAL SURVEY

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This report describes the results of a cross-sectional anonymised online survey on adherence to, and side effects from oseltamivir when offered for prophylaxis, among pupils from one primary and two secondary schools with confirmed cases of influenza A(H1N1)v in London in April-May 2009. Of 103 respondents (response rate 40%), 95 were estimated to have been offered oseltamivir for prophylaxis, of whom 85 (89%) actually took any. Less than half (48%) of primary schoolchildren completed a full course, compared to three-quarters (76%) of secondary schoolchildren. More than half (53%) of all schoolchildren taking prophylactic oseltamivir reported one or more side effects. Gastrointestinal symptoms were reported by 40% of children and 18% reported a mild neuropsychiatric side effect. The results confirmed anecdotal evidence of poor adherence, provided timely information with which to assist decision-making, and formed part of the body of growing evidence that contributed to policy changes to restrict widespread use of prophylaxis for school contacts of confirmed cases of influenza A(H1N1)v.

Background

During April-May 2009, a number of London schools were advised to close due to confirmed cases of influenza A(H1N1)v in schoolchildren and antiviral prophylaxis (oseltamivir, Tamiflu®; a neuraminidase inhibitor) was offered to close contacts in the school setting. Anecdotal evidence (from family doctors in London) was suggestive of non-compliance (because of side effects) particularly when it was offered to children and adolescents. There was an urgent need to understand and provide preliminary information on adherence to, and side effects from oseltamivir, to assist decisions about strategic direction and operational policy in relation to antiviral use in United Kingdom schools.

The main objectives were: to measure the degree of adherence to oseltamivir; to measure the extent of self-reported adverse drug reactions (ADRs) to oseltamivir; and to describe reported ADRs.

Methods

We conducted a cross-sectional anonymised online survey among pupils from one primary and two secondary schools in London with confirmed influenza A(H1N1)v cases. The schools emailed a weblink to the questionnaire to parents, with a letter describing the study, seeking consent and participation. Parents/guardians were also offered the opportunity to complete the questionnaire with the child (e.g. for younger children).

As the main method of communication of each school with parents or guardians was via email, internet access (email use) was not a decisive criterion in selecting participants. The selection process varied depending on which classes the confirmed cases were in, which year groups had been offered prophylaxis, and on negotiation with school management regarding feasibility. In two schools (one primary and one secondary school) we selected all classes who were offered prophylaxis, i.e. all pupils in the primary school (age range 4-11 years; n=122), and all of one year group in the secondary school (age range 13-14 years; n=68). In the other secondary school, while the whole school was offered prophylaxis, the questionnaire was offered only to pupils in two classes in the year group with the highest attack rate, and pupils in two classes in a year group with no confirmed cases (age range 11-13 years; n=66).

The questionnaire included questions on student class and year group; whether they took any oseltamivir if offered it and for what duration; presence or absence of influenza-like symptoms before taking oseltamivir; other medication taken with oseltamivir; and symptoms after taking oseltamivir (including specific gastrointestinal and neuropsychiatric symptoms). The questionnaire included a section for parental comments.

As preliminary information was required quickly, the weblink to the questionnaire was emailed to parents/pupils on the morning of Thursday 14 May asking for completion by midnight that night. Data from the initial responses was downloaded on Friday 15 May,

and a preliminary report produced. The survey closed at 09.00 on Monday 18 May.

Due to concerns raised by the schools regarding deductive disclosure (i.e. discerning of an individual respondent's identity and responses through the use of known characteristics of that individual), particularly where there were small numbers of cases in a class or school, pupils were not directly asked if they had been prescribed oseltamivir for treatment or for prophylaxis. As previously stated, questions were asked about the presence or absence of influenza-like symptoms, the duration of oseltamivir course taken, and the school year and class of the respondent. This helped to determine those given oseltamivir for prophylaxis. Children without symptoms could not be a case (as they would not meet the clinical criteria for testing) and therefore would have been offered oseltamivir for prophylaxis; those with influenza-like symptoms could be a confirmed case (and offered 5-day treatment course) or a discarded case (and offered 10-day prophylaxis course). Hence, no symptoms or course duration of 6-10 days would imply a course of prophylaxis (according to a tiered weight-based dosing regimen, see Table). In addition, as the specific classes of all cases were known, pupils in other classes could not have been cases.

Results

Response rate

The weblink was sent to 256 schoolchildren, with a final overall response rate of 40% (103/256); 35% (43/122) in the primary school, and 42% (28/66) and 47% (32/68) in the secondary schools respectively.

Adherence to oseltamivir when offered for prophylaxis

Ninety-five schoolchildren (41 in the primary, and 54 in the secondary schools) were estimated to have been offered oseltamivir for prophylaxis, of whom 85 (89%) actually took any. The ten children who took none of the prescribed course were all primary school pupils.

Two thirds (66%, 56/85) of those who took 'any oseltamivir' completed (or said they would complete) a full 10-day prophylaxis course. However, less than half (48%, 15/31) of primary schoolchildren completed a full course, compared to three-quarters (76%, 41/54) of secondary schoolchildren.

Adverse drug reactions (ADRs)

More than half (53%, 45/85) of all schoolchildren taking prophylactic oseltamivir reported one or more side effects. The most frequently reported symptom overall was nausea (29%), followed by stomach pain/cramps (20%) and problems sleeping (12%).

Gastrointestinal side effects (defined as one or more of the following symptoms - feeling sick/nauseous, vomiting, diarrhoea, stomach pain/cramps) were reported by 40%, and almost one in five schoolchildren (18%) reported a neuropsychiatric side effect (one or more of the following symptoms - poor concentration/unable to think clearly, problems sleeping, feeling dazed/confused, bad dreams/nightmares, behaving strangely). A neuropsychiatric side effect was more commonly reported by secondary (20%) than primary (13%) schoolchildren (see Figure).

Parental comments

Comments showed that parents often made their own risk assessment as to the likely benefit of oseltamivir to their child. Despite oseltamivir (Tamiflu®) being recommended by healthcare professionals, parents often appeared sceptical of the need for medication, especially when the indication was to prevent onward transmission rather than give a specific benefit to the individual

asymptomatic child. Many parents questioned the scientific basis of our advice, recognising that prophylaxis would not confer longer lasting immunity or protection. They also raised the possibility that we may be doing more harm than good i.e. in relation to the 'risk' (potential side effects) from oseltamivir compared to the 'risk' from influenza A(H1N1)v. There were also comments on the need to have sufficient information about the type and nature of any potential side effects in order to enable parents to make informed decisions.

Discussion and conclusion

This study was undertaken in the containment phase of the response to influenza A(H1N1)v in the United Kingdom (UK). It provided preliminary information on adherence to, and side effects from oseltamivir in schools; and a useful snapshot of attitudes and behaviours regarding oseltamivir use.

Managing school incidents is always challenging, ensuring communications are appropriate and often managing high levels of anxiety. Containment through interventions at school level is hindered by the high level of mixing between children in schools

TABLE

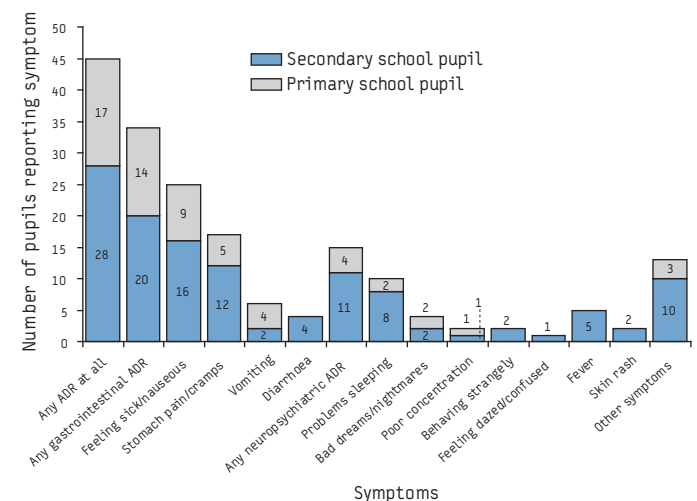
Tiered weight-based dosing regimen for 10-day course of oseltamivir prophylaxis in children

Age	Weight	Dose*
Children aged 1-13 years	<15 kg	30mg once daily
	15-23 kg	45mg once daily
	24-40 kg	60mg once daily
	> 40 kg	75mg once daily
Adolescents > 13 years	—	75mg once daily

*Adjust dose in renal failure: If creatinine clearance (CrCl) <30, reduce dose by 50%

FIGURE

Main symptoms reported by schoolchildren taking oseltamivir for prophylaxis in three London schools, May 2009 (n=85)



ADR = Adverse drug reaction

(siblings in different years and/or different schools, facilities shared with other schools, children involved in complex inter-school networks due to shared after-school activities - formal and informal). Case identification, risk assessment, and organisation of mass prophylaxis will frequently be outside the 48 hours quoted in the literature for the use of oseltamivir for prophylaxis [1]. In addition, little is known about how children adhere to such prolonged treatment (5-day course) and prophylaxis (10-day course).

A key component of influenza therapy and prophylaxis is the possibility for development of resistance. The magnitude and duration of neuraminidase inhibitor concentrations at the site of infection are thought to be an important factor in determining the likelihood of drug resistance arising in influenza viruses [2]. Low drug concentrations which only partly block viral replication and result in suboptimal virus suppression could enhance the risk by providing an environment for drug-resistant virus to emerge [2,3]. In our study, not all who started a course of oseltamivir for prophylaxis completed that course. While some reported discontinuing the course due to side effects, others reported doing so due to concerns about the effectiveness of oseltamivir and its necessity. Such incomplete adherence to the recommended course of oseltamivir could contribute to the development of drug-resistant virus.

The commonest adverse effect reported in the literature on oseltamivir is dose-related nausea [4-8], which occurs twice as frequently (as with placebo) when used as prophylaxis [9]. In controlled clinical trials, approximately 10% of patients reported nausea without vomiting, and an additional 10% experienced vomiting [5,10]. Insomnia has also been reported [5].

In recent years, there have been a number of post-marketing case reports (mainly from Japan) of neuropsychiatric events (such as delirium, hallucinations, confusion, abnormal behaviour leading to injury, convulsions, and encephalitis [4,11]), particularly in children younger than 16 years [4]. While a review of the available information on the safety of Tamiflu® in paediatric patients by the United States (US) Food and Drug Administration (FDA) suggested that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to Tamiflu® in that population, and a coincident period of intensive monitoring of adverse events [4], this prompted the addition of associated precautions to the US product label for oseltamivir [12]. A retrospective cohort study funded by Roche (who make Tamiflu®) noted a higher rate of episodic mood disorders among those aged 17 years and below receiving oseltamivir compared to those who received no antiviral treatment [12].

In our study, more than half of all schoolchildren taking prophylactic oseltamivir reported one or more side effects. The commonest symptoms reported were gastrointestinal, most frequently nausea, as in the published literature [4-8]. Although no serious neuropsychiatric events were described in our study (as have been described in Japanese case reports [4,11]), almost one in five respondents reported a neuropsychiatric symptom, most frequently difficulty sleeping, bad dreams/nightmares and poor concentration, which would impact on school and studying for those concerned. This may be of particular concern to exam-year students (and their parents).

The possibility of group psychological effects leading to an apparent cluster of symptoms has been suggested. The children are socially linked, and social contact may facilitate spread of “psychogenic”

symptoms [13,14], but not typical “biological” symptoms. However, previous reports suggest such symptoms often remit with dispersion of the group [14]. The three schools in our study were closed for the period when children were taking oseltamivir prophylaxis.

Many of the children will have been told to take oseltamivir rather than seeking it out; this may also result in higher self-reported side effects. If it is rumoured that side effects are frequent, students may over-report through a desire to conform. However, while the possibility of “autosuggestion” through discussion of symptoms on Facebook was raised by a parent of one secondary school pupil, there was no increased reporting of similar symptoms from other students in the same class.

While the high level of reported side effects may have had a “psychogenic” component, e.g. children with high anxiety levels (due to the outbreak or due to other factors such as concomitant exams) might somatise and exhibit more nausea and vomiting, or have more difficulty sleeping, comments made by some parents regarding the nature of side effects experienced by their children (particularly in relation to observed disturbed sleep, altered behaviour, and being unusually tearful) are not likely to have been influenced by this. A telephone survey of 1,000 residents (over 18 years of age) of England, Scotland and Wales, carried out between 8 and 12 May just prior to our survey, explored public perceptions, anxiety and behaviour change in relation to the influenza A(H1N1)v outbreak [15]. Results from this survey suggest that anxiety among the general public about the outbreak at this time was low, with only 24% of participants reporting any anxiety and only 2% reporting high anxiety [15].

There are some striking similarities to the literature on adherence to antimicrobial prophylaxis (to prevent inhalational anthrax) among postal workers during the 2001 anthrax incidents in the United States [16,17]. In an environment characterised by uncertainty, and also by changing recommendations for screening or treating at-risk individuals as more was learned during the outbreak investigation, study participants in the anthrax incidents used multiple sources of information and support as they weighed the risk from anthrax against their perceptions of the advantages and disadvantages of antibiotics [16]. Anxiety [18], experiencing adverse events to prophylaxis [18], and following the advice of private physicians [16] who often contradicted public health recommendations regarding antibiotic prophylaxis, were all risk factors for discontinuing anthrax prophylaxis [16]. Changing recommendations were often perceived as conflicting information and advice [16].

In this study also, comments showed that parents often made their own risk assessment as to the likely benefit of oseltamivir to their child. It was suggested, in the comments in our survey, that some parents had on occasion received different advice from other healthcare professionals than that given by the Health Protection Agency. There was also a suggestion of a possible impact of changing recommendations, as in the anthrax studies [16].

A number of limitations apply to our study. The numbers are small. As the survey had to be done quickly, there was limited time for a full negotiation with schools regarding methodological issues, and limited time to give to pupils and their parents to complete the survey (initial responses were requested from pupils and their parents by the end of the same day they received the survey), which may have influenced the low response rate.

Regarding representativeness, the three schools surveyed were

independent (non-state) schools, with a bias towards well educated parents from higher socio-economic groups, who are used to debate/negotiation (using information from multiple sources) before reaching an individual decision. They are thus not representative of the broader UK school population (but perhaps of pupils attending similar schools in London and elsewhere). The low uptake of antivirals seen in our study was also reflected in another outbreak in an independent boarding school in South East England, where estimated uptake of antivirals among those for whom it was recommended was only 48% [19].

However, while there may be sources of bias in the methodology and results, we believe the comments made by parents are legitimate and provide insight into parental attitudes and concerns. As such they are very helpful as they reflect factors which may have an influence on implementation of national policy in future. The use of an online questionnaire format (with internet-aware parents and pupils) enabled this survey to be done quickly, providing timely information with which to assist decisions about operational policy in an evolving incident.

The study findings formed part of the body of growing evidence that contributed to policy change in the UK. Current UK advice is to limit antiviral prophylaxis in schools to the small number of contacts considered most at risk. Further studies are planned in other schools in London and nationally to provide further information about attitudes, including child and parental perception of risks associated with Influenza A(H1N1)v, as well as behaviours and practical implementation of antiviral prophylaxis in the current influenza A(H1N1)v outbreak. In addition, these studies will explore the possible role of psychological mechanisms in generating “adverse drug reactions”.

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COMMUNITY TRANSMISSION OF INFLUENZA A (H1N1)v VIRUS AT A ROCK FESTIVAL IN BELGIUM, 2-5 JULY 2009

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On 6 July 2009 the Belgian enhanced surveillance system for influenza-like illness among travellers returning from influenza A(H1N1)v affected areas detected a case linked to a rock festival which took place on 2-5 July. The health authorities implemented communication and control measures leading to the detection of additional cases. This paper describes the outbreak and its impact on the management of the influenza pandemic in Belgium.

Background

In response to the ongoing influenza A(H1N1)v pandemic, first detected in North America in April 2009 [1], many European countries developed active surveillance systems for influenza-like illness among travellers returning from affected areas [2,3,4,5].

Amplifying events, like school outbreaks of influenza A (H1N1)v infections reported by the United Kingdom (UK) and France [6,7,8] confirmed sustained community transmission [9] and required the surveillance systems to adapt accordingly [5,10].

In Belgium the enhanced surveillance system for influenza-like illness in travellers returning from affected areas [11] detected an outbreak around the "Rock Werchter" festival that took place from 2 to 5 July 2009.

This communication describes the epidemiology of this outbreak and the control measures taken as well as the impact of this event on the management of the current influenza A(H1N1)v pandemic in Belgium.

The index case and initial investigation

The first case found was an Israeli citizen who arrived in Belgium (via London) on 2 July 2009 and visited the festival from 3 to 5 July. He felt sick on 3 July but only sought medical care at the festival, in the Belgian Red Cross facility, on 5 July. The same day respiratory tract swabs were taken from this patient and sent to the National Reference Laboratory for Influenza where influenza A(H1N1)v infection was confirmed by real-time reverse transcription PCR on 6 July. The patient was isolated and treated

with oseltamivir. Four of his friends, considered as close contacts, were also isolated and given post-exposure doses of oseltamivir.

Descriptive epidemiology

Setting

The outbreak occurred at the Rock Werchter festival, one of the four biggest annual rock music festivals in Europe. It lasts four days and can host 80,000 guests at a time. It is estimated that about 69,000 participants attend all four days, which adds up to a total of 113,000 different attendees. Visitors come mainly from Belgium but also from the Netherlands, the UK, and many more countries.

Case definitions

The case definitions used for identifying cases of influenza A(H1N1)v at the Rock Werchter festival are summarised in Table 1.

Outbreak description

We found 12 confirmed cases of A(H1N1)v infection out of a total of 30 people with influenza-like symptoms who were linked to the festival and were tested for influenza A(H1N1)v virus from 2 to 13 July in Belgium.

These cases are shown in the Figure, together with all confirmed cases reported in Belgium from 12 May to 13 July 2009 by date of onset of symptoms. Note that the Interministerial Influenza Coordination Committee decided to stop the enhanced surveillance system on 13 July, which may explain the smaller number of cases for whom symptoms onset was 11 or 12 July.

The mean age of cases linked to the festival was 23 years (range 18-45) and median 20 years. There were nine men and three women among the cases (ratio male: female = 3).

Taking the index case as the common source, the generation interval for secondary cases ranged from 3 to 7 days (median four days)

After a request to the UK, Spain, Germany, France and the Netherlands, an additional case linked to Werchter was notified by

the Dutch surveillance system: a 22-year-old man with onset of symptoms on 6 July 2009. Luxembourg reported another laboratory-confirmed case: a 20 year-old man with symptoms onset on 7 July.* These two cases were not included in our analysis.

Clinical epidemiology

The distribution of symptoms among the cases is illustrated in Table 2. These were typical of influenza-like illnesses. No cases were admitted to hospital.

The public health response

Medical care at the festival was ensured by the Belgian Red Cross in collaboration with the university hospital of the Catholic University of Leuven. No active case finding was set up at the festival site but the abovementioned medical care facilities had procedures in order to diagnose, notify and manage cases in line with the national enhanced surveillance system.

Case finding: Communication through the press, the festival's website and case definition update

The official daily press releases on the influenza pandemic from the Belgian Interministerial Influenza Coordination Committee reported cases linked to the festival on 6 July and from 8 to 12 July. Mass media (including press, internet, TV and radio) published this information and conducted a careful follow up of the event describing every confirmed case of influenza A(H1N1)v related to the festival [12,13]. On 6 July a separate message for those having visited the festival was published on the official Belgian influenza website [14]. Additionally on 7 July, a communication in

Dutch, English and French was displayed on the festival's website in coordination with the festival organisers. All these messages advised the participants of the festival to visit a physician if fever or respiratory symptoms appeared [15].

As a consequence of this outbreak, the case definition used by the national surveillance system was updated to include participation in the festival and the criterium of travel to an affected area was removed as of 6 July 2009.

Case management and contact tracing

Cases were managed individually, within the regular healthcare system, by general practitioners in coordination with provincial health inspectors. According to the protocols, patients were isolated at home, contact tracing was performed and prophylactic treatment for close contacts recommended [11]. No epidemiological link, apart from attending the same event, was found for any of the cases linked to Werchter festival.

Beside the index case from Israel, three of the cases linked to the festival consulted their physician on 7 July, one on 8 July, five on 9 July, one on 10 July and one on 11 July 2009.

Discussion and conclusions

This outbreak of influenza A(H1N1)v is one of the first associated with a mass gathering event. The index case, detected by the enhanced surveillance system, was imported probably from Israel or, less likely, from the UK, where he was in transit the day before the onset of symptoms.

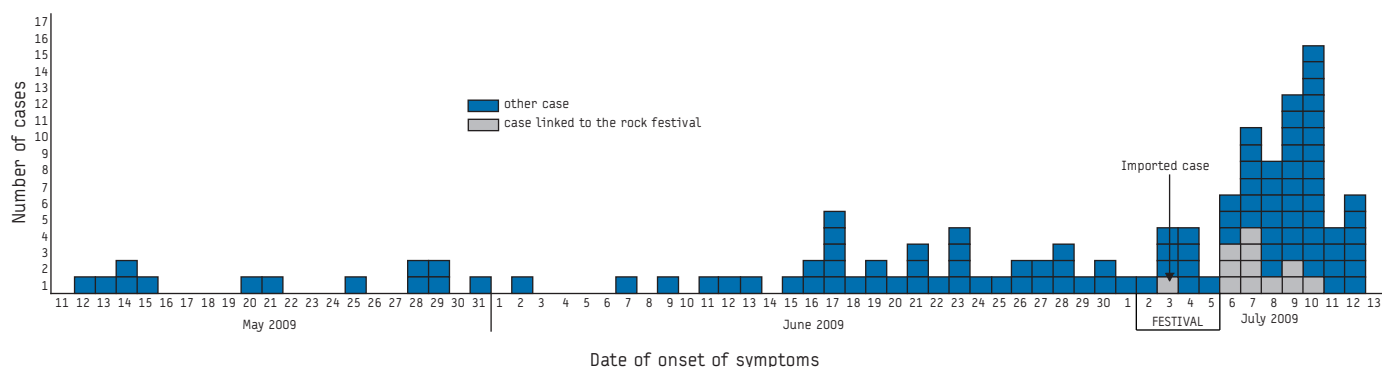
TABLE 1

Case definition of influenza A(H1N1)v used for investigating cases linked to Rock Werchter festival in Belgium, 2-5 July 2009

Case linked to Werchter	A person with onset of influenza-like illness symptoms from 2 to 12 July 2009 AND laboratory confirmation by real time reverse transcription PCR for influenza A(H1N1)v AND one of the following epidemiological criteria: 1) Having visited the "rock Werchter festival" between 2 and 5 July 2009 OR 2) Being a close contact (less than one metre distance) to a laboratory confirmed case that had visited the "rock Werchter festival"
Other case	A person with a laboratory confirmation for influenza A(H1N1)v, with date of onset of influenza-like illness symptoms between 12 May and 13 July 2009 who is not a case linked to Werchter

FIGURE

Distribution of laboratory-confirmed cases of influenza A(H1N1)v by date of onset, including cases with epidemiological link to "Rock Werchter festival", Belgium, 12 May-28 June 2009 (n=123)*



*Note: The total number of confirmed cases for this period is 131 but for eight cases the date of onset of symptoms was not available. None of these were linked to the festival.

An initial assessment led to isolation and post-exposure prophylaxis of four close contacts. The fact that the index case had attended the “Rock Werchter festival” for three days while being symptomatic prompted the Belgian Interministerial Committee for Influenza to implement further communication and control measures.

The eleven cases found in Belgium as well as the one reported in the Netherlands and one in Luxembourg* might have acquired the infection at the festival. This is plausible because their symptoms started within five days after the end of the festival hence within the incubation period estimated to be from one to seven days for influenza A(H1N1)v [16].

However, given the lack of epidemiological link among the cases and the fact that community transmission existed in neighbouring countries where many attendees came from, we believe that other cases, apart from the index case identified, were present at the festival and could therefore have been seeding cases as well. The average generation interval (number of days between onset of symptoms in the source case and in the secondary case) for secondary cases found in our previous analysis of influenza A(H1N1)v cases in Belgium (not published) was two days compared to three found in the Netherlands [4]. This makes it difficult to believe that all eleven cases were contaminated by the same index case, as for eight cases the generation interval was estimated to be four to seven days, i.e. at least twice as long as expected.

The likelihood of community transmission having occurred independently of the festival can not be ruled out either. If this was the case, increased awareness of physicians and patients, after the public health messages by the press and the authorities, might have contributed to the detection of some of the cases, especially those with latest symptoms onset.

This latter possibility highlights the role of chance in detecting this outbreak: had the index case not been an imported one, it would not have been detected and subsequently cases linked to Werchter would not have been diagnosed either because at that time the case definition included a visit to an affected country.

This outbreak demonstrated that community transmission was taking place in Belgium. The festival itself could have been the seeding event leading to community transmission although other sources must have played a role because the number of cases not linked to Werchter was already rising steeply. The outbreak also challenged the surveillance system at that time forcing us to update

the case definition. Furthermore a shift into a mitigation strategy was decided on 13 July 2009, one week after the index case had been diagnosed.

Communication measures raised public awareness; this is shown by the fact that after the information on the first case linked to the festival was published, subsequent cases sought medical attention and were identified.

As pointed out by this investigation, mass gatherings can concentrate infectious diseases and amplify their transmission. Once more, preparedness and communication become essential in order to detect and respond to infectious disease outbreaks in complex situations.

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*Authors' correction

Information on the case detected in Luxembourg was added after the publication of the article, upon the request of authors. This change was made on 10 August 2009.

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TABLE 2

Distribution of symptoms among cases of influenza A(H1N1)v linked to Rock Werchter festival in Belgium, 2–5 July 2009 (n=12)

Symptom	Number of cases	Percentage
Cough	12	100%
Discomfort	11	92%
Fever	11	92%
Dyspnoea	2	17%
Diarrhoea	1	8%
Vomiting	1	8%

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PUBLIC HEALTH PREPAREDNESS FOR TWO MASS GATHERING EVENTS IN THE CONTEXT OF PANDEMIC INFLUENZA (H1N1) 2009 - SERBIA, JULY 2009

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Preparedness planning for two large mass gatherings events were considered in Serbia in the context of pandemic influenza (H1N1) 2009. Planning included approaches to prevention, detection and response in order to mitigate the situation at this early stage of the epidemic in Serbia. Cases of influenza A(H1N1)v were identified nationally immediately prior to the mass gatherings but also identified in association with both events, as expected in the context of the pandemic situation. This article describes the experiences of planning and the epidemiological situation during the period of the mass gathering events.

Introduction

Mass gatherings present a particular challenge for public health. Unusual population increases, high crowd density, international visitors, temporary catering and accommodation facilities, are some factors that may contribute to increased risk for communicable diseases and consequently demands on local health services [1]. Therefore preparations for mass gatherings may also require public health planning. In the context of the current pandemic influenza (H1N1) 2009, preparedness becomes even more important, especially for a country not affected at the time of planning. In this rapid communication we report on experiences in preparedness planning for two mass gatherings in Serbia.

Background

During July 2009, Serbia hosted two large international mass gatherings. Firstly, the 25th Universiade, an international sporting event for young university athletes, took place from 1 to 12 July, involving 53 sites in nine locations (Belgrade, Indjija, Lazarevac, Novi Sad, Obrenovac, Smederevo, Stara Pazova, Vrsac, Zrenjanin), with 8,600 athletes from 143 countries, 10,000 volunteers, 5,000 staff and an estimated 500,000 spectators [2]. This sporting event included both indoor and outside venues, and a restricted-entry accommodation and hosting facility site 'Universiade village' for all the delegations that included a medical clinic. Secondly, the 10th EXIT music festival held at Petrovaradin fortress, Novi Sad, Autonomous Province of Vojvodina. This was held from 9 to 12 July (closing 13 July 05:00), with an estimated 190,000 visitors

[3], including 20,000 from abroad. The open-air festival included over 12 stages within the fortress. Visitors were hosted in local hotels, hostels, private accommodation and a dedicated campsite for 6,000 persons.

Risk assessment and considerations for pandemic influenza (H1N1) 2009

Following international reporting of the new influenza virus in April 2009 [4], considerations for preparedness for these mass gathering events were included in the regular meetings of the National Working Group on Pandemic Planning, under the co-ordination of National Institute of Public Health (IPH) and Ministry of Health of Serbia. Recommendations were then implemented by Military Medical Academy (providing medical support to the Universiade event), Institutes of Public Health and healthcare facilities in the districts where mass gathering sites were located. By early June, when preparedness activities for the two mass gathering events were being finalised, no case of influenza A(H1N1)v had yet been identified in Serbia. However, with global travel to and from affected areas and continuing spread worldwide, cases were anticipated to be detected at any time, irrespective of the mass gathering events.

As the circulating strain was considered mild-moderate at declaration of the pandemic by the World Health Organization (WHO) [5], and containment in Serbia was regarded unfeasible, a mitigation approach was implemented both as national policy and towards the mass gathering events. Overall key objectives were to detect first cases wherever they may appear, reduce possible spread of infection where possible, monitor the epidemiological situation and mitigate morbidity and mortality through timely diagnosis and treatment of cases according to national guidelines.

In addition, further prevention actions were taken for the first mass gathering, Universiade, because no cases had yet been reported in Serbia one month before the event and the delegations were a reachable population. Information was sent on 4 June 2009 to delegations recommending persons to reconsider travel

to Serbia if presenting with any influenza-like symptoms. Criteria for recommending cancellation of Universiade were also set in case of a rapidly evolving situation. These criteria were: 1% of the attending population diagnosed with influenza A(H1N1)v, a case of acute respiratory distress, or a death in a confirmed case.

Detection and management of influenza A(H1N1)v cases

National approach

According to pandemic plans, enhanced national surveillance for influenza A(H1N1)v was implemented with daily reporting of confirmed cases by the national reference laboratory 'Torlak' integrated with information reported from district IPH on individual case assessments. Guidelines were produced by the National IPH on requirements and procedures for reporting cases using case definition for influenza A(H1N1)v according to WHO case definition as of 27 April 2009 [6]. At the national level reported cases were categorised as travel-related or domestic (no travel abroad known during the incubation period, or contact with a confirmed case in Serbia). Influenza-like illness (ILI) surveillance was continued after week 20 in accordance with recommendation of WHO.

Strategies to detect cases included:

- Posters and information leaflets on symptoms and phone numbers for arriving travellers at airports on when and where to seek medical help;
- Communication to the general public through media and posters on prevention measures and when to seek medical help;
- Sensitising medical facilities and health care workers in all districts to the presentation, management and reporting of cases through cascade of training from national IPH to district IPHs and to health facilities;
- 24/7 on duty and epidemiology mobile teams to respond to queries about suspected cases to assess and triage persons to be tested.

On 22 July there was an alteration in the national testing policy, with suspected cases no longer all being laboratory-tested for influenza A(H1N1)v.

Management of cases

Quarantine measures were not implemented. However, suspected cases were provided isolation at medical facilities until diagnosis, with results aimed to be provided within 24 hours. Furthermore, based on individual medical assessment, confirmed cases were subsequently advised on self-isolation or hospitalised if medical care needed. All confirmed cases were provided antiviral treatment. Masks were not widely distributed to the general public, but used by health care workers as standard infection control practices and provided to suspected or confirmed cases to minimise spread. Contact tracing was undertaken where feasible including medical monitoring, but prophylaxis not given as according to national guidelines.

Mass gathering events

Enhanced daily surveillance was implemented for both mass gathering events for the following diseases: influenza A(H1N1)v, haemorrhagic fever, polio/AFP, diphtheria, measles, botulism, meningococcal meningitis, and all diseases which request urgent reporting in accordance with national law for communicable diseases (cholera, plague, smallpox, yellow fever, malaria) and reporting of outbreaks of acute diarrhoeal syndrome or acute haemorrhagic diarrhoeal syndrome.

At Universiade, the Military Medical Academy provided daily further epidemiological information on cases to both the national IPH and IPH of Belgrade. Event-based surveillance for influenza and other abovementioned diseases were supplemented through daily epidemic intelligence [7] activities performed by the European Centre for Disease Prevention and Control (ECDC), as done earlier in other international mass gathering events [8,9]. A special edition threat bulletin was developed by ECDC together with IPH Serbia and circulated daily to all district IPHs (24 districts and the city of Belgrade), Military Medical Academy and Ministry of Health.

Strategies to detect cases included:

- posters at Universiade sites in French, English and Serbian about prevention measures and when to seek medical help;
- obligatory daily zero-reporting for suspected cases by all delegation doctors to the Military Medical Academy, that no influenza-like symptoms had been observed in their teams;
- guidelines by Military Medical Academy for diagnosis and referral of suspected cases at the Universiade village clinic to the Military hospital;
- in Novi Sad (site of the EXIT festival), leaflets in English and Serbian provided in public areas such as taxis, bus stops, restaurants, hotels and other locations about prevention measures, symptoms and phone numbers and locations where to seek medical attention;
- information on disease symptoms, prevention measures and contact numbers printed inside the EXIT festival programme;
- mobile teams on site at festival to respond to any suspected case-presentation;
- contact tracing where feasible for cases who could be reached.

Management of cases

- as national approach;
- in Universiade:
 - an isolation area was available in the clinic at the Universiade village;
 - referral and transfer of confirmed or seriously-ill suspected cases to isolation facilities at Military Medical Academy hospital;
 - recommendation to self-isolate in accommodation for confirmed cases not needing hospitalisation;
- for EXIT festival:
 - basic isolation area in some medical tents at festival site;
 - mobile medical assessment teams on site at festival and camp;
 - contact phone numbers to local epidemiology teams for triage of suspected cases;
 - referral and transfer of suspected cases presenting at festival site or campsite to local health facilities in Novi Sad;
 - treatment of confirmed cases at health facilities in Novi Sad.

Results

Prior to mass gathering events

On 24 June, six days before the start of Universiade, the first imported case of influenza A(H1N1)v in Serbia was detected and laboratory-confirmed in Belgrade in a returning traveller from Argentina (Figure 1). A further 10 travel-associated cases and two domestic cases (contacts with travel-related cases) were detected nationally, until the first mass gathering event officially opened on 30 June. Among these 13 cases, eight were reported from three of the six districts hosting Universiade events (Belgrade city, South Backa and Srem). By 6 July when the EXIT festival campsite opened, a further eight travel-associated cases (returning residents) were reported, all in the district of South Backa.

Universiade sport event

As of 24 July, six athletes and one volunteer had confirmed influenza A(H1N1)v (Figure 2) with 22 other suspected cases presenting at the Universiade clinic but testing negative. According to incubation periods and contact histories, three cases among athletes were considered as travel-related (Argentina, Australia,

Uganda), whereas three athletes (one from France and two from Zambia) and one volunteer were suspected to have been infected within Serbia. Cases were aged between 20 and 25 years and all experienced mild symptoms.

EXIT music festival

As of 24 July, a total of 62 confirmed cases were identified associated with EXIT festival, including secondary cases to cases exposed at the festival site (Figure 3). Fifteen cases in total were classified as travel-associated (11 from United Kingdom, two from Canada, one from the Former Yugoslav Republic of Macedonia and one from the Netherlands). Ninety-five percent of all cases were aged between 16 and 30 years and all presented with mild symptoms. Fifty-two of the confirmed cases had been referred from the festival to Novi Sad health facilities. A total of 23 confirmed cases associated with the festival were residents from Novi Sad.

An additional 32 probable cases, of whom four were among staff working at the festival site, were identified in Novi Sad after 15 July as likely associated with the festival, as a primary or secondary contact, but were not confirmed due to the new testing policy.

No complications or deaths were reported among any cases.

Discussion

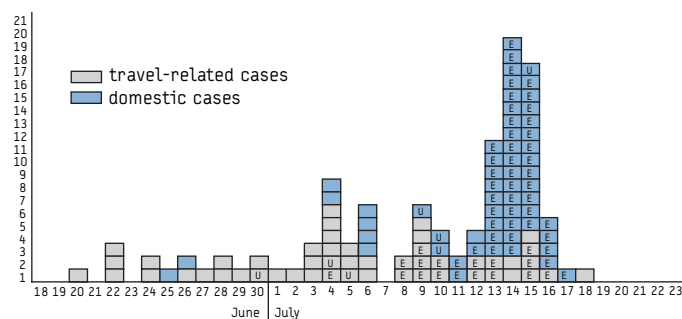
Cases of influenza A(H1N1)v had been detected in Serbia before the mass gatherings occurred but were also associated with these events, as was expected in the context of the pandemic situation. The choice of an overall mitigation approach was in accordance with WHO recommendations at the stage of the global pandemic in June [10]. Preparedness planning assisted towards detecting and responding to the evolving situation in Serbia.

Outbreaks of ordinary seasonal influenza in populations similar in size and age-group structure have been reported at other mass gatherings worldwide [11] thus transmission under these events is not unexpected. Relatively few influenza A(H1N1)v cases were identified among athletes and staff associated with Universiade. Though further cases may have presented among delegations after departure (as reported in Montenegro [12]), this suggests transmission at Universiade was limited which may have been influenced by both the directed travel information as well as health monitoring by delegations. No cases were passively detected or reported among spectators of the Universiade event.

Cases at EXIT festival were first identified among foreign visitors, suggesting importation of the virus to the festival site, however, travel-related cases had been detected in Novi Sad prior to the festival. Though the age groups involved in the festival were similar to Universiade, many more cases were identified in association with EXIT and within a shorter timeframe. This difference could be partly explained by the active contact-tracing undertaken in the local districts. However it might also reflect the characteristics of this mass gathering event including higher person density in specific areas and differences in social interaction.

The number of probable cases detected in Novi Sad after the festival suggests local spread. However, it is difficult to assess the impact of either of these mass gathering events on the development of the epidemic in Serbia as the virus was already present in the country and cases may have been under detected nationally.

FIGURE 1
Cases of laboratory-confirmed influenza A(H1N1)v virus infections in Serbia, reported until 24 July 2009, by day of symptom onset (n=109)



U=associated with Universiade, E= associated with EXIT

FIGURE 2
Cases of laboratory-confirmed influenza A(H1N1)v virus infections associated with Universiade 2009 sport event in Serbia, reported until 24 July 2009, by day of symptom onset and import status (n=7)

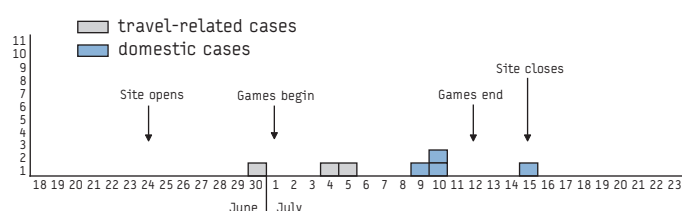
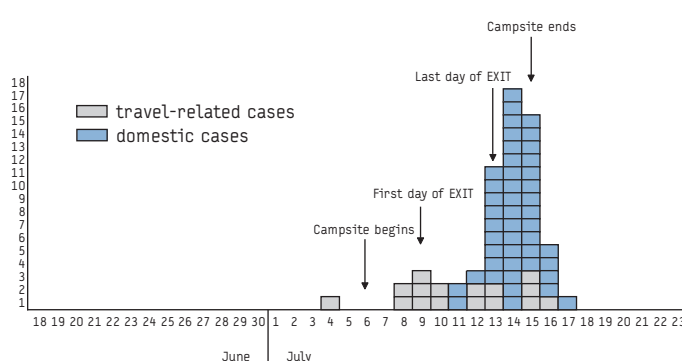


FIGURE 3
Cases of laboratory-confirmed influenza A(H1N1)v virus infections associated with EXIT 2009 music festival in Serbia, reported until 24 July 2009, by day of symptom onset and import status, (n=62)



Conclusions

Both mass gathering events went ahead as planned. Transmission of influenza A(H1N1)v at both events was inevitable due to the nature of the infection, but preparations were put in place to mitigate the situation, including detection, isolation options and treatment of cases, during this early stage of the epidemic in Serbia.

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A PRELIMINARY ANALYSIS OF THE EPIDEMIOLOGY OF INFLUENZA A(H1N1)V VIRUS INFECTION IN THAILAND FROM EARLY OUTBREAK DATA, JUNE-JULY 2009

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As the influenza A(H1N1)v pandemic unfolds globally, it is vital to monitor closely for signals of change in the current patterns of transmission. We estimate the basic reproduction ratio for A(H1N1)v virus in Thailand and propose a method to keep track of the actual case count notwithstanding the exponential growth rate.

Introduction

The threat of an influenza pandemic posed by a novel reassortant influenza A virus was identified in late April in Mexico. The influenza A(H1N1)v virus has since spread into five continents infecting at least 134,503 people and causing 816 deaths as reported by World Health Organization (WHO) on 27 July 2009. Further spread of the virus especially within affected countries is considered inevitable at this point. Also, the increasing number of cases in many countries is making it difficult for laboratories to individually test and confirm all suspected cases.

The first two cases of A(H1N1)v in Thailand were reported on 10 May. After a two week lapse and despite intense containment measures, more cases were reported, building up into an exponential growth phase in early June. The basic reproduction ratio (R_0), estimated from the daily case reports in the exponential growth phase, is useful in assessing the ultimate course of the epidemic in Thailand. The reproduction ratio as a function of time (R_t) generally drops after the primary exponential phase due to a drop in susceptibles as well as due to control measures, and varies throughout the epidemic until it ultimately drops below 1 long enough to suppress further transmission.

We calculate the intrinsic growth rate (r) during the exponential growth phase from 1 to 12 June and estimate R_0 and the *final size* [1,2] - the proportion of the population that would be ultimately infected assuming 100% susceptibility at the outset and minimal control measures - of the epidemic. Furthermore, we give a rough estimate for the case fatality ratio (CFR) from early fatality counts and use it to extrapolate the number of infected cases at a later date, after laboratory testing of all suspected cases was abandoned (20 June) paving the way for significant underreporting. All reported deaths up to 14 July are analysed to compare the CFR between age groups.

Methods

Our data come from two sources. First, we counted the cases by symptom onset date from the records at the WHO National Influenza Centre, which was used to calculate r , R_0 and CFR. The age distribution of the infected population up to 14 July was inferred from the daily incidence reports from the Bureau of Emerging Infectious Diseases, Department of Disease Control (DDC), Ministry of Public Health in Thailand (http://beid.ddc.moph.go.th/th/index.php?option=com_content&task=view&id=1784902&Itemid=240) while the disease onset dates and age of the deceased were obtained directly from DDC.

Estimate of r , R_0 and final size

The intrinsic growth rate r is estimated by Poisson regression of the epidemic curve over the exponential growth phase, R_0 is derived by (where $R_0 = 1 + rT_c$ is T_c the mean generation interval [GI])

and the final size by a Newton-Raphson numerical solution [1] of $\ln(1 - \chi) + R_0\chi = 0$.

The mean GIs derived in two previous studies ($T_1=2.6$ [2.1-3.0] [3] and $T_2=1.9$ [1.3-2.7] [4]) were used as no information was available for the current epidemic. The equation used to calculate R_0 gives the Laplace transform of the GI distribution assuming it is exponentially distributed, whereas the error for non-exponentially distributed GIs are known to be small [3]. Visual inspection of the epidemic curve revealed significant deviations from the exponential curve toward the latter part of the period of 1-12 June, necessitating the choice of a valid combination of points in order to achieve a realistic goodness of fit. Goodness of fit (or lack of it) of the model was assessed by a combination of the R-squared measure and Pearson's statistic.

Estimate of CFR and present case count

We estimated the CFR for cases with symptom onset on or before 18 June using our daily onset data for that period and the number of fatalities subsequently arising from these cases until 15 July. This rough estimate was used to extrapolate the number of infected cases from the number of deaths on later dates. The normalised age-specific CFR was calculated by dividing the age distribution of all deceased patients as of 14 July against the age distribution

of all reported cases as of 7 July, and further dividing each value by the overall CFR for the total population. Since the seven-day gap is not sufficient to account for the delay from onset to death, there are two implicit assumptions made here: the age distribution of the infected population is constant over time, and the time from onset to death is independent of the patient's age. Underreporting bias is effectively eliminated by normalising, provided the rate of underreporting was similar across all age groups.

Results

The epidemic curve for the period 1-12 June minus the counts for 8, 10, and 11 June (Figure 1 and Table) yielded the best fit for exponential growth ($R_2 = 0.9802$), giving $r=0.41$ [95%CI: 0.35-0.47]. The corresponding R_0 were 2.07[1.92-2.22] for T_1 and 1.78[1.67-1.89] for T_2 . The final-size were 81.5[77.4-84.8]% for T_1 and 72.5[67.7-76.4]% for T_2 .

A total of 690 confirmed cases with disease onset on or before 18 June gave rise to four deaths (as of 15 July) yielding a CFR of 0.58%. The reported number of deaths arising from patients with disease onset on or before 30 June was 16 (as of 15 July), hence the expected value for the actual number of cases at the same date is 2,760 assuming a constant CFR, which is 87% higher than the number of confirmed cases (1,473) reported on 1 July. The normalised age distribution of the CFR (overall CFR=1) is shown in Figure 2.

Discussion

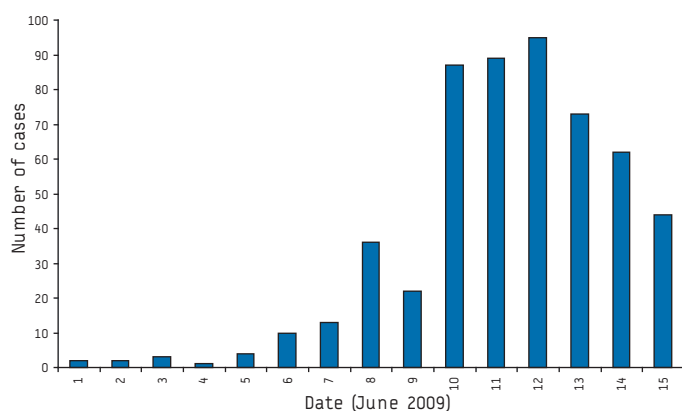
The basic reproduction ratio gives us a fairly good idea about the infectiousness of the virus within a particular demographical area and the potential effect it would have on the community if no public health intervention or changes in social habits take place. Generally, the reproduction ratio decreases after the initial exponential phase due to intervention and a reduction of the number of susceptibles. Thus, R_0 gives us a reasonable upper bound for the reproduction ratio as well.

Making an estimate of R_0 is not trivial due to various limitations in the information we have about an epidemic at the beginning. Firstly, it is highly dependent on the generation time interval [5] which is not easy to estimate when the transmission network is not known. We use mean T_c values estimated elsewhere: T_1 from a comprehensive analysis of household transmission data [3] found to be consistent with viral shedding data from experimental studies; and T_2 from an independent estimate of the influenza A(H1N1)v outbreak in Mexico [4].

Another limitation is the difficulty of fitting the real-life epidemic curve to an exponential growth model. Human errors in reporting as well as stochastic errors arising from the relatively small numbers involved required an arbitrary decision on which data points displayed exponential growth.

FIGURE 1

Epidemic curve for influenza A(H1N1)v in Thailand by date of onset, 1-15 June 2009 (n=543)



TABLE

Epidemic growth rates estimated for the exponential growth phase (1-12 June) of A(H1N1)v in Thailand and corresponding basic reproduction ratio and final-size estimates for two different generation intervals

Period (dates removed)	R^2	Pearson	r	SD	95% CI		T=2.6				T=1.9							
							R_0	95% CI		final size	95% CI		R_0	95% CI		final size	95% CI	
8, 10, 11 June	0.9802	0.6485	0.41	0.029	0.35	0.47	2.07	1.92	2.22	81.5%	77.4%	84.8%	1.78	1.67	1.89	72.5%	67.7%	76.4%
9, 11, 12 June	0.9695	0.3018	0.54	0.041	0.46	0.62	2.40	2.19	2.61	87.9%	84.2%	90.6%	2.02	1.87	2.18	80.3%	75.8%	83.9%
8, 12 June	0.968	0.1264	0.43	0.028	0.37	0.48	2.11	1.97	2.25	82.4%	78.7%	85.3%	1.81	1.71	1.91	73.6%	69.4%	77.1%
8, 10, 12 June	0.9644	0.2452	0.47	0.036	0.40	0.54	2.22	2.03	2.40	84.7%	80.5%	87.9%	1.89	1.75	2.02	76.3%	71.5%	80.3%
10 June	0.9454	0.0082	0.40	0.025	0.35	0.45	2.05	1.92	2.17	80.9%	77.3%	83.8%	1.76	1.67	1.86	71.8%	67.8%	75.4%
9 June	0.928	0.001	0.39	0.023	0.35	0.44	2.02	1.90	2.13	80.1%	76.7%	83.0%	1.74	1.66	1.83	71.0%	67.2%	74.4%
12 June	0.9258	0.001	0.47	0.031	0.41	0.53	2.22	2.06	2.38	84.7%	81.1%	87.5%	1.89	1.77	2.00	76.3%	72.1%	79.8%
8 June	0.9244	0	0.42	0.026	0.37	0.47	2.08	1.95	2.21	81.8%	78.4%	84.7%	1.79	1.70	1.89	72.9%	69.0%	76.3%
None	0.9131	0	0.40	0.024	0.35	0.45	2.04	1.92	2.16	80.8%	77.4%	83.6%	1.76	1.67	1.85	71.7%	67.9%	75.1%
11 June	0.8972	0	0.39	0.024	0.35	0.44	2.03	1.90	2.15	80.4%	76.8%	83.3%	1.75	1.66	1.84	71.3%	67.2%	74.8%

Note: All plausible combinations of dates that may yield a better fit were tested.

Underreporting at the beginning of an epidemic is also usually a confounding factor [6], but we believe the effect of this was minimal in our data due to a highly vigilant healthcare department which sprang into action just after the first few cases were reported in North America.

Our estimate of R_0 for A(H1N1)v in Thailand is higher than one estimate for the Mexican outbreak which used T_2 as the GI [4], but it is lower than another estimate for the same outbreak [6]. The results should be interpreted with caution due to the many uncertainties described above. Nevertheless, they may be used to compare the epidemiological factors of the A(H1N1)v outbreak in Thailand with those from other countries, provided the assumptions behind the calculations are kept in mind.

The final size is a good indicator of the potential magnitude of the epidemic, which may be used by public health officials to estimate the level of damage the epidemic would have on the society should there be no control measures. The case fatality ratio is another vital indicator of the effect of the epidemic on society in general and needs to be continually kept track of until the epidemic is over.

Nevertheless, significant underreporting of infected cases expected after the first few weeks of the infection may result in a CFR estimate significantly higher than the actual value, given that fatalities will not be overlooked as easily even in the middle of the epidemic. Thus, it is imperative to estimate the CFR with data from the initial phase. We used this rate to extrapolate the case counts for later dates after the reporting rate has decreased. Also, our normalised CFR for each age group clearly shows a marked increase in fatality risk with age. However, relatively few infections were seen in the elderly, possibly compensating, at least partly, for the higher fatality rate.

Our rough estimate for the CFR in Thailand, though highly prone to stochastic errors considering the low number of deaths, is not so different from the CFR for Mexico estimated previously [4], but a more recent study [7] showed much lower CFRs for developed countries. Their multiplier method essentially assumes 10-30 unreported cases for each diagnosed case, and incorporating this into the calculation brings down the CFR estimate from a value which would have been in the same order as ours into something drastically lower. Considering the largely undefined nature of asymptomatic or mildly symptomatic infections, we refrain from assigning a number to these cases as that may bring some

confusion in the interpretation and comparison of CFR estimates from different countries or regions. Nevertheless, this issue is undoubtedly valid for Thailand as well, more so after the initial growth phase. Another reason for this comparatively higher CFR may be attributed to differences in the healthcare infrastructure and awareness levels of the public in general.

Acknowledgements

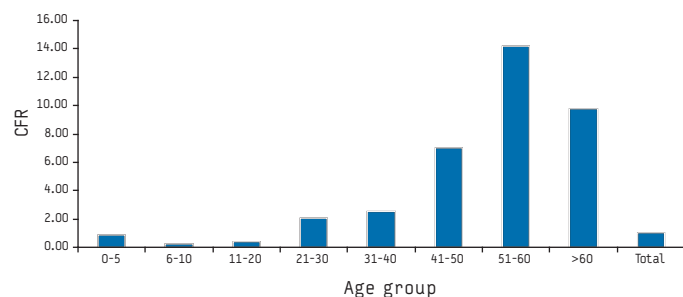
We appreciate the kind cooperation extended to us by the Bureau of Emerging Infectious Diseases and the National Institute of Health in providing data. This work was partially supported by the program of the Founding Research Centre for Emerging and Re-emerging Infectious Diseases launched by a project commissioned by the Ministry of Education, Cultures, Sports, Science and Technology (MEXT) of Japan. We are grateful for administrative support from Yoshitake Nishimune, director of RCC-ERI.

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FIGURE 2

Normalised case fatality ratio (CFR) by age group, influenza A(H1N1)v in Thailand, June 2009 (n=23 deaths)



INTERIM ANALYSIS OF PANDEMIC INFLUENZA (H1N1) 2009 IN AUSTRALIA: SURVEILLANCE TRENDS, AGE OF INFECTION AND EFFECTIVENESS OF SEASONAL VACCINATION

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Between May and September each year, influenza sentinel surveillance is conducted in general practices in Melbourne and the state of Victoria in southern Australia. We describe the first 11 weeks of sentinel surveillance in 2009 (weeks 18-28), during which time pandemic influenza (H1N1) 2009 virus became established, and investigate the protective effect of seasonal influenza vaccine against laboratory-confirmed infection caused by the pandemic virus. At the time of reporting, the peak ILI activity in 2009 had been reached and was similar to the peak recorded in 2007 but below the peak of 2003. The proportion of cases positive for any influenza virus increased from 6% in the first week of surveillance (week 18) to 59% by week 28, during which time the proportion of influenza viruses detected as pandemic influenza increased from zero to 95%, with at least 91% of all influenza viruses confirmed as pandemic influenza by the eighth week of surveillance (week 25). The median age of all 223 patients with pandemic influenza for whom age was known was 21 years (range 2-63 years) compared with the median age of 53 patients with seasonal H1N1 influenza in 2007 or 2008 of 23 years (range 1-75 years). There was no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group.

Introduction

Australia reported its first case of pandemic influenza (H1N1) 2009 on 8 May 2009 in a traveller returned from the United States [1]. Ten days later the state of Victoria in southern Australia reported its first three cases, in three brothers from one family, also recently returned from the United States [2]. Victoria has used an existing sentinel general practice network, established with laboratory support in 1998 [3], to monitor the pandemic. Sentinel monitoring is designed to overcome the potential testing biases that arise from monitoring all diagnosed cases, including those identified from outbreaks and contact tracing. During the current pandemic, sentinel surveillance general practitioners have been encouraged to test those patients who satisfied the case definition of fever (reported or observed), cough and fatigue/malaise [4], as they have done in previous years [5-10].

We have previously demonstrated the feasibility of estimating influenza vaccine effectiveness (VE) using a case control study of patients tested for influenza as a component of sentinel surveillance [11]. We now aim to describe the first 11 weeks, from 27 April to 12 July (weeks 18-28), of sentinel surveillance in Victoria in 2009, during which time pandemic influenza (H1N1) 2009 virus became

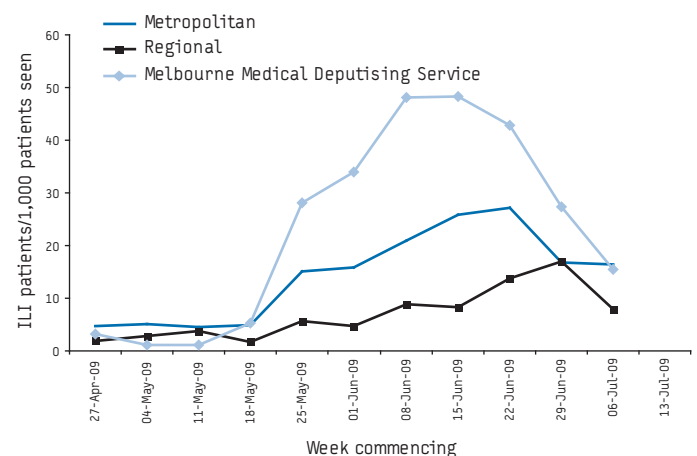
established. We compare influenza-like illness (ILI) in 2009 with previous seasons and compare our surveillance system with ILI surveillance using the novel Google Flu Trends. We investigate the protective effect of seasonal influenza vaccine against medically attended ILI due to laboratory-confirmed infection caused by the pandemic virus in this period.

Methods

The Victorian sentinel general practice network

Victoria is a southern Australian state with a temperate climate. The influenza season occurs in winter and often extends into the early months of spring. Between May and September each year, sentinel surveillance is conducted in general practices scattered throughout Melbourne and regional Victoria. Victoria's population is more than 5 million, with 3.9 million people living in the state capital, Melbourne. For each season, participating general practitioners (GPs) report weekly on the total number of consultations and any patients presenting with ILI, defined as fever (reported or observed), cough and fatigue/malaise [4].

FIGURE 1
Influenza-like illness (ILI) from GP sentinel surveillance and the Melbourne Medical Deputising Service, Victoria, Australia, 27 April-19 July 2009



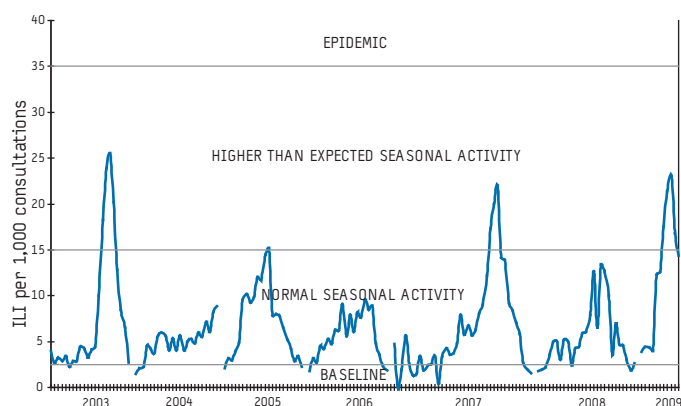
Laboratory-confirmed influenza has been a gazetted notifiable disease in Victoria since 2001. Because of the legal requirement for the laboratory to notify positive cases, formal ethics approval is not required for the surveillance program. However written consent is obtained from sentinel patients, indicating that aggregate anonymous data will be used for surveillance purposes and influenza positive results will be notified to the state government Department of Human Services, Victoria. After consent is obtained GPs collect data on the age, sex, symptoms and vaccination status (recording the date of administering the vaccine) of the sentinel patients. GPs collect a combined nose and throat swab from consenting patients. The swab is couriered to the Victorian Infectious Diseases Reference Laboratory (VIDRL), a WHO National Influenza Centre, for laboratory testing. In 2009 sentinel surveillance commenced on 27 April (week 18), with a network of 87 sentinel GPs, 60 in

Melbourne and 27 in regional Victoria. Optional on-line data entry was introduced and we continued to use surveillance data from the Melbourne Medical Deputising Service (MMDS) [12]. We compared publicly available ILI data from the Google website, (http://www.google.org/flutrends/intl/en_au/) expressed as the Google search ratio, with our surveillance data, expressed as ILI consultations per 1,000 consultations.

We used data from all surveillance sources to describe the first 11 weeks of the influenza season and compared features of the 2009 season with previous influenza seasons. Seasonal thresholds were based on the proportion of ILI cases per 1,000 consultations. Baseline activity, normal seasonal and higher than expected seasonal activity were defined as below 2.5, between 2.5 and <15, and between 15 and <35 per 1,000 consultations, respectively. According to these thresholds, 'epidemic influenza activity' was defined by proportions at or above 35 cases per 1,000 consultations [13].

FIGURE 2

Influenza-like illness (ILI) from GP sentinel surveillance, 2003 to 2009, Victoria, Australia



Laboratory testing

Specimens were tested in the Viral Identification Laboratory at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Viral RNA was extracted and tested for all influenza types and specific subtypes using a series of in-house polymerase chain reaction (PCR) assays directed at matrix gene sequences of influenza A and B. Any sample positive for influenza virus A was subtyped as influenza A(H1N1), influenza A(H3N2) or pandemic influenza A(H1N1) using specific PCR assays directed at hemagglutinin gene sequences. Any positive samples were referred to the World Health Organization Collaborating Centre for Influenza Reference and Research where an attempt to culture an isolate was made.

Estimating influenza vaccine effectiveness

Analysis was restricted to patients who presented for medical attention to any of the sentinel surveillance practices and who subsequently had a swab taken for the identification of influenza

TABLE 1

The proportion of influenza detections and the proportion of detections due to pandemic influenza H1N1 2009 from sentinel surveillance patients, Victoria, Australia, 2009

Week number	Date commencing	Patients tested	Number (%) of influenza detections	Patients with subtyping data available (% of patients with influenza)	Number (% of patients with influenza) of influenza detections due to pandemic (H1N1) 2009
18	27 April	16	1 (6%)	0	Not available
19	4 May	17	2 (12%)	2 (100%)	0
20	11 May	23	1 (4%)	1 (100%)	0
21	18 May	20	3 (15%)	3 (100%)	1 (33%)
22	25 May	69	11 (16%)	6 (55%)	6 (55%)
23	1 June	82	20 (24%)	5 (25%)	5 (25%)
24	8 June	73	32 (44%)	1 (3%)*	1 (3%)
25	15 June	105	55 (52%)	50 (91%)	50 (91%)
26	22 June	123	75 (61%)	70 (93%)	70 (93%)
27	29 June	84	56 (67%)	51 (91%)	51 (91%)
28	6 July	70	41 (59%)	39 (95%)	39 (95%)
18-28	27 April - 12 July	682	297 (44%)	228 (77%)	223 (75%)**

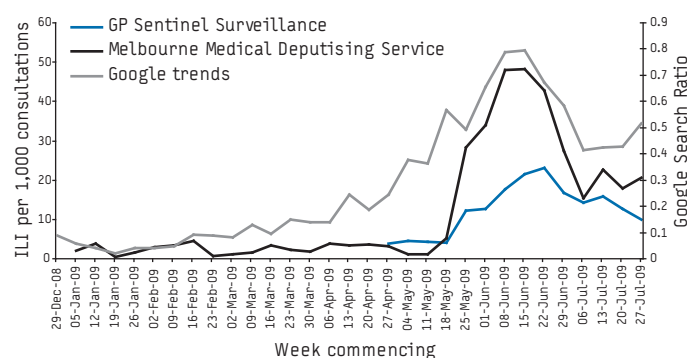
* Confirmed as pandemic (H1N1) 2009

** Per cent underestimated because subtyping is incomplete to date

virus by real-time PCR. Patients whose PCR tests were inhibited were excluded from the analysis, as were patients whose vaccine status or age was unknown, and patients for whom subtyping data were not available. We used a case control design to estimate VE, where case and control status were not defined at the time of recruitment. Counting all patients from whose swabs pandemic (H1N1) 2009 influenza virus was detected as cases and all patients

whose swabs were negative for influenza as controls, we estimated unadjusted VE (%) = (1-OR) x 100, where OR, the odds ratio, was the odds of being a vaccinated case divided by the odds of being a vaccinated control. We performed age-stratified analyses and adjusted for age by logistic regression using the following age groups: 0-4 years, 5-19 years, 20-49 years, 50-64 years and 65 years and above. The southern hemisphere seasonal vaccine contained A/Brisbane/59/2007-like virus as the H1N1 component.

FIGURE 3
Influenza-like illness (ILI) from GP sentinel surveillance, Melbourne Medical Deputising Service and Google Flu Trends, Victoria, Australia, 2009



Results
The 2009 influenza season

The influenza season of 2009 appeared to be already established when surveillance commenced at the end of April, with ILI activity above the threshold designated as normal seasonal activity. ILI activity increased quickly, crossing the threshold designated as higher than normal activity in the week commencing 8 June. Activity appeared to peak in week 26, and decreased again almost to the threshold of normal seasonal activity by the end of week 27 (Figure 1).

At the time of reporting the peak ILI activity in 2009 was similar to the peak recorded in 2007 (in week 34) but below the peak of 2003, also recorded in week 34 (Figure 2).

The proportion of cases positive for any influenza virus increased from 6% in the first week of surveillance to 59% by week 28, by which time the first 223 cases of pandemic H1N1 influenza had been detected. During this same period the proportion of

TABLE 2
Proportion of detections of seasonal H1N1 influenza 2007 or 2008 and pandemic H1N1 influenza 2009 compared with population proportions by age group, Victoria, Australia, 2009

Age group (years)	Seasonal H1N1 influenza detected 2007 or 2008 N (%)	Pandemic H1N1 influenza detected 2009 N (%)	Per cent Victorian population 2008* N = 5,297,560
0-4	3 (6%)	7 (3%)	6%
5-19	14 (27%)	81 (37%)	19%
20-49	30 (57%)	118 (53%)	43%
50-64	5 (9%)	15 (7%)	18%
65+	1 (2%)	0	14%
All	53	221	100%

Australian Bureau of Statistics 32010D0001_200806. Population by Age and Sex, Australian States and Territories, June 2008.

TABLE 3
Vaccine effectiveness of seasonal influenza vaccine against pandemic influenza H1N1 2009 by age group, Victoria, Australia, 2009

Age group (years)	Patients tested (age and vaccine status known)	Number (%) positive for pandemic influenza (cases)	Number (%) negative for influenza (controls)	Number (%) vaccinated	Cases (%) vaccinated	Controls (%) vaccinated	Vaccine effectiveness (%)	95% confidence interval
0-4	35	7 (20%)	28 (80%)	7 (20%)	1 (14%)	6 (21%)	39%	-510 to 94
5-19	158	80 (51%)	78 (49%)	12 (8%)	6 (8%)	6 (8%)	3%	-216 to 70
20-49	311	111 (36%)	200 (64%)	57 (18%)	19 (17%)	38 (19%)	12%	-62 to 52
50-64	52	14 (27%)	38 (73%)	25 (48%)	8 (57%)	17 (45%)	-65%	-467 to 52
>=65	21	0 (0%)	21 (100%)	15 (71%)	0	15 (71%)	not defined	
All	577	212 (37%)	365 (63%)	116 (20%)	34 (15%)	82 (22%)	33*	-56 to 40

*Adjusted for age-group as a discrete variable

influenza viruses detected as pandemic influenza increased from zero to 95%, with at least 91% of all influenza viruses confirmed as pandemic influenza by the eighth week of surveillance (week 25) (Table 1).

Comparison of ILI surveillance using sentinel practices and the MMDS with Google Flu Trends showed remarkable correlation between all three systems, with the comparison shown for surveillance extended to week 31, ending 2 August (Figure 3).

Although males comprised 56% of the sample of sentinel patients, pandemic influenza virus was detected in equal proportions of males and females (37.7% vs 36.8%). The median age of infection of all 221 patients with pandemic influenza for whom age was known was 21 years (range 2-63 years) compared with the median age of infection of 53 patients with seasonal H1N1 infection in 2007 or 2008 of 23 years (range 1-75 years). By contrast the median age of infection of patients with seasonal H3N2 was 28 years in 2007 (n=147) and 33 years in 2008 (n=43). Although the proportion of patients in whom pandemic H1N1 influenza was detected was higher in 2009 than the proportion in whom seasonal H1N1 influenza was detected in 2007 or 2008 (37% vs 6%, respectively), there was no significant difference by age group in the proportion of seasonal H1N1 infection detected in 2007 or 2008 compared with the proportion of pandemic H1N1 infection detected in 2009 (Table 2, Fisher's exact $p=0.17$). However the proportion of the 5-19 year old age group with seasonal or pandemic influenza H1N1 was higher than the proportion of this age group in the population (Table 2).

Vaccine effectiveness

By week 28, sentinel practitioners had seen 81,992 patients, had notified 982 (1.2%) of these patients with ILI and taken nose and throat swabs from 682 (69%) of them. Influenza virus was detected in 297/682 (44%) patients, and in 223/297 (75%) patients pandemic influenza (H1N1) 2009 was detected. After exclusion of patients for whom definitive subtyping is pending (n=69), patients for whom age was unknown (n=10), patients with unknown vaccination status (n=22) and patients with influenza due to a non-pandemic subtype (n=6), 577 patients were available for analysis, of whom 212 (37%) had pandemic influenza virus detected and the remainder had no virus detected. These patients were used for the estimates of VE.

Twenty per cent of patients were vaccinated against influenza but, as expected, the proportion of patients differed significantly by age group, with people aged at least 50 years more likely to have been vaccinated ($p<0.001$, Table 3). Pandemic influenza virus was detected in 37% of all patients, again with significant differences by age group ($p<0.001$, Table 3). People aged 5-19 years were most likely to have influenza virus detected (80/158, 51%), compared with none of 21 patients aged at least 65 years and 7/35 (20%) patients aged 0-4 years (Table 3).

There was no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group, with point estimates ranging from 39% in persons aged less than 5 years to -65% (OR = 1.65) in persons aged 50-64 years (Table 3). Age adjusted VE was 3% (95% CI -56 to 40) for all patients, 10% (95% CI -54 to 48) in patients aged 5-49 years and 1% (95% CI -70 to 42) in patients aged 20-64. In patients younger than 50 years, VE was 12% (95% CI -48 to 48) and VE was -65% (95% CI -467 to 52) in patients aged 50 years or older.

The latter estimate was based only on patients aged 50-64 years, as pandemic influenza was not detected in the group of patients aged 65 years and older. The oldest patient in whom pandemic influenza was detected was aged 63 years.

We further restricted our analysis to weeks 25-28 inclusive, when pandemic influenza comprised at least 90% of all influenza detections, and the age groups 5-49 years, where most infections occurred. This period accounted for 352 patients with known age and vaccination status (61% of all comparable patients) and 201 cases (95% of all comparable cases). For all ages in this four-week period, age-adjusted VE was 24% (95% CI -37 to 58) and, for ages 5-49 years, VE was 20% (95% CI -52 to 48).

Discussion

The seasonal pattern of ILI in Victoria between 27 April and 12 July 2009 was similar comparing data from sentinel general practices and the Melbourne Medical Deputising Service (MMDS). Both surveillance systems peaked in the same week, although the peak from the MMDS was higher. We have shown these two surveillance systems can be used interchangeably to monitor ILI in the community but, as seen in the first 11 weeks of surveillance in 2009, the correlation between the two systems is better for lower ILI activity [14]. These two systems also showed remarkable concordance with Google Flu Trends. Google used historical data from the Victorian sentinel surveillance system from 2006-2008 to validate its Australian version of Flu Trends (<http://blog.google.org/2009/06/google-flu-trends-for-australia-and-new.html>) so that retrospective similarity of data is expected. The prospective similarity is interesting. Unfortunately there is no detailed published information on the approach used by Google for ILI surveillance in the southern hemisphere, preventing a more detailed comparison.

With complete subtyping, influenza in sentinel patients was shown to be exclusively due to pandemic influenza in weeks 30 and 31 (not included in Table 1, available from: http://www.vidrl.org.au/surveillance/flu%20reports/flu_idx.html). However, considering only patients for whom subtyping data were complete in previous weeks when these patients comprised at least 90% of all influenza detections, influenza in these sentinel patients was entirely due to pandemic influenza from week 25 (commencing 15 June, Table 1).

We have previously suggested the median age of patients infected with influenza A(H1N1) was similar for patients infected with seasonal and pandemic influenza H1N1 strains [15, 16] and the surveillance data presented here confirm these original observations. Infections with influenza A(H3N2) tend to occur in older people [15, 17] and comparisons of the age of infection with pandemic H1N1 influenza with the age of infection of all seasonal influenza may be misleading if previous seasons were dominated by influenza A(H3N2). A younger median age of infection with pandemic H1N1 influenza is likely to reflect the age of infection with influenza A(H1N1) viruses. We detected no sentinel patients with pandemic influenza over the age of 63 years, consistent with some protection afforded to older people as demonstrated by the detection of cross-reacting antibodies to the pandemic H1N1 virus in people aged 60 years and above [18].

We found no evidence of protection against medically attended laboratory-confirmed pandemic influenza from receipt of the seasonal vaccine in age-stratified or age-adjusted analyses. However, we do not collect data on co-morbidities and could not adjust for potential confounders, other than age. The ILI case

control observational study design has limitations, some of which may bias the VE estimate towards the null. Sampling of patients is not systematic and the sampling proportion increased to 69% in 2009 from 40% in the five influenza seasons from 2003 to 2007 [11]. Seasonal influenza infection may be asymptomatic or afebrile [19] and the same is no doubt true for infection with pandemic H1N1 influenza. Sentinel patients therefore represent the mid-range of the influenza morbidity spectrum, although this is likely to be true for both seasonal and pandemic infections. Given the high level of community concern, patients may have been more likely to attend their general practitioner with an ILI in 2009, compared with previous seasons, and GPs may have been more likely to swab patients. However the proportion of 44% of sentinel patients positive for influenza in the first 11 weeks of surveillance in 2009 is not significantly different to the proportion of 42% positive in the five influenza seasons between 2003 and 2007 [11].

Because of the high workload in the early weeks of the pandemic in Victoria, not all influenza positive specimens have been definitively subtyped. However, the distribution of vaccination status and pandemic influenza infection in the weeks where subtyping is incomplete would need to be remarkably different to the distribution in the weeks with almost complete data for this lack of data to bias our estimate of VE. Because of low case numbers in the early weeks, we did not adjust for week of presentation in the interim analysis, but performed an analysis restricted to the four weeks when subtyping data were almost complete and in which pandemic influenza comprised at least 90% of all influenza detections. There was no significant difference in VE estimates comparing these four weeks with the entire period. We did not adjust for time between symptom onset and date of specimen collection since GPs are instructed to collect a specimen only within four days of symptom onset.

While there are potential limitations with interim analyses of VE from observational studies using routinely collected data, the results reported here, showing no protection from seasonal vaccine against laboratory confirmed medically attended infection due to pandemic influenza (H1N1) 2009, are not unexpected.

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DESCRIPTION OF THE EARLY STAGE OF PANDEMIC (H1N1) 2009 IN GERMANY, 27 APRIL-16 JUNE 2009

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We report characteristics of the early stage of the pandemic (H1N1) 2009 in Germany. Until 16 June 2009, 198 confirmed cases were notified. Almost half of the cases (47%) were imported, mostly from Mexico and the United States. About two thirds of indigenous cases were outbreak-related (with two large school-associated outbreaks, n=74). According to our results Germany is still in the early stage of the pandemic with limited domestic transmission.

Introduction

After identification of the first cases in April 2009, the rapid spread of the new influenza A(H1N1)v pandemic is a clear signal that global spread of this new virus is inevitable. Within six weeks the novel influenza A(H1N1)v virus has spread as far as previous pandemic influenza viruses have spread within six months [1].

As of 15 July, the European Centre for Disease Prevention and Control (ECDC) reported 125,993 confirmed human cases worldwide from 129 countries with a total of 667 deaths. Most deaths occurred by far in the United States (n=211), Argentina (n=137) and Mexico (n=124) [2].

The first German case was notified on 27 April 2009. However, the dynamics of the unfolding pandemic in Germany and the rest of Europe differed markedly from that of North America.

We present data reported during the first two months including cases notified until 16 June 2009. The information is therefore focussed on the characteristics of the early stage of the evolving pandemic in Germany.

Methods

Immediately after the first cases in the United States became public the Robert Koch Institute (RKI) established a case-based reporting of influenza A(H1N1)v. Information on possible, probable and confirmed cases was collected in a database.

A possible case was defined as a person with febrile ($\geq 38^{\circ}\text{C}$) respiratory illness and with (a) an epidemiological link to a country with domestic transmission or (b) contact to a probable or confirmed case, (c) residence in a county or region with at least five cases that had no epidemiological link to a country with domestic transmission or a confirmed case or (d) laboratory exposure.

A probable case was defined as a person with a laboratory diagnosis of influenza A with a negative test result for seasonal influenza (A/H1 and A/H3).

A confirmed case was defined as a person who had a sample positive for influenza A(H1N1)v virus confirmed by the National Reference Laboratory (NRL) or by a laboratory approved for surveillance by the NRL.

A case was considered as imported if the date of onset of symptoms was within seven days after departure from a country with sustained community-level transmission. By 16 June 2009 according to the definition of the Robert Koch Institute this included: Argentina, Australia, Chile, Costa Rica, El Salvador, Honduras, Israel, Canada, Mexico, New Zealand, Panama, Singapore, Spain, United Kingdom, Uruguay and the United States. If no recent travel history to one of these countries fulfilling the RKI definition at the time of travel was reported, the case was considered as indigenous.

For laboratory-confirmed cases (self-) isolation was recommended (adults: for seven days, children: for 10 days after onset of symptoms)

Contact management in the early phase was as follows:

All contacts of confirmed and probable cases were registered at local health authorities and informed about pandemic influenza (H1N1). Contacts were classified in two categories: 1) close contacts (e.g. household contact or sexual partner or unprotected person involved in patient care or treatment) and 2) repeated casual contacts (including conversation and physical contact).

Measures for close contacts included home quarantine for seven days after the last relevant contact, daily health monitoring by local health authorities and consideration of antiviral prophylaxis for 10 days. Less close contacts were advised to reduce contact to vulnerable persons for seven days.

Results

As of 16 June 2009, 198 laboratory confirmed cases of influenza A(H1N1)v have been detected in Germany (Figure 1).

Of the 190 confirmed cases, for whom the sex was reported, 110 (58%) were female. Cases ranged in age from 1 to 67 years, with an average of 23 years and a median of 18 years (Figure 2). The majority of the female cases in the age-group 10-19 years can be explained by the high number of infected girls associated with a school outbreak, where 70% of students in the two affected classes were female.

The confirmed cases were distributed over 14 districts (Figure 3).

While in the beginning most cases were imported, the proportion of indigenous cases has increased since 2 June 2009 (Figure 1). Overall 93 cases (47%) were imported.

The most frequently involved countries were: United States with 77 cases (83%), Mexico with 10 (11%), Argentina with three (3%) and United Kingdom, Canada and Panama with one case each (total 3%).

105 domestic cases (53%) were notified. Amongst these the source of the infection was known in 96 cases (91%). Out of these

FIGURE 1
Laboratory-confirmed cases of influenza A(H1N1)v by date of notification and source of infection, Germany, as of 16 June 2009 (n=198)

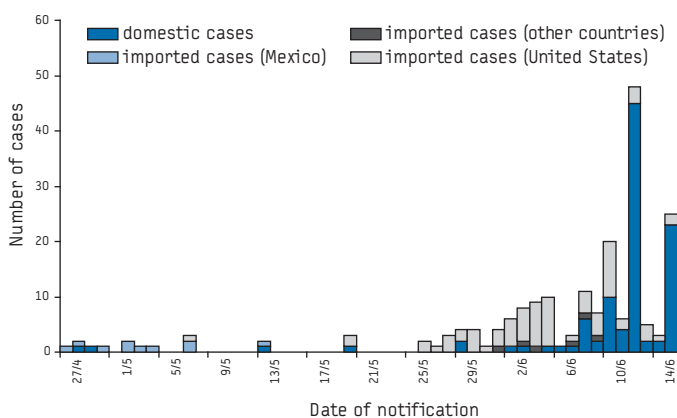
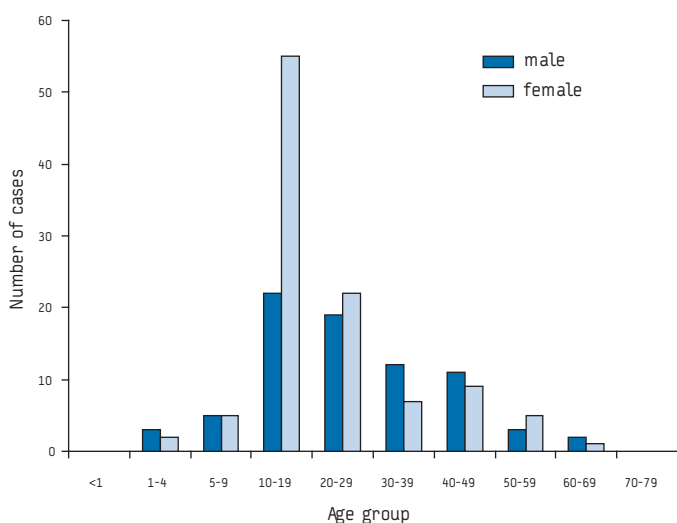


FIGURE 2
Age and sex distribution of laboratory-confirmed cases of influenza A(H1N1)v, Germany, as of 16 June 2009 (n=183)*



*Note: Data on age or sex was unavailable for 15 cases

96 cases 73 (76%) were outbreak-related and 23 related to an imported case (20 secondary cases=direct contact to an imported case, and 3 tertiary cases=direct contact to a secondary case). The infections of these 96 cases were most likely acquired in the following settings: school (73 cases), family/household (8), private party (6), healthcare (3), child care centre (3) and unknown (3).

For nine cases notified in June that were not restricted to a certain area the source of infection was unknown, i.e. the case did not report any travel history or contact to a confirmed case and was not part of an outbreak.

Four larger outbreaks (≥ 5 cases) have been identified: one outbreak associated with a child care centre (5 cases), one outbreak following a private party (6 cases) and two recent outbreaks related to two schools in North Rhine-Westphalia (16 and 58 confirmed cases so far).

The clinical features of the confirmed cases are shown in Figure 4. In 29% of all confirmed cases information about symptoms was not (yet) available. Asymptomatic infection occurred in 3% of cases.

Reliable information on comorbidities is only available for a limited number of cases, who have been followed up intensively. Among 18 of these cases four reported underlying medical conditions including metastasising carcinoid, arterial hypertension, hypothyroidism and chronic respiratory disease.

Hospitalisation was reported for 40 cases (20%), the reasons were primarily infection control measures, not disease severity. Detailed information on the severity of the infection is pending, but up to 16 June 2009 no case was known to require mechanical ventilation and no deaths were been reported.

Data on vaccination status was available for 49% of confirmed cases. Of these, 11% (n=11) had a history of vaccination with seasonal influenza vaccine.

In 55% of cases information on contacts ascertained by the local health authorities was available. The mean number of contacts per case was five (range 0-291). The type of contact and applied infection control measures are currently under investigation.

For those cases (n=22) that have been followed up intensively the number of contacts who acquired influenza A(H1N1)v infection was calculated per case. Seven contacts had a PCR-confirmed infection, corresponding to 0.3 infected contacts per case. None of the symptomatic contacts with a confirmed infection had received timely antiviral prophylaxis. This calculation was performed for cases notified before 4 June 2009. With an increasing number of indigenous cases and the occurrence of larger outbreaks this ratio is now expected to increase considerably.

Discussion

The characteristics of cases in the beginning of the pandemic closely resemble the data presented by other European countries (e.g. United Kingdom [3]) and Japan [4] in the early phase of the pandemic.

The majority of cases in the beginning were imported from Mexico and the United States. Strategies for early detection and

FIGURE 3

Geographical distribution of laboratory-confirmed cases of influenza A(H1N1)v, Germany, as of 16 June 2009 (n=198)

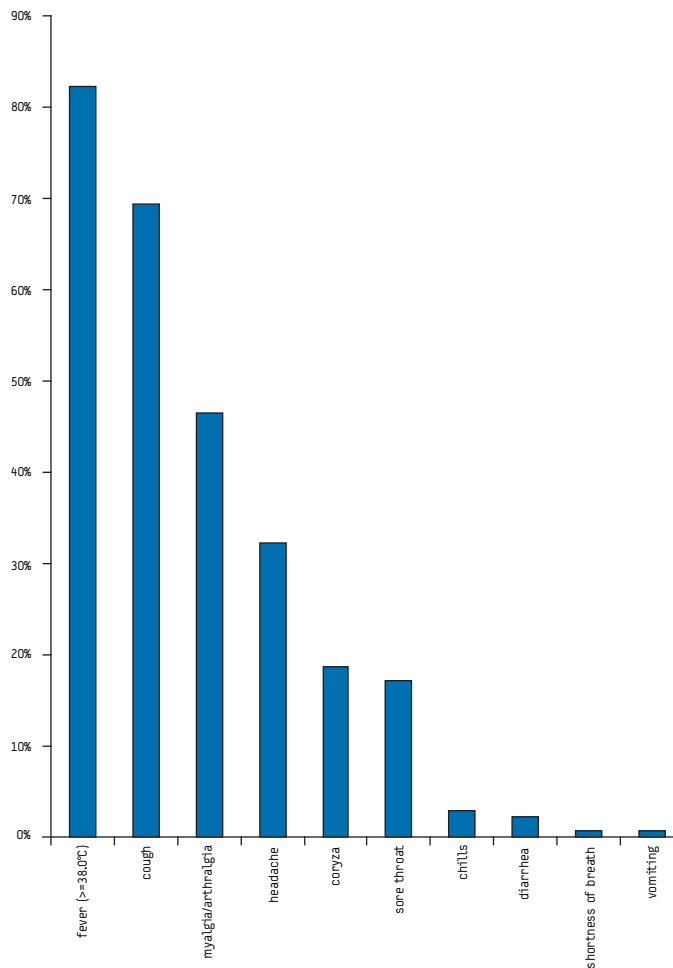


management of these cases seemed to work in this stage as no recommendations for travel restriction were in place. In the time period described Germany did not experience an exploding number of cases, however this might not only be due to the effect of the control measures taken but also due to other factors [5].

According to our results the first two months represented the early stage of the pandemic in Germany characterised by a high proportion of cases being imported, short chain of infections and limited outbreaks within the general population. The number of cases showed a rapid incline since mid-July 2009 with 7,963 confirmed cases notified until 5 August 2009 (of these, 6,259 cases (79%) were imported). However the overall picture has not changed considerably since 16 June since the recent increase is mainly due to travellers, in part German high-school graduates, returning from Spain and UK.

Due to the increasing case numbers the surveillance system has by now been changed from reporting of suspected cases individually

FIGURE 4
Clinical presentation of laboratory-confirmed cases of influenza A(H1N1)v, Germany, as of 16 June 2009 (n=140)*



*Note: Data on symptoms was unavailable for 58 cases

by fax to the routine case-based electronic notification to the state and national level of laboratory-confirmed cases and cases with an epidemiological link to a laboratory-confirmed case.

Taking into account the mildness of symptoms in the majority of cases the strategy for contact management has been adapted recently. Only close contacts (definition as above) with either a) an increased risk of severe infection (e.g. immunocompromised or chronic ill patients or pregnant women or infants) or b) with close contacts to vulnerable groups or with a high risk of causing outbreaks (e.g. in schools) are being followed up. The adapted measures are now focused on close contacts.

Furthermore, information on hospitalisation, treatment and risk groups are collected through the electronic notification system as with an increasing number of cases the burden of disease and severity of the clinical presentation becomes the main focus of the monitoring.

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WHAT WILL THE NEXT INFLUENZA SEASON BRING ABOUT: SEASONAL INFLUENZA OR THE NEW A(H1N1)v? AN ANALYSIS OF GERMAN INFLUENZA SURVEILLANCE DATA

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For the next influenza season (winter 2009-10) the relative contributions to virus circulation and influenza-associated morbidity of the seasonal influenza viruses A(H3N2), A(H1N1) and B, and the new influenza A(H1N1)v are still unknown. We estimated the chances of seasonal influenza to circulate during the upcoming season using data of the German influenza sentinel scheme from 1992 to 2009. We calculated type and subtype-specific indices for past exposure and the corresponding morbidity indices for each season. For the upcoming season 2009-10 our model suggests that it is unlikely that influenza A(H3N2) will circulate with more than a low intensity, seasonal A(H1N1) with more than a low to moderate intensity, and influenza B with more than a low to median intensity. The probability of a competitive circulation of seasonal influenza A with the new A(H1N1)v is low, increasing the chance for the latter to dominate the next influenza season in Germany.

Background

A new influenza A(H1N1) variant has spread globally since its first appearance in April 2009 [1] and its transmissibility has been estimated in a range similar to that known from seasonal influenza. Nevertheless it is unclear if this new influenza A(H1N1)v will replace seasonal influenza A or there may be co-circulation or successive circulation, in particular considering that A(H1N1)v has been circulating very early, ahead of the season. Cross immunity of the new influenza A(H1N1)v with seasonal influenza viruses is very low and probably negligible except for elderly people [2]. Hence a general susceptibility of the population to the new A(H1N1)v is assumed, even though not immunity-based mechanisms may additionally influence susceptibility [3,4]. For seasonal influenza A partial immunity of the population due to previous infections can be assumed. A rather constant drift with significant antigenetic changes - when a new successful lineage evolves - allows the virus to overcome this immunity [5]. The imbalance of population immunity and drift is seen as a driving force for intense virus circulation. The exact correlate of molecular or antigenic drift - as characterised by laboratory methods - on this balance is unknown.

In most European countries primary care sentinel surveillance systems are used to estimate the "intensity" of seasons and laboratory testing of a sub-sample indicates the viruses circulating.

These data do not provide exact measurements of virus circulation and subsequent population immunity. However, assuming a stable relationship between population immunity and virus circulation, the latter can serve as a proxy measure of type- and subtype-specific population immunity. For the upcoming season a seasonal influenza vaccine and a vaccine against the new influenza A(H1N1)v will be available with some remaining uncertainties regarding the amount of each. Therefore anticipating the circulation of the different seasonal influenza viruses - still present in the population - and the new A(H1N1)v virus may be helpful for setting up the vaccination strategy.

Materials and methods

We calculated type- and subtype-specific indices of past exposures and morbidity indices by season. We used data of the German influenza sentinel system (AGI) which has been registering acute respiratory tract infections in the winter seasons since 1992 (available at <http://influenza.rki.de/>). In this system the presence of influenza viruses is monitored through syndromic sentinel surveillance and, additionally, a sub-group of participating physicians swab patients with acute respiratory tract infections and send samples for testing to the national influenza reference centre (NIC).

In order to allow the calculation of indices for as many seasons as possible, in addition, virological data from NIC for the five seasons before 1992-3 were used.

For each season we estimated the total influenza-associated morbidity from weekly excess consultations (as percentage above baseline) during periods of laboratory-confirmed influenza activity [6]. Splitting this total excess morbidity by the percentages of detected influenza types and subtypes gave the type- and subtype-specific morbidity index for each season.

To calculate indices of past exposure we used the morbidity indices of the five preceding seasons. However, it is unclear for how long immunity acquired during past exposures persists. We therefore used weighting factors to adjust for the decreasing influence of more distant seasons. Each of the five included

seasons was weighted with a factor that was kept constant for all calculations. The set of weighting factors giving the best linear correlation for all seasons between the morbidity index of each season and the morbidity indices of the respective five preceding seasons was chosen. The sum of the five weighted morbidity indices gave the past exposure index for the respective season.

Results

The figures show the distribution of the value pairs of the estimated past exposure and morbidity indices for each season (1992-3 to 2008-9), by influenza type and subtype. Estimates obtained using data exclusively of the NIC are plotted in grey, estimates obtained using data of the AGI are in blue, and the estimate for the past exposure index for the upcoming season (2009-10) is plotted as a blue arrow. For influenza A(H3N2) and

B the best linear correlation (-0.55 for A(H3N2) and -0.62 for B) was seen when the morbidity index of just the directly preceding season was used to estimate the past exposure index. For seasonal influenza A(H1N1) the best correlation (-0.46) was obtained with weighting factors that left a greater relative contribution to more distant seasons (preceding season: weighting factor = 1; two years ago = 1.4⁻¹; three years ago = 1.9⁻¹; four years ago = 2.7⁻¹; five years ago = 3.8⁻¹).

For all seasonal influenza viruses the distribution pattern is similar: the probability of a high excess morbidity - as correlate of intense virus circulation - is low when the past exposure index is high. For median past exposure indices low to moderate seasons can be expected and for low past exposure indices severe seasons may but do not need to occur. These distributions of the value pairs (past exposure and morbidity indices) are typical of distributions which reflect a limiting influence, i.e. the past exposure indices represent a kind of upper bound for the morbidity indices of the corresponding seasons. Seasons with no measurable intensity are rare for influenza A(H3N2), frequent for seasonal A(H1N1) and occur with intermediate frequency for influenza B.

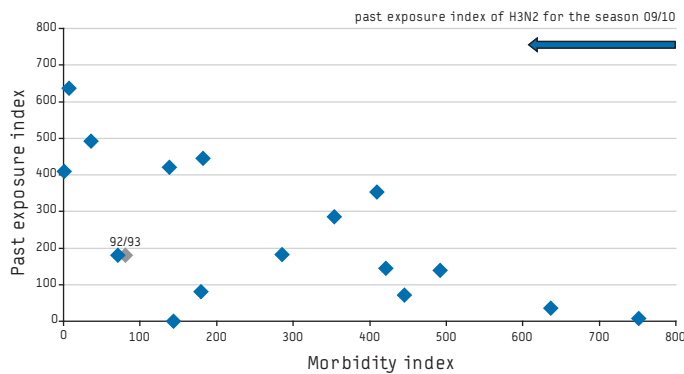
Influenza A(H3N2) reaches the highest indices of past exposure and morbidity. However, direct comparability of past exposure indices is only given between influenza A(H3N2) and influenza B. Their respective past exposure indices are based on the same number of seasons and the identical weighing factors.

For the next influenza season in Germany the results of our model suggest that it is very unlikely that influenza A(H3N2) will circulate with more than a low intensity. The same can be concluded for seasonal A(H1N1) with a slight chance to reach a moderate intensity level. Influenza B may circulate with up to a median intensity.

Discussion

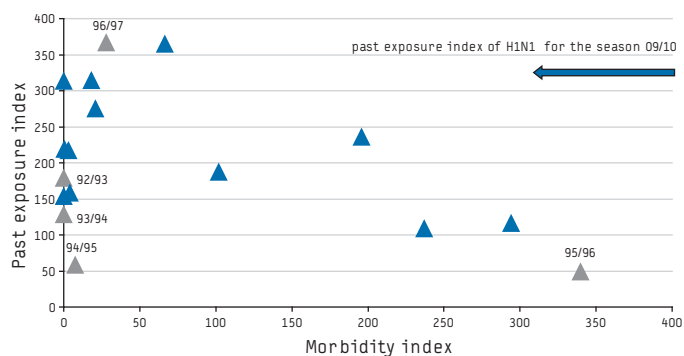
Predictions of the circulation of influenza viruses in upcoming seasons are highly desirable but generally accepted models are still

FIGURE 1
Estimates of past exposure and morbidity indices of influenza A(H3N2), Germany, 1992-3 to 2008-9



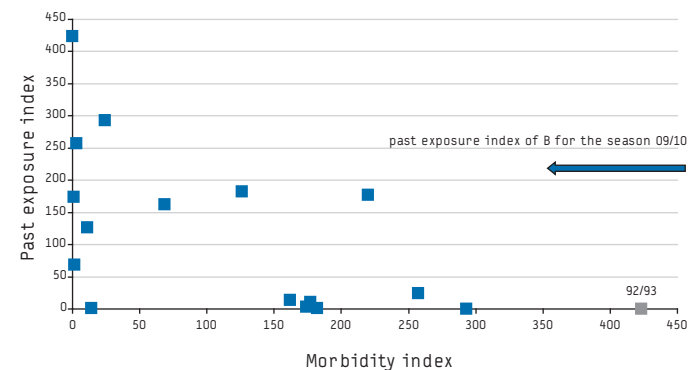
Note: Estimates obtained using only virological data from the national influenza reference centre (NIC) are plotted in grey, estimates obtained using data of the influenza sentinel system (AGI) are in blue, and the estimate for the past exposure index for the upcoming season (2009-10) is plotted as a blue arrow.

FIGURE 2
Estimates of past exposure and morbidity indices of seasonal influenza A(H1N1), Germany, 1992-3 to 2008-9



Note: Estimates obtained using only virological data from the national influenza reference centre (NIC) are plotted in grey, estimates obtained using data of the influenza sentinel system (AGI) are in blue, and the estimate for the past exposure index for the upcoming season (2009-10) is plotted as a blue arrow.

FIGURE 3
Estimates of past exposure and morbidity indices of influenza B, Germany, 1992-3 to 2008-9



Note: Estimates obtained using only virological data from the national influenza reference centre (NIC) are plotted in grey, estimates obtained using data of the influenza sentinel system (AGI) are in blue, and the estimate for the past exposure index for the upcoming season (2009-10) is plotted as a blue arrow.

lacking [7-9]. This is mainly due to the multitude of factors involved and limited data availability and quality. The data we used on morbidity and virus circulation have been collected systematically for 17 years, thus providing a reasonable basis for the approach we used.

This analysis is based on the assumption of a type- and subtype-specific link between past exposure and virus circulation in the following season. In our results for influenza A(H3N2) and B a short lived “protection” of past exposure is suggested. These results are in line with a short-lived strain overlapping immunity as suggested by modelling studies [7].

We consider the chances for the seasonal influenza viruses to lead to considerable morbidity during the upcoming influenza season 2009-10 to be very low. Should the A(H1N1)v virus circulation during the upcoming season 2009-10 be high enough, the expected low seasonal activity may lead to a rapid total replacement, as seen in previous pandemics (except for the 1977 H1N1). However, if the activity of the A(H1N1)v during the season 2009-10 is a pre-wave and a severe circulation of A(H1N1)v will be seen in the following season 2010-1, the possibly low past exposure index for the 2010-1 season in Germany may hamper a total replacement [7].

This model has several limitations. Regional differences in virus circulation are not taken account of. The frequency of laboratory testing varies during one season and, additionally, depends on type- and subtype-specific disease severity, thus potentially biasing the relative contributions of the different virus types and subtypes. In addition, a relatively short time series (17 value pairs for each type/ subtype) limit the applicability of complex statistics.

In conclusion, our systematic approach may reduce the unpredictability of influenza activity and thus contribute to strategic planning, e.g. regarding vaccination priorities. These results should be confirmed with data obtained from different surveillance systems. Further improvements of this model may then address its current limitations and additionally offer the possibility to include other factors, such as weather conditions [8], holidays or historical experiences regarding timing and trend [9].

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EPIDEMIOLOGICAL AND TRANSMISSIBILITY ANALYSIS OF INFLUENZA A(H1N1)V IN A SOUTHERN HEMISPHERE SETTING: PERU

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We present a preliminary analysis of 1,771 confirmed cases of influenza A(H1N1)v reported in Peru by 17 July 2009 including the frequency of the clinical characteristics, the spatial and age distribution of the cases and the estimate of the transmission potential. Age-specific frequency of cases was highest among school age children and young adults, with the lowest frequency of cases among seniors, a pattern that is consistent with reports from other countries. Estimates of the reproduction number lie in the range of 1.2 to 1.7, which is broadly consistent with previous estimates for this pandemic in other regions. Validation of these estimates will be possible as additional data become available.

Introduction

On 24 April 2009, the World Health Organization (WHO) informed about an epidemic caused by new swine-origin influenza A(H1N1)v virus originating from Mexico, and declared a public health emergency of international importance. The level of influenza pandemic alert was raised sequentially up to phase 6 on 11 June 2009 after global spread of the pandemic virus was confirmed [1].

In this study we present an analysis of 1,771 confirmed cases of influenza A(H1N1)v who developed the disease by 17 July 2009 and were reported to the National Surveillance Network in Peru, which since 2006 has conducted virological surveillance of influenza and other respiratory viruses by establishing sentinel sites throughout the country [2]. The patients' age distribution, their clinical characteristics as well as their spatial distribution were studied. Estimates of transmission potential from the initial epidemic phase were also derived and compared with published estimates from other regions of the world.

Methods

Surveillance system

On 24 April 2009, the public health authorities of Peru implemented new regulations for epidemiological surveillance and outbreak control of influenza A(H1N1)v defining the procedures of

FIGURE 1

Geographical distribution of confirmed cases of influenza A(H1N1)v in Peru, as of 17 July 2009 (n=1,771)



detection, notification, investigation, follow-up and epidemiological control of A(H1N1)v cases in Peru.

An active surveillance system was established at all airports (especially in travellers returning from affected areas) and healthcare facilities, including private clinics. Also a telephone hotline (INFOSALUD) was made available by the Ministry of Health for citizens reporting influenza-like illness. A suspected case was defined as a person with a sudden onset of fever ($\geq 38^{\circ}\text{C}$) and respiratory symptoms. Suspected cases and their contacts were visited in their homes for clinical evaluation and nasal or pharyngeal specimens were taken from symptomatic persons and submitted to the National Institute of Health or the United States Naval Medical Research Center Detachment for RT-PCR as described by the Centers for Disease Control and Prevention (CDC). Suspected cases were informed about control measures to limit spread (voluntary isolation, use of face masks, and increased hygiene). Contacts of cases were monitored daily via phone calls or home visits. Symptomatic contacts were subjected to the same procedure as suspected cases. Clinical and epidemiological data were collected utilising a case report form (CRF) from all patients who met the case definition. Antivirals were given to all suspected cases until early July when the containment strategy was replaced by mitigation approach and treatment began to be administered only to high-risk groups.

Descriptive epidemiology

Based on the clinical and epidemiological data of the National Surveillance Network, we characterised the descriptive

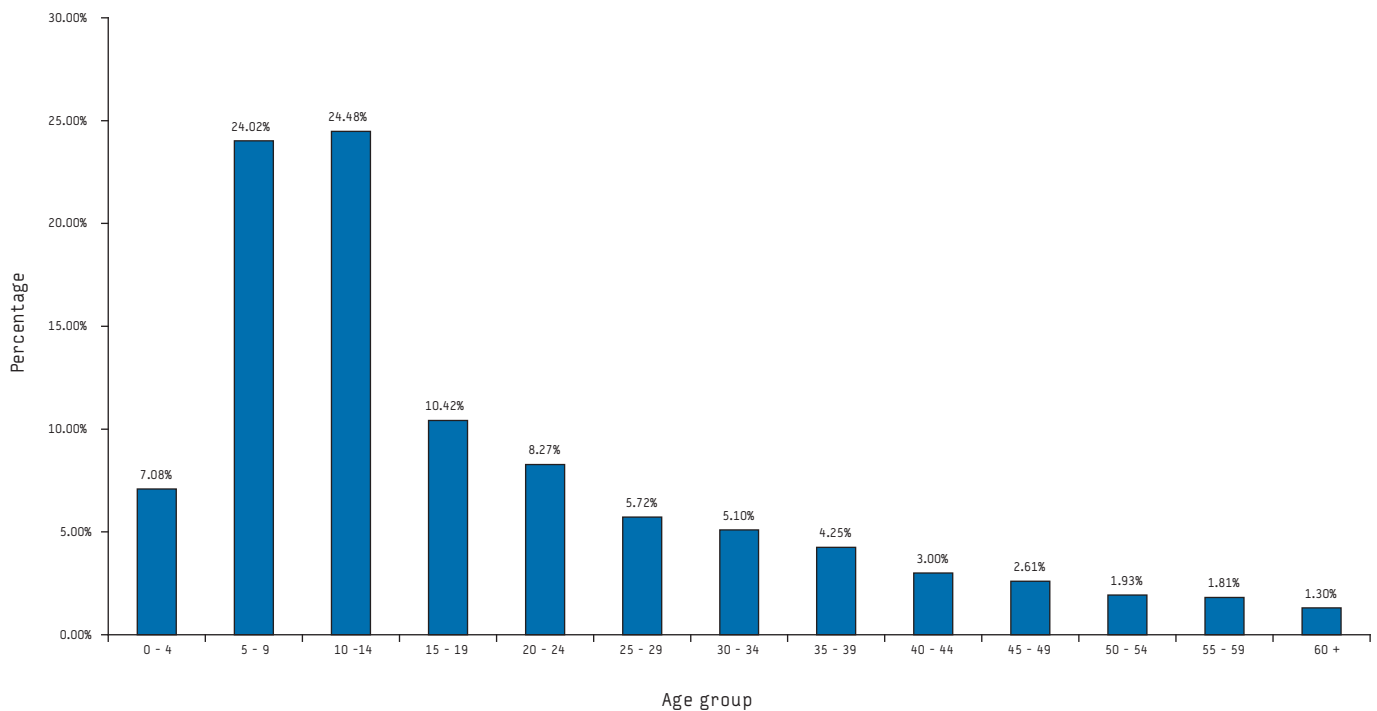
epidemiological features of influenza A(H1N1)v infection in Peru. First, we described the distribution of cases as a function of space, age and gender. Time-dependent characteristics were more analytically examined to estimate the transmission potential (see below). We also examined travel history of cases returning from countries with ongoing epidemics of A(H1N1)v infection, and the age-distributions between imported and indigenous cases were compared by means of non-parametric Mann-Whitney test. Second, we characterised frequency of symptoms reported for confirmed cases. The clinical-epidemiological forms were entered into a database created in Microsoft (MS) Office Access 2003, and data were analysed using MATLAB (The Mathworks, Inc.).

Estimation of transmission potential

A key epidemiological quantity which informs the expected magnitude of an epidemic is the basic reproduction number (denoted by R_0), defined as the average number of secondary cases generated by a primary case in an entirely susceptible population [3,4]. When $R_0 > 1$ an epidemic can occur while $R_0 < 1$ cannot support an epidemic. The reproduction number, R was estimated exploring time-evolution of confirmed cases. Statistical methods were based on pure birth process (to estimate the intrinsic growth rate r) and renewal process (to estimate R using r), and were identical to those given elsewhere [5]. Whereas we analysed the temporal distribution including all possible primary cases (i.e. including imported cases) as the number of imported cases was in a negligible order, we also examined the estimate excluding imported cases (as it can then exclude imported cases from the category of secondary cases).

FIGURE 2

Age distribution of confirmed cases of influenza A(H1N1)v reported in Peru as of 17 July 2009 (n=1,765*)



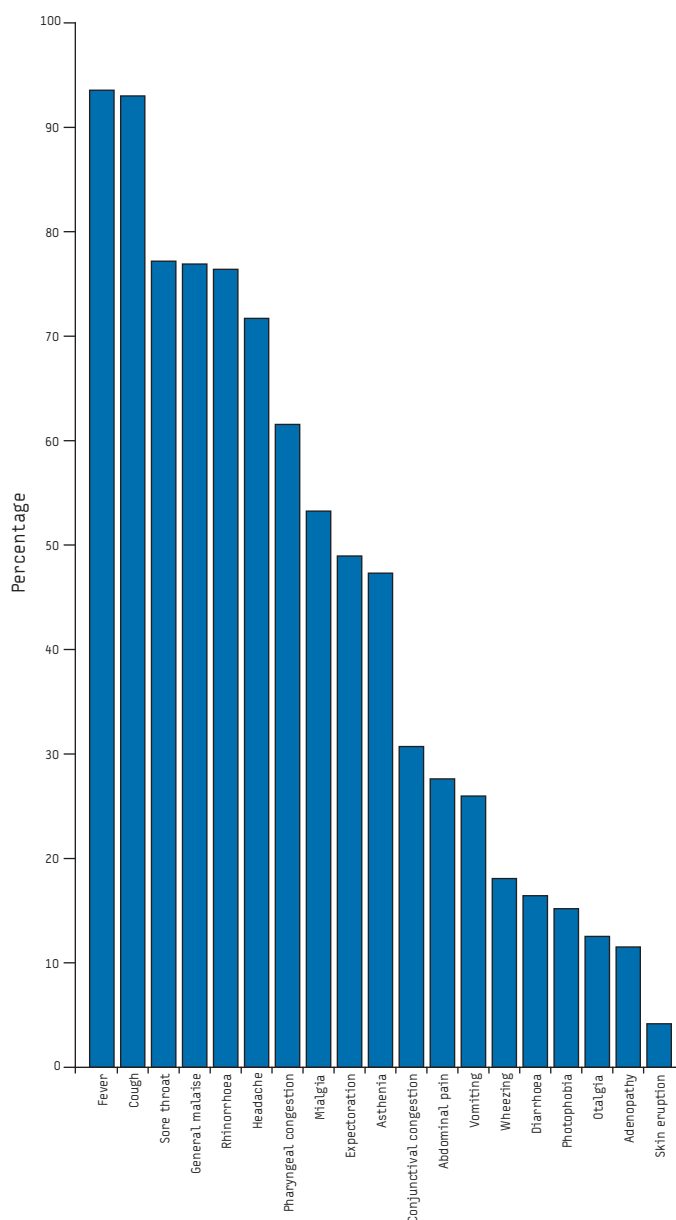
*Number of cases with available data on age

Results

The first influenza A(H1N1)v confirmed case in Peru was a Peruvian citizen returning from New York on 9 May with a respiratory disease. Since then the pandemic has quickly spread throughout the country. As of 17 July 2009, a total of 1,771 cases, involving eight deaths, have been confirmed. This yields a crude case fatality ratio of 0.33 % (95% confidence interval: 0.14, 0.65). Of the 1,771 cases, 1,420 (80.1%) were from Lima, the capital city, 84 (4.7%) from Piura and 81 (4.6%) from La Libertad. Figure 1 shows the geographic distribution of confirmed cases of influenza A(H1N1)v in Peru.

FIGURE 3

Clinical characteristics of confirmed cases of influenza A(H1N1)v reported in Peru as of 17 July 2009 (n=1,771)



A total of 78 (4.4%) confirmed cases had a history of recent travel to the United States, Dominican Republic or Argentina. Imported cases generated clusters of different sizes that established indigenous transmission in Peru. For example, between 8 and 30 May, 600 private high school students travelled to Punta Cana in the Dominican Republic for vacations. One student presented influenza-like illness before returning and other 11 students developed symptoms upon returning to Peru.

Females (52%) were slightly more affected than males (48%). The most affected age group was that of 5-14 years (Figure 2). The age of the cases ranged from 0 to 87 years with a mean of 18.5 years and a median of 13 years. The mean age of the imported cases was 28 years while indigenous cases had a mean age of 18 years (Mann-Whitney test, $P < 0.001$).

Figure 3 summarises the clinical characteristics of the confirmed cases of influenza A(H1N1)v infection. The most frequent symptoms were fever (94%), cough (93%), sore throat (77%), general malaise (77%) and rhinorrhoea (76%). Gastrointestinal symptoms including abdominal pain (28%), vomiting (26%) and diarrhoea (16%) were not uncommon.

Epidemic curve and transmissibility

Figure 4A shows the temporal distribution of confirmed cases as a function of the date of onset. The number of cases greatly increased from mid-June to mid-July. It should be noted that cases in mid-July are likely underestimated due to reporting delay, and the temporal dynamics are also influenced by spatial spread from Lima to the rest of the country in the subsequent time periods. Based on the epidemic curve, the first three weeks (from 6 to 29 May) were considered as “random phase”. Informed by deviation of our simple model from the observed data (i.e. Akaike Information Criterion obtained from negative loglikelihood and a single parameter to be estimated), 30 May was assumed to be the starting time point of exponential growth (and called Day 1). We also assumed that the exponential growth phase continued up to 20 June (for three weeks which should capture the dynamics of the first 6-10 generations), while allowing plus/minus two days. Including all imported cases, the intrinsic growth rate, r was estimated at 0.117 (95% CI: 0.106, 0.128) per day. Excluding all imported cases, r was estimated at 0.135 (95% CI: 0.122, 0.149) per day. Assuming that the mean generation time = 2.8 days, and coefficient of variation (CV) = 47.1%, R for these settings was estimated at 1.37 (95% CI: 1.33, 1.41) and 1.44 (95% CI: 1.39, 1.49), respectively. Figure 4B compares observed and predicted epidemic curves. We also examined the sensitivity of R for different lengths of mean generation time (ranging from 1.6 to 4.0 days) (Figure 4C), and the maximum likelihood estimate of R ranged from 1.2 to 1.6. When we use different windows (18 June to 22 June as the latest time points of exponential growth), R appeared to range from 1.3 to 1.4 (Figure 4D).

Discussion

The current pattern of spread of influenza A(H1N1)v in Peru is dominated by a wave that emanates from the capital city, Lima, the early dynamics of which may most likely be associated with high frequency of international travel, thereby increasing the chances of a major epidemic in the capital city.

Our early findings indicate that public health interventions need to be in accord with the epidemiological behaviours (e.g. temporal

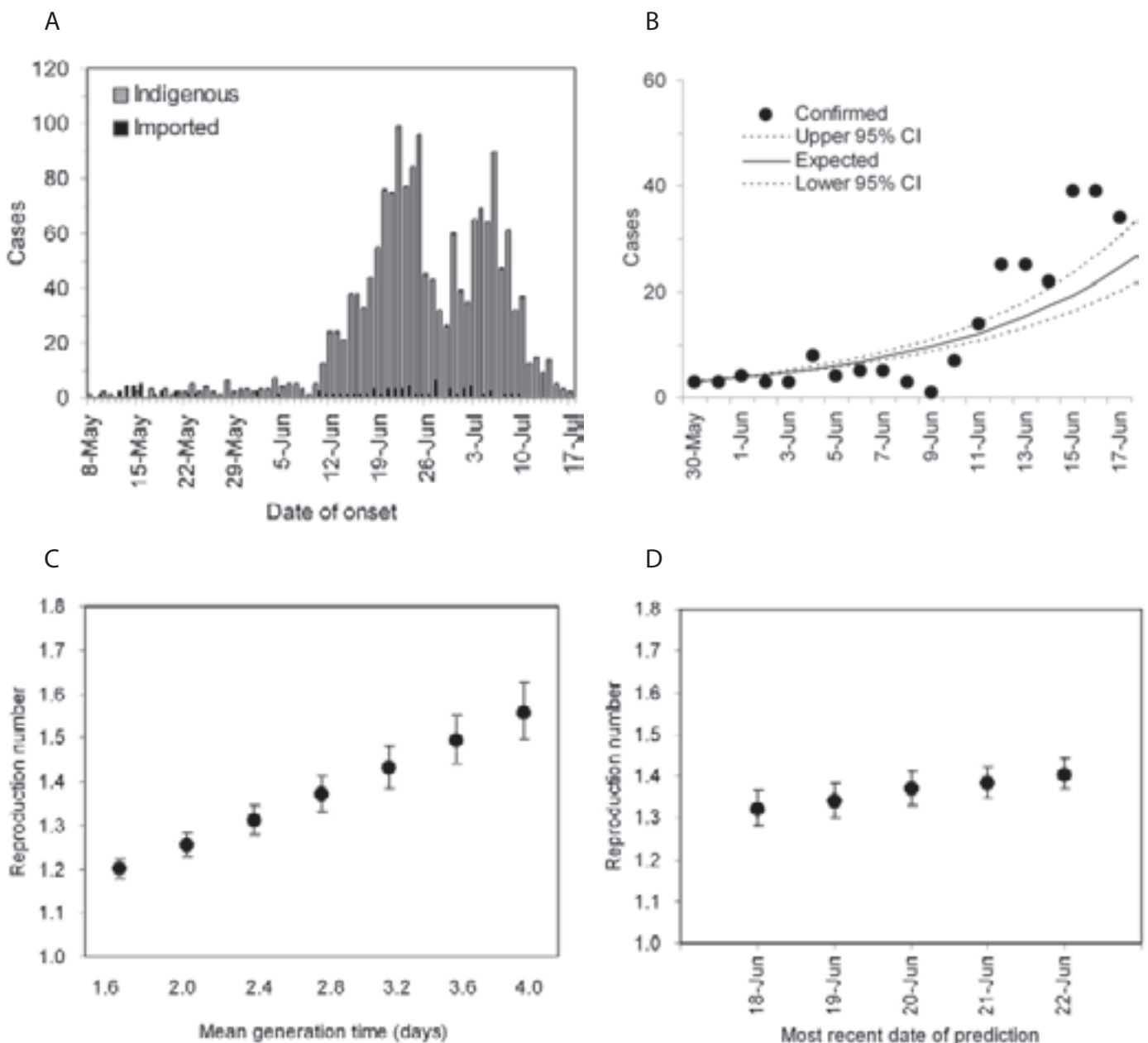
and spatial increase) and moderate severity of the disease. For instance, while in some countries radical control measures aimed at rapid containment, such as contact tracing and complete proactive school closures, were conducted during the early phase of this pandemic, the epidemic in Peru without obvious school clusters during the early phase did not offer an opportunity to implement similar countermeasures. In such settings it may be more realistic

to focus interventions on minimising mortality at the population level (e.g. early diagnosis and treatment of severe cases).

Despite the lack of obvious large clusters, the great majority of cases were documented among school age children and young adults, with the lowest frequency of cases among seniors, a pattern that is consistent with reports from other countries [5-8]. It should be noted that the age-distribution of cases could change as the

FIGURE 4

A) Epidemic curve of confirmed cases of influenza A(H1N1)v in Peru by date of symptoms onset, 8 May 2009 to 17 July 2009; B) Exponential growth fit to the early epidemic phase of influenza A(H1N1)v in Peru. Data are the black dots, the solid line is the exponential fit to the data, and dashed lines correspond to uncertainty bounds of the expectation based on the confidence limits of the intrinsic growth phase; C) The reproduction number estimates from the early epidemic phase of the epidemic curve of influenza A(H1N1)v cases in Peru as a function of plausible mean generation times and D) using different end dates of the initial growth phase.



epidemic develops. Also, it should be noted that the impact of high school and university students (i.e. those aged from 15 to 19 years) on the transmission dynamics is presumably smaller than that observed in Japan [5]. While this age group, especially the presence of high-school clusters, may have contributed more significantly to generating a higher estimate of R in Japan [5], our estimate of R is probably less affected by such school clusters and therefore not so likely to be an overestimate.

The frequency of respiratory symptoms recorded for A(H1N1)v cases in Peru is in line with those reported for other influenza-like infections in Peru [8], but the gastrointestinal symptoms that included abdominal pain, vomiting and diarrhoea were remarkably more common among cases infected with the pandemic virus. Similar observations were made in other countries including Mexico [6] and Japan [9].

R was estimated at 1.37 in our setting in Peru. Sensitivity analysis revealed that the estimates lied in the range of 1.2 to 1.7, which is broadly consistent with previous estimates for this pandemic in other regions [10-12] and in line with estimates for seasonal influenza in temperate countries [13]. Nevertheless, it must be remembered that due to antiviral treatment which was administered to a substantial fraction of confirmed cases in early June our R calculation might be slightly underestimated. In addition, there is significant uncertainty associated with estimation of R in a setting where the reporting biases are likely to be changing on a daily basis. Validation of these estimates will be possible as additional data become available on population-based serosurveys and growth patterns observed in individual community-level outbreaks.

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Disclaimers

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Rapid communications

CASES OF INFLUENZA A(H1N1)v REPORTED IN TURKEY, MAY-JULY 2009

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Following the declaration by the World Health Organization (WHO) of human cases of infection with a new influenza A(H1N1)v virus of swine origin, the Turkish Ministry of Health launched a case-based reporting of influenza A(H1N1)v throughout the country on 27 April 2009. The index case was detected on 15 May 2009. As of 17 July 2009 the number of laboratory-confirmed cases of influenza A(H1N1)v totalled 128 of whom 38 were indigenous cases.

Introduction

Since the detection of the first human case of infection with a triple reassortant influenza A(H1N1)v virus in mid-April in California, United States [1], human cases of infection with this variant have been reported from countries throughout the world [2].

Here we report the first 128 cases of influenza A(H1N1)v identified in Turkey along with control measures taken by the Ministry of Health (MoH) for containment of the epidemic from 27 April to 17 July 2009.

Methods

Surveillance

Sentinel surveillance for seasonal influenza has been conducted in Turkey since 2003 in 14 out of 81 provinces. On 27 April 2009, after the official declaration of the first human case of new influenza A(H1N1)v by the World Health Organization, the Turkish MoH

implemented a case-based reporting of influenza A(H1N1)v that was extended throughout the year and included all 81 provinces of the country and the Turkish community in Cyprus. In this case-based reporting system the local health authorities (LHAs) were supplied by the MoH with case definition and patient information forms to be disseminated to all healthcare institutions in their province. LHAs in each province designated hospitals and clinics where all suspected cases were directed to, in order to better track and contain the infection. These designated hospitals and clinics were asked to take samples from patients who fulfilled the case definition criteria and send them for confirmation to the designated reference laboratories.

Laboratories

Turkey has two national influenza reference laboratories, the Refik Saydam National Public Health Agency (RSHM) that is located in Ankara and the National Influenza Reference Laboratory (NIRL) at Istanbul Faculty of Medicine that is located in Istanbul. Both reference laboratories were prepared for testing influenza A(H1N1)v with the real-time RT-PCR protocol and reagents supplied by the United States Centers for Disease Control and Prevention (CDC). The reference laboratory in Ankara was assigned 58 out of 81 provinces whereas the reference laboratory in Istanbul was assigned the remaining 23 provinces for testing samples from suspected cases. These 23 provinces include the cities that harbour major

TABLE 1

Case definition for influenza A(H1N1)v, Turkey, 2009

Clinical criteria	Any person with one of the following two symptoms: <ul style="list-style-type: none">• Fever >38°C with symptoms of acute respiratory infection• Infections accompanied with respiratory distress
Epidemiological criteria	<ul style="list-style-type: none">• Travel to a country within the past 7 days where human to human transmission of influenza A(H1N1)v has been confirmed.• Close contact with persons of confirmed influenza A(H1N1)v within the past 7 day.
Laboratory criteria	Positive results with one of the following: <ul style="list-style-type: none">• RT-PCR• Viral culture (in BSL3 facilities)• Fourfold increase in influenza A(H1N1)v virus specific neutralizing antibody titer.
Case definition	<ul style="list-style-type: none">A. Probable case• Any person meeting the clinical and epidemiological criteriaB. Confirmed case• Any person meeting the laboratory criteria

air and sea ports and resort towns. Laboratories report the results directly to the MoH immediately after the results are obtained. The MoH then informs the LHAs who contact the physicians and give necessary guidance to the physicians for the care of the patients.

Patients and samples

A probable case with influenza A(H1N1)v is defined as a person with high fever (≥ 38 °C) and/or at least two acute respiratory symptoms along with epidemiological criteria listed in the case definition protocol published by WHO [2]. Table 1 summarises the case definition that was prepared in light of the information released by WHO. However, during the first month of the pandemic, in addition to probable cases, samples were also taken from individuals with no detectable symptoms but with either travel history to areas of high prevalence and/or close contact with a confirmed case, who presented in hospitals and asked to be tested. Nasal and/or nasopharyngeal samples along with patient information forms from suspected cases were transported to reference laboratories in a viral transport medium (Virocult, Medical Wire&Equipment, UK). A total of 977 samples from suspected cases were sent to the reference laboratories between 27 April and 17 July 2009 from various cities in Turkey (n=899) and from the Turkish Cypriot community (n=78).

Laboratory diagnosis (real-time RT-PCR)

Both laboratories used the same “in-house” real-time PCR protocol provided by CDC for detection of influenza A(H1N1)v. RNA extraction was done with QIAamp viral RNA mini kit (Qiagen, Valencia, CA, USA) or with a High Pure Viral RNA isolation kit from Roche. Real-time RT-PCR was performed on ABI 7000 and/or 7500 [3]. NA, HA and M genes of the isolate from the index case were partially sequenced and the resulting sequences were analysed by CLC Main Workbench 4.1.1 Software program (Denmark).

Control measures and patient management

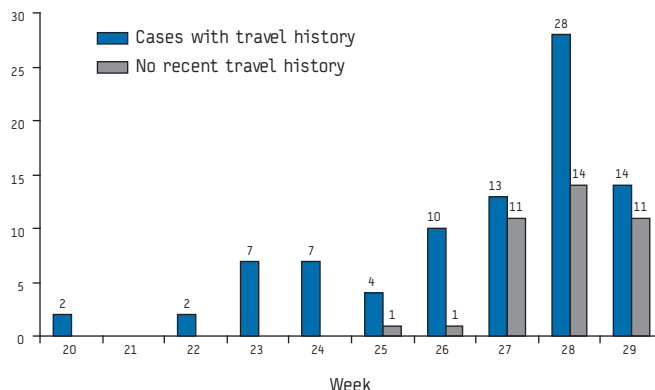
After the declaration of the pandemic by WHO on 11 June, the MoH held a meeting with its scientific advisory committee for revision of the pandemic plan. Revisions included the pandemic vaccination strategies (e.g. determining the priority order for vaccination), antiviral stockpiling and other measures. Two million doses of oseltamivir and 113,000 doses of zanamivir were distributed to all local healthcare centres. Four hundred thousand protective healthcare kits (each containing masks, gloves, hand disinfectant, goggles and foot covers) were distributed to healthcare providers, giving priority to those working at designated hospitals and clinics.

Special attention was given to the country points of entry such as airports and seaports. A thermal camera system was installed at airports and seaports in order to detect probable cases entering the country from regions of high prevalence. All travellers from abroad were requested to declare their health status and those captured by thermal camera system were further examined by physicians and suspected cases were isolated for transfer to the designated hospitals. Co-travellers sitting at close proximity (three seat lines in the front and back and on the sides) to confirmed cases were contacted by phone, informed about the situation and offered guidance on what they needed to do in case they developed symptoms and supplied with prophylactic doses of oseltamivir.

Two million pamphlets providing information on the flu pandemic were distributed to all flight crews and made available to travellers at airports and seaports. In addition, informative posters were posted at prominent places at ports and all public hospitals.

FIGURE 1

Figure 1. Number of travel-associated and indigenous cases of influenza A(H1N1)v, by week of laboratory confirmation, Turkey, May-July 2009 (n=125*)

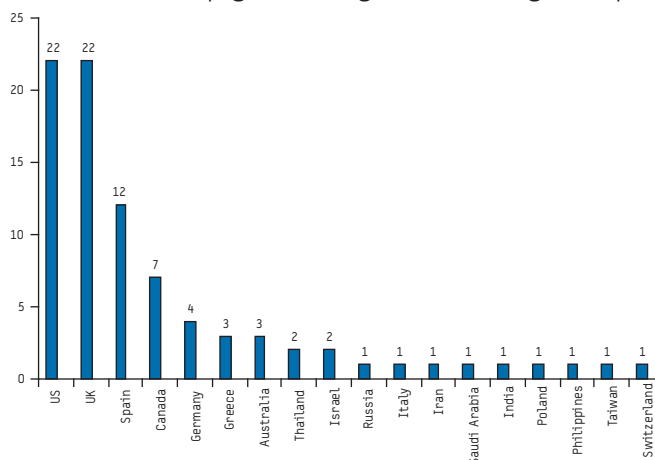


*Number of cases with available date of the laboratory confirmation. Case numbers collected by the Turkish Ministry of Health include cases from the Turkish Cypriot community.

FIGURE 2

Travel history of confirmed imported cases of influenza A(H1N1)v, Turkey, May-July 2009 (n=86*)

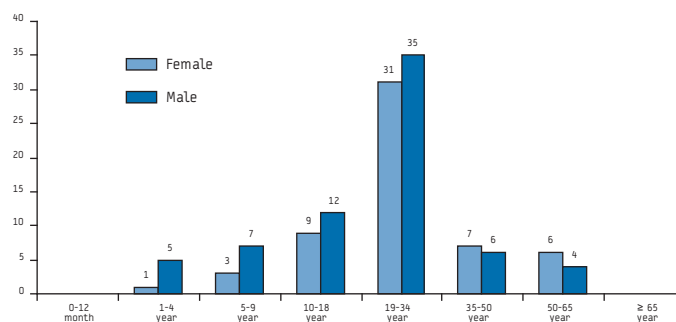
An interactive web page was designed to inform general public



*Number of cases with available data on travel history. Case numbers collected by the Turkish Ministry of Health include cases from the Turkish Cypriot community.

FIGURE 3

Age and sex distribution of confirmed cases of influenza A(H1N1)v, Turkey, May-July 2009 (n=126*)



*Number of cases with available data on age and sex. Case numbers collected by the Turkish Ministry of Health include cases from the Turkish Cypriot community.

and professionals about the pandemic influenza which included information on individual care for protection from contacting and transmitting influenza (www.grip.saglik.gov.tr). A telephone hotline was launched to serve public inquiries seven days a week 24 hours a day (Alo 184 SABİM). Television spots were prepared mainly to emphasise the importance of hand washing and usage of disposable tissue papers in protecting against contracting and transmitting the influenza virus. Daily press briefings were held during the first month of the pandemic to keep public informed about the pandemic status in Turkey.

Results

All samples received before the index case was detected on 15 May 2009 were processed immediately and results were reported to the MoH regardless of the time of arrival of the sample to the laboratory. After 15 May both laboratories provided results seven days per week. The average time between the swabbing to final diagnosis was 24 hours.

The index case was a United States resident travelling from Tennessee to Iraq through Ataturk Airport in Istanbul where his high temperature was captured by thermal camera. He was hospitalised in a designated hospital in Istanbul and treated with oseltamivir until laboratory tests were negative for influenza A(H1N1)v. By 17 July influenza A(H1N1)v was detected in 128 (13%) out of 977

samples tested. Of these 128 positive samples, 17 were from the Turkish Cypriot community*, the remaining 111 were from various provinces in Turkey. The number of samples positive for influenza A(H1N1)v increased remarkably from June onward. Figure 1 presents the number of travel-associated and indigenous cases of influenza A(H1N1)v, by week of laboratory-confirmation. Of the 111 confirmed cases in Turkey, 25 were domestic secondary cases. Of the 17 confirmed cases in the Turkish Cypriot community, 13 were indigenous. The travel history of the imported confirmed cases is summarised in Figure 2 and the age and sex distribution of all confirmed cases is shown in Figure 3.

The partial sequence analysis results of matrix, HA and NA segments were submitted to the National Center for Biotechnology Information (NCBI) GenBank with accession numbers GQ200600, GQ200598, and GQ200599 respectively. According to the topological phylogenetic analysis, results obtained from the partial nucleic acid sequencing isolate from the index case were closely related to isolates from the US and A/Catalonia/10/2009 (H1N1).

The majority of influenza A(H1N1)v-positive cases (n=80) were detected in samples received from Istanbul (Figure 4) which also included the majority of indigenous cases (n=22). The remaining three indigenous cases in Turkey were from Denizli, Antalya and Eskisehir. Two indigenous cases from Istanbul were detected in healthcare workers, one in a physician examining a laboratory-confirmed patient and another in a nurse responsible for taking the patient's sample in a private hospital setting. The physician and the nurse developed symptoms five days after contacting the patient; subsequent laboratory analysis confirmed these cases as influenza A(H1N1)v-positive.

Confirmed cases manifested moderate clinical symptoms. Three indigenous cases who contracted the virus from confirmed cases were asymptomatic. Clinical symptoms and their frequency in the confirmed cases are presented in Table 2.

The average time elapsed between the onset of the symptoms and the visit to the hospital (including those detected by thermal camera) was 1.68 days.

Of the 128 confirmed cases, 13 (10.2%) had received seasonal influenza vaccine in the past year. A similar proportion of vaccinated was found among patients who tested negative for influenza A(H1N1)v. All individuals who reported to the hospitals were closely monitored and those who were confirmed with influenza A(H1N1)v received antiviral treatment with oseltamivir. None of the confirmed cases developed any complications and no deaths occurred.

Conclusion

Influenza A(H1N1)v entered Turkey through travellers mainly coming from the United States and the United Kingdom. While the majority of confirmed cases in Turkey had a travel history to highly affected areas, confirmed cases from the Turkish Cypriot community* were mostly indigenous cases with no history of travel. The majority of the confirmed cases consisted of young adults as reported from other countries. This could be related to the frequency of travel among the young population [4]. The clinical manifestation of A(H1N1)v infection in the confirmed cases was similar to that observed in seasonal influenza. All cases manifested moderate clinical symptoms similar to those reported in other countries [5]. Cough was the most frequent symptom (68.7%) followed by fever >38°C (62.5%)**. None of the confirmed cases developed complications and no death was reported.

FIGURE 4
Geographical distribution of confirmed cases of influenza A(H1N1)v, Turkey, May-July 2009 (n=128)

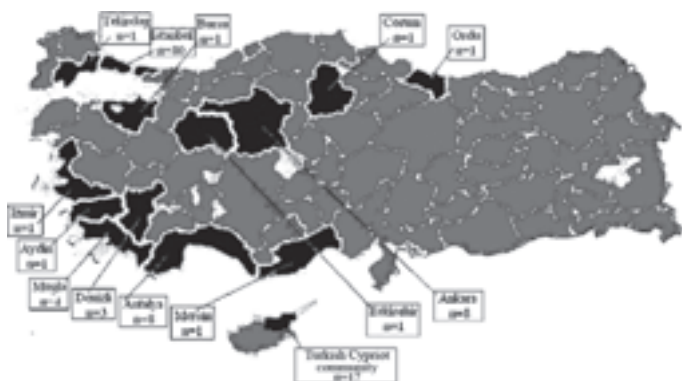


TABLE 2
Clinical characteristics of confirmed cases of influenza A(H1N1)v, Turkey, May-July 2009 (n=128)*

Symptoms	Number of cases with the symptom (%)
Cough	88 (68.7)
Fever ($\geq 38^{\circ}\text{C}$)	80 (62.5)
Sore throat	62 (48.4)
Headache	60 (46.8)
Coryza	59 (46.1)
Myalgia	56 (43.7)
Weakness	7 (5.5)
Pneumonia	3 (2.3)

*Case numbers collected by the Turkish Ministry of Health include cases from the Turkish Cypriot community.

Two confirmed indigenous cases were healthcare providers who contracted the disease in hospital while attending a confirmed case. This type of transmission in a hospital setting has been rare to date and it may require special attention [6].

After the detection of the index case on 15 May all confirmed cases were kept at the designated hospitals for treatment with oseltamivir and all contacts of these cases were traced and prophylactic oseltamivir doses were administered to these persons regardless of the symptoms. However, with increasing number of confirmed cases and individuals reporting to hospitals the MoH revised its policy on case investigation and management of the suspected cases on 5 June. With the new policy, confirmed patients with no signs of complications were put on oseltamivir therapy at home instead of hospitalisation, and prophylactic oseltamivir was no longer given to asymptomatic contacts of confirmed cases. Also, the practice of following up co-travellers of confirmed cases was ended by 5 June.

The amount of pandemic vaccine doses needed for vaccinating healthcare providers, public service providers and risk groups has been determined and necessary budget plans have been developed for purchasing 20 million doses to vaccinate 10 million individuals when the pandemic vaccine becomes available. Based on current knowledge of the pandemic, elderly people over 65 years were excluded from risk groups (in contrast with the seasonal vaccination recommendations) [7]. TV and radio spots have proven to be effective means of keeping the public calm and increasing awareness of pandemic influenza.

The MoH is planning to change its strategy and adopt measures for mitigation instead of containment of the pandemic in the coming weeks.

*Erratum: "Northern Cyprus" was replaced by "Turkish Cypriot community" throughout the text and the following information was added to the relevant tables and figures: Case numbers collected by the Turkish Ministry of Health include cases from the Turkish Cypriot community. These corrections were made on 17 August 2009.

**Author's correction: On request of the authors, the percentages in the sentence "Cough was the most frequent symptom (68.7%) followed by fever >38°C (62.5%)" were corrected on 20 August 2009.

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EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF INFLUENZA A(H1N1)v INFECTION IN CHILDREN: THE FIRST 45 CASES IN CYPRUS, JUNE – AUGUST 2009

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Following the first imported case in a tourist in Cyprus on 2 June 2009, the influenza A(H1N1)v virus has spread on the island affecting mainly young adults and children. We describe here the first 45 cases in children. Fever, cough, rhinorrhoea and sore throat were the most common symptoms of infection. Half of the children had fever for one day or only for a few hours. Five children were hospitalised, and overall their symptoms were mild. Adherence to oseltamivir treatment was very high, with low frequency of gastrointestinal side effects such as nausea and vomiting. Camping places and summer schools played a significant role in spreading the infection among children of school age.

Introduction

Despite the rapid spread of the pandemic influenza A(H1N1)v virus [1,2], most cases did not have a serious course of disease. About 2-5% of people with laboratory-confirmed infection needed hospitalisation in the United States (US) and Canada [3]. Between half and two thirds of hospitalised cases had co-morbidities such as asthma, other chronic pulmonary disease, diabetes, and autoimmune disorders [3,4]. Fatalities due to pandemic H1N1 influenza have also occurred [5].

Based on seasonal influenza data, children under the age of five years and especially those under the age of two years, as well as those with underlying chronic conditions are at substantially higher risk of hospitalisation compared to older or otherwise healthy children. Pulmonary complications such as bronchitis or pneumonia, neurological complications (e.g. encephalitis or encephalopathy) or a sepsis-like syndrome in neonates have been reported even in previously healthy children [6]. Recent data support the development of neurological complications in children in association with the influenza A(H1N1)v infection in the US [7]. These data as well as the uncertainties about the severity of the evolving epidemic among children resulted in an Emergency Use Authorization decision of the US Food and Drug Administration supporting the use of the neuraminidase inhibitor oseltamivir during the current epidemic even for children under the age of one year [8].

On 2 June 2009, the first confirmed case of pandemic H1N1 influenza was reported in Cyprus. Here we describe the epidemiological and clinical characteristics of the first 45 cases of influenza A(H1N1)v virus infection among children under the age of 16 years, seen at the Archbishop Makarios Hospital in Nicosia.

Methods

Definitions of suspected, probable and confirmed cases were issued by the Department of Medical and Public Health Services at the Ministry of Health (MOH) in accordance with those issued by international organisations. All cases under 16 years of age seen from 4 July to 6 August 2009 at the Archbishop Makarios Hospital (AMH) in Nicosia are described. The AMH is the only referral hospital for mother and child care in Cyprus. For each child examined or admitted to the AMH, a questionnaire was obtained with information on age, residence, possible epidemiological link to A(H1N1)v influenza cases, symptoms, underlying risk factors for severe disease, treatment with oseltamivir and follow-up. Diagnosis was confirmed by testing respiratory samples (nasopharyngeal and pharyngeal swabs) with RT-PCR with specific primers for influenza A(H1N1)v virus. Cases were reported to the Department of Medical and Public Health Services with demographic information as well as clinical details.

Results

The first paediatric case was a 15 year-old boy who developed symptoms on 2 July 2009. He was a household contact of his older sister who had developed influenza-like illness after spending her holidays at a tourist resort in Cyprus. A few days later the third sibling also fell ill with similar symptoms. Two of the children tested positive for influenza A(H1N1)v virus in their respiratory secretions. By 6 August, a total of 45 laboratory-confirmed cases, all 15 years-old or younger, had been detected (Figure 1).

The confirmed cases were between 40 days and 15 years-old with a median age of nine years (Figure 2). Ten of these cases were five years-old or younger and four of them were under the age of one year.

TABLE

Clinical findings in children with laboratory confirmed influenza A(H1N1)v virus infection

Symptom	Number of children / all children for whom this information was available	(%)
Fever	44/45	98
Cough	43/45	96
Rhinorrhoea	34/43	79
Vomiting	8/39	21
Diarrhoea	7/40	18
Conjunctivitis	3/45	7
Sore Throat*	25/34	73
Malaise*	21/31	68
Headache*	17/30	57
Arthralgia*	8/34	24

* assessed in children over the age of five years (n=35)

FIGURE 1

Cases of laboratory-confirmed influenza A(H1N1)v in children, by day of symptom onset, Cyprus, 2 July – 6 August 2009 (n=45)

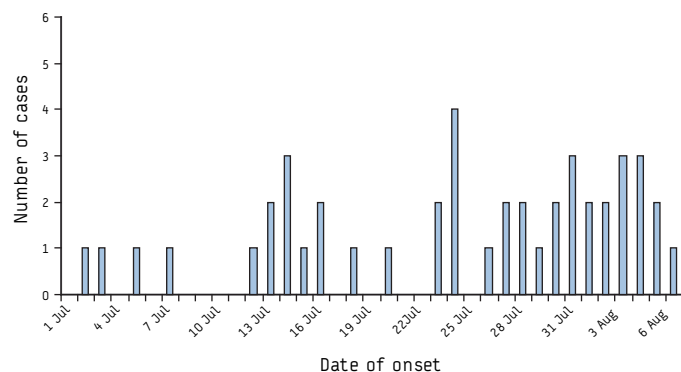
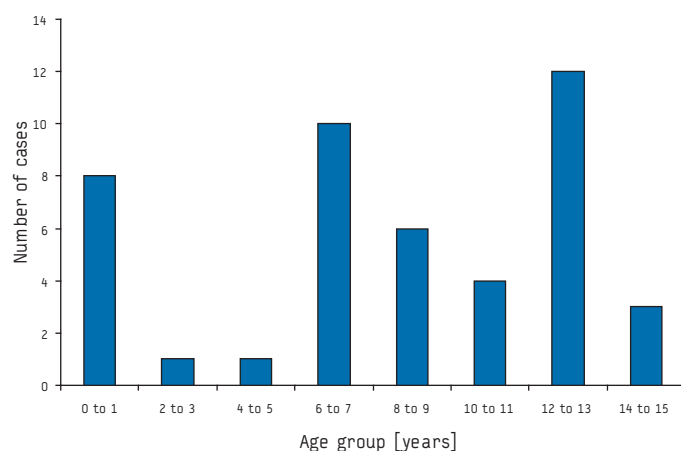


FIGURE 2

Cases of laboratory-confirmed influenza A(H1N1)v in children, by age group, Cyprus, 2 July-6 August 2009 (n=45)



As of 20 August 2009, no influenza-related fatalities have occurred in Cyprus. Five of the children were hospitalised, one due to very young age (40 days-old), one because of mild complicating pneumonia, and the remaining three children because of concurrent problems not necessarily related to influenza. Mean duration of hospitalisation was 3.4 days (range 1-7 days). Only two of the hospitalised children required treatment with oseltamivir. None of the hospitalised children had underlying chronic diseases.

Only three of the children diagnosed with influenza A(H1N1)v virus infection had underlying risk factors for severe influenza infection, all of them chronic asthma. One of them was additionally obese. All three received oseltamivir and made a quick recovery.

Cases generally presented with symptoms typical of influenza infection as described in the Table. Subjective symptoms such as headache or sore throat were only assessed in over five year-olds. Half of the 34 children with complete fever information had fever for only one day, in nine children the fever lasted for two days, and in eight cases it lasted for three or more days. The median duration of fever in laboratory-confirmed cases was one day.

Fourteen confirmed cases were linked to an index case though their household or a close friend, two of them were travel-related and the remaining 26 cases were linked to six different clusters. For three cases no epidemiological link could be identified. The six clusters were related to camping places (three clusters), summer schools (two clusters) and a handball team that had visited Italy (4 cases). In seven out of 10 cases in children under five years, the transmission was related to household members. For the remaining three, one was associated with family travel, one with a summer school cluster, while the transmission link for the last was unknown.

Policy for the management of cases and contacts

During the first few weeks of the outbreak, oseltamivir treatment was given to all suspected, possible and confirmed cases until confirmatory laboratory results were available. Contacts were traced and offered antiviral prophylaxis. Suspected, probable and confirmed cases were requested to stay at home and avoid contact with other people for at least seven days. Following new guidance from the Ministry of Health on 22 July 2009, treatment with oseltamivir was not offered to every paediatric case but only given to children who had severe symptoms or were up to five years old, and to those with an underlying risk factor that could contribute to severe disease. Furthermore, since no prophylaxis was given to the contacts, contact tracing for index cases was abandoned and only household members and close friends were advised to seek medical advice in case of fever or respiratory symptoms.

Treatment with oseltamivir, compliance and side effects

Nineteen of the confirmed cases were treated with oseltamivir. Seven children received oseltamivir because of the initial 'treatment for all' policy before 22 July 2009, three because of underlying chronic asthma, four because of persistent fever more than five days or because of complicating pneumonia, and five children because of their very young age (under two years-old). Compliance was assessed by telephone interviews during the follow up assessment of confirmed cases. Fifteen of 17 contacted parents reported that their child had taken the full course of treatment as prescribed. Only two of those who received the medication presented with side effects. Both of them developed gastrointestinal symptoms such as vomiting and nausea. In one of those cases vomiting was so severe that the antiviral treatment was discontinued. No children developed stomach pain or neuropsychiatric side effects.

Discussion

The H1N1 influenza pandemic started late in Cyprus as the first case was detected on 2 June. After the first case however, the disease spread quickly, initially among younger people who visited tourist resorts and entertainment clubs or school-aged children who stayed at camping places or summer schools. Most children of preschool age as well as infants and toddlers, who represent 22% of our cases, acquired the infection mainly through household contacts. Similar rates of household transmission were noted in the first descriptions of the outbreak in the United Kingdom (UK), although the UK rates were not based only on infants and toddlers [9].

The incidence rate of gastrointestinal symptoms such as diarrhoea among confirmed cases in children was found to be 17%. It is difficult to compare with similar series in other countries as no other paediatric series has been published as yet. In series not differentiating children, the frequency of diarrhoea ranged from 3% in Germany to 28% in the UK [9,10].

As observed elsewhere [11,12], the course of disease in our patients appeared to be mild, as half of them had fever for a maximum of one day. Despite the fact that five of the children in our series were hospitalised, only one of them had mild pneumonia as a complication related to influenza. The other children were mostly admitted for monitoring.

Compliance with oseltamivir treatment in our study was high with over 80%. Furthermore, the rate of side effects, two of 19 cases, was low. The only side effects seen in the children were nausea and vomiting, the most common side effects reported in the literature [13,14]. In a recent study on school-age children in the UK, who received oseltamivir for influenza prophylaxis, the rate of adverse effects was much higher, since 40% of the students developed gastrointestinal symptoms, and 18% had mild neuropsychiatric side effects such as poor concentration, sleeping problems, bad dreams and strange behaviour [15]. No patient in our series presented with any kind of neuropsychiatric side effects as described in that report.

Our study's limitations include the possibility that paediatric cases in the Nicosia district might have been underdiagnosed, since many children with viral upper respiratory illness and strong epidemiological link to influenza cases, including children who became ill in summer camps, did not visit the hospital for assessment, but preferred to visit their private family paediatricians. In addition, patients were only considered suspected cases and were tested for the influenza A(H1N1)v virus if they fulfilled the strict definition of suspected case and therefore fever was a necessary prerequisite. All but one case of confirmed influenza infection in our series (98%) had fever, whereas in various reports from other countries, fever was present in 90 to 95% of cases [4,9]. Finally, the number of patients with pandemic H1N1 influenza in Cyprus is relatively small in comparison to the number of cases reported in other countries. Therefore, our conclusions regarding the severity of the illness may change as the number of cases increases.

Conclusion

Influenza A(H1N1)v virus infection has spread rapidly in Cyprus. Symptoms among children were classic and the majority of paediatric cases had a mild clinical course. Treatment with antivirals appears to have not had any major adverse effects. Despite the summer season and the schools being closed, places such as summer schools and camps contributed significantly to the

spread of the disease among children. Regardless of the above, we need to focus on the coming influenza season and apply different methods including the coming influenza A(H1N1)v vaccine in order to avoid severe cases, which may inevitably occur due to the low level of immunity to the pandemic virus strain or affect vulnerable segments of the population.

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THE IMPORTANCE OF SCHOOL AND SOCIAL ACTIVITIES IN THE TRANSMISSION OF INFLUENZA A(H1N1)v: ENGLAND, APRIL – JUNE 2009

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During the containment phase in the United Kingdom (April to June 2009), a cluster of influenza A(H1N1)v cases was identified prompting further investigation and public health action by the Health Protection Agency. The first confirmed case, a pupil at a school in England, was imported. During the following two weeks, 16 further cases were confirmed with epidemiological links to the first imported case. In this cluster, we found that significant transmission occurred in two classes with attack rates of 17% and 7%. In each of the two classes a case had attended school whilst symptomatic. Other settings included a party and a choir. Minimum and maximum attack rates were 14% and 25% for the party. For the choir both the minimum and the maximum attack rate was 4%. We did not find any evidence of transmission on two school bus trips despite exposure over 50 minutes to a symptomatic case and over two periods of 30 minutes to a case during the prodromal phase (i.e. within 12 hours of symptom onset). Nor was there onward transmission in another school despite exposure over several hours to two cases, both of whom attended school during the prodromal phase.

Introduction

The first case of influenza A(H1N1)v in the United Kingdom (UK) was reported by the Health Protection Agency (HPA) in April 2009 [1]. Since then, the number of cases has been steadily rising. HPA data suggest that in England children under the age of 15 years are predominantly affected, with much higher rates of primary care consultation seen amongst the under 15 year-olds compared to the over 65 year-olds [2].

In the cluster of cases described below, the first confirmed case (X1), a pupil at school X, had acquired the infection whilst visiting a country with sustained human-to-human transmission of influenza A(H1N1)v. Over the following two weeks a further 16 people became ill and were confirmed as having influenza A(H1N1)v; they all had an epidemiological link to the same index case (X1).

Investigation by the HPA identified a number of school and social interactions amongst children and adults associated with three schools, including participation in a choir, use of school buses, and a party, where transmission may have occurred. Five of the 16 further cases were confirmed in pupils at school X, seven were pupils at two other schools (schools Y and Z), one was a sibling of a pupil at school Z and three were adult members of the choir.

Estimates of the risk of transmission associated with exposure in different settings and during the prodromal phase are scant in the

literature to date. This paper describes the chains of transmission observed in a small but intensively investigated cluster in the early stages of the pandemic in the UK, and will contribute to the understanding of the risk of transmission as the pandemic continues.

Methods

During the investigation of this cluster, all cases were assessed using the HPA guidance algorithm in use at the time. Therefore, all possible cases who had either a history of travel to a country with sustained human-to-human transmission or an epidemiological link to a laboratory-confirmed case were tested using nose/throat swabs. Confirmed cases were investigated further and information on chronology, symptoms, travel history and any other exposures, as well as close contacts that may have needed prophylaxis were collected by the HPA.

For the purposes of this study, a line list was compiled of all laboratory-confirmed cases associated with the affected schools, the choir and the party. These confirmed cases were then analysed to elucidate probable chains of transmission based on day of onset of symptoms and association with different school or social settings.

Case definitions

A confirmed case was defined as an individual presenting with influenza like illness (ILI), in whom laboratory testing of a nose/throat swab had given a positive result for influenza A(H1N1)v. A secondary case was a confirmed case in whom onset of illness was between 24 hours and one week after direct contact with the index case (X1). A tertiary case was a confirmed case in whom onset of illness was between 24 hours and one week after contact with a secondary case and in whom there was no direct contact with the index case (X1).

Results

Chains of transmission

The epidemiological links observed between the confirmed cases (recorded by day of onset) are shown in the Figure. These are believed to be the most probable chains of transmission, taking into account information collected by the HPA.

School X

X1 attended school for approximately four hours whilst symptomatic with ILI on day 2 (but did not attend again until fully recovered). X1 had also attended school for the whole day on day 1. For some of that time X1 would have been in the prodromal phase,

attack rates were calculated for the case's class, for other classes in the same year (excluding the case's class) and for the whole year. This is to reflect differences in cumulative exposure times. Both X1 and Z1 spent approximately four hours at school whilst symptomatic. During this time they were in contact with other pupils from their class. However, mixing with other pupils from the same year but different classes may occur for assembly and individual subjects. As a minimum, contact occurred during school breaks (morning break, lunch break) and in corridors between classes, with cumulative exposure times of at least one hour. For the choir and the party, both maximum and minimum attack rates

have been calculated to reflect uncertainty around where and how infection was acquired and the possibility of co-primary infections. For example X3, who was close friends with X2, may have acquired the infection from X2 during the time spent together within the choir or outside the choir, i.e. in a different setting.

Attack rates were highest within the setting of the party and the classroom. The maximum attack rate for children at the party was 25% (2/8) and the minimum, 14% (1/7). Within the classes of X1 and Z1, attack rates were 17% (4/23) and 7% (2/27) respectively. These attack rates were substantially lower when the cases' year groups, rather than the class, were considered. The maximum and minimum attack rate for the choir was 4%.

There was no onward transmission on either of the two school buses, nor in school Y.

Public health measures

At the time of this cluster, the UK was following a policy of epidemic containment. A risk assessment in line with HPA guidance was carried out in each setting to ascertain whether there was potential for transmission, and if school closure and the use of antiviral prophylaxis were indicated to prevent further spread of infection.

All three schools were advised to close for a period of one week, although in two cases this extended into scheduled school breaks. Antiviral treatment for cases and prophylaxis for contacts was provided as described in Table 2. In addition, all household contacts of confirmed cases were given antiviral prophylaxis. Advice was given to report any cases of ILI to the HPA, all of which were investigated with nose/throat swabs.

TABLE 1

Numbers affected and attack rates of laboratory-confirmed cases by setting, England, April-June 2009 (n=16, excluding index case X1)

Setting	Numbers affected	Attack rate(s) (%)	
School X			
Class of X1	4/23	17	
Other classes in the same year	1/96	1	
Total for whole year	5/119	4	
Choir	Minimum	Maximum	Minimum Maximum
	6/167	7/168	4 4
Party	Minimum	Maximum	Minimum Maximum
	1/7	2/8	14 25
School Z			
Class of Z1	2/27	7	
Other classes in same year	0/57	0	
Total for whole year	2/57	4	

TABLE 2

Summary of public health measures that were implemented at each of the settings: schools X, Y, Z, the choir, school buses, and the party, England, April-June 2009

Setting/ Age group	Days between last exposure to case and prophylaxis	Group identified for prophylaxis	Proportion of group that were given prophylaxis	School Closure (if applicable)	Number of subsequent cases
School X/ Age 11-12	3	Year group of index case	100%	Closed for 10 days	5 in the same year (4 in the same class)
School Y/ Age 12-13	4	Year group of children who were prodromal whilst at school (i.e. within 12 hours of onset of illness)	93%**	Closed for 19 days (including half-term break)	0
School Z/ Age 7-8	3	Year group of first case identified at school.	100%	Closed for 21 days (including half-term break)	2****
Choir/ All age groups including adults	4	All choir members who attended events	78%***	Not applicable	6
Bus of X1/ Mixture of age groups	3	All children on the bus	100%	Not applicable	0
Bus of Y3/ Mixture of age groups	5	All children on the bus	100%	Not applicable	0
Party/ Mixture of age groups	3*		Not applicable	Not applicable	1

* Except for two who received prophylaxis one day and four days after the last exposure respectively.

** A number of pupils refused.

*** 35 members refused.

**** There were three more cases but not believed to be directly linked to the first case at school Z

It is possible that the patterns of transmission seen in this cluster were modified by the public health measures implemented, although, the same measures being applied in all settings, the direction of any effect should be the same across all settings.

Discussion

In this intensively investigated cluster of cases, high attack rates for influenza A(H1N1)v were observed in the classroom, at a choir and a party. In each of these settings there was cumulative exposure of several hours duration to a symptomatic case. Transmission of influenza A(H1N1)v was much lower amongst year groups of symptomatic cases who had shorter exposure times. There was no evidence of transmission on two school bus trips, despite exposure times of 50 minutes to a symptomatic case, and two periods of 30 minutes to a case who was in the prodromal phase. Nor was there any onward transmission in school Y despite exposure over several hours to two cases who had attended school during the prodromal phase.

Estimates of the risk of transmission of influenza A(H1N1)v in different settings and during the prodromal phase are scant in the literature to date. However, attempts have been made to model how children interact and thereby predict the likely patterns of spread in the event of a pandemic. One such modelling study [3] predicted that the school class and household were two of the most critical settings in terms of duration of contact and risk of transmission of infection. Events such as parties, though infrequent, were also associated with high predicted risk of transmission, as when they did occur, contact was prolonged. Other studies modelling the spread of respiratory pathogens have drawn similar conclusions, with school and social group activities generally involving closer contact of longer duration than travel activities [4].

The patterns of transmission anticipated by these modelling studies are partially borne out by our experience with this cluster of cases: higher transmission was seen amongst classmates and social groups compared with those sharing transport. On the other hand, very little transmission was seen amongst household contacts of confirmed cases. This may be due to effective antiviral prophylaxis which was administered to all household contacts as soon as a swab result tested positive for influenza A (before typing confirmed H1N1v).

Aside from duration of exposure, which in this cluster was a strong determinant of onward transmission, specific characteristics of the exposure setting may have contributed to the spread, particularly closeness of contact as predicted in certain social settings [3], and in the case of the choir, increased aerosolisation of respiratory secretions during singing. This has been documented with high levels of transmission of tuberculosis within choir settings before [5-6].

As part of the management of this cluster, all children, in the same year or sharing a school bus with a case who was within the prodromal phase, were given antiviral prophylaxis. This was in line with HPA guidance [7] at the time, during the containment phase. Policy with regard to school closure and use of antiviral prophylaxis changed later as the UK moved from the containment phase to the treatment phase.

In this cluster, we did not see any onward transmission of influenza A(H1N1)v from cases Y2 and Y3, both of whom were at school during the prodromal phase. Neither did we observe any transmission as a result of contact with Y3 on the school bus. This

would indicate that risk of transmission during the prodromal phase is low. However, it is possible that the short incubation periods (of approximately 24 hours) observed before the onset of symptoms in X2 (following exposure to X1), and in those members of the choir who became symptomatic on day 4 (X3, Y1 and P1), may be accountable, in part, to exposure to cases (X1 and X2 respectively) during their prodromal phases.

Limitations

The patterns of transmission described are highly possible based on public health investigation of laboratory-confirmed cases. Given the small numbers described, caution in interpretation is needed. Although the HPA advised all individuals to report symptoms, there is a possibility that some individuals did not. Patterns of transmission are likely to have been modified by the public health response. Moreover we have no measure of the extent, if any, of asymptomatic carriage.

Conclusions

This study describes a small cluster in of influenza A(H1N1)v cases which was thoroughly investigated and epidemiological links characterised with reasonable precision. Our findings add weight to the argument that social activities are important routes of transmission which means that in the containment phase, school closure alone may not be enough to interrupt transmission. On the other hand, we did not find any evidence for transmission on school buses in this cluster. Given that the closeness and frequency of contact on public transport is likely to be less than amongst children using dedicated school buses, it may also be hypothesised that risk of transmission on public transport would also be low. Further work is warranted looking at the usefulness of social distancing measures in each of these settings (school, social groups, transport) in interrupting transmission of influenza A(H1N1)v.

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EPIDEMIOLOGY OF FATAL CASES ASSOCIATED WITH PANDEMIC H1N1 INFLUENZA 2009

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This article describes the characteristics of 574 deaths associated with pandemic H1N1 influenza up to 16 July 2009. Data (except from Canada and Australia) suggest that the elderly may to some extent be protected from infection. There was underlying disease in at least half of the fatal cases. Two risk factors seem of particular importance: pregnancy and metabolic condition (including obesity which has not been considered as risk factor in previous pandemics or seasonal influenza).

Introduction

To date, there are few data on risk factors, severe cases and deaths associated with pandemic H1N1 influenza 2009. Estimating and interpreting case fatality ratios (CFR) is difficult, mainly due to the challenge of accurately estimating the numerator (N deaths) and the denominator (N cases) [1], especially during a pandemic that is still evolving. Furthermore, many countries have abandoned individual case counts and systematic screening of all suspect cases. This article aims to describe the characteristics of reported deaths, to assess the CFR and high-risk profiles linked with underlying disease, while assessing possible bias.

Methods

The study is based on an analysis of available data until 16 July 2009, as compiled by the epidemic intelligence team at the French institute for public health surveillance (Institut de Veille Sanitaire, InVS), using a well-defined methodology [2]. The individual or aggregated data originated from validated official sources (Ministries of Health, local or national public health authorities, European Centre for Disease Prevention and Control, United States Centers for Disease Control and Prevention, World Health Organization), completed by informal sources when needed.

Results

The first (retrospectively) confirmed death occurred in Oaxaca State, Mexico, (onset of symptoms on 4 April 2009). As of 16 July 2009, InVS was aware of 684 confirmed deaths reported worldwide since the start of the pandemic (Figure 1) for a total of 126,168 reported cases (Figure 2). At this stage, no deaths had been reported and scarce data was available from African countries.

Data were available for 574 deaths associated with pandemic H1N1 influenza 2009: individual data for 449 cases in 26 countries (Table 1, Figure 2) and aggregated data for 125 cases in Mexico [3].

The quality and completeness of the data regarding age, sex, date of death and the notion of underlying disease varied greatly for each case. The overall 'computed CFR' (number of reported deaths per number of reported cases as of 16 July 2009) was 0.6% and varied from 0.1% to 5.1% depending on the country (and the accurate quantification of deaths and overall case counts) (Table 1).

Deaths by sex and age

Data on sex were available for 503 fatal cases worldwide (257 men and 246 women, sex ratio=1.04). Data on age were available for 468 fatal cases worldwide (343 with individual data and 125 with aggregated data). Data on both information (age and sex) were available for 448 fatal cases (Figure 3).

Although previous reports suggested that cases of pandemic H1N1 influenza 2009 occurred mainly in children [4], the mean and median age of the 343 fatal cases in our analysis were 37 years (range 0-85 years). Most deaths (51%) occurred in the age group of 20-49 year-olds, but there was considerable variation depending on country or continent (Table 2). Overall, 12% of deaths occurred in cases aged 60 years or more, but 36% of reported deaths in Canada (mainly female) and 28% in Australia occurred in this age group.

Underlying risks

Pregnancy

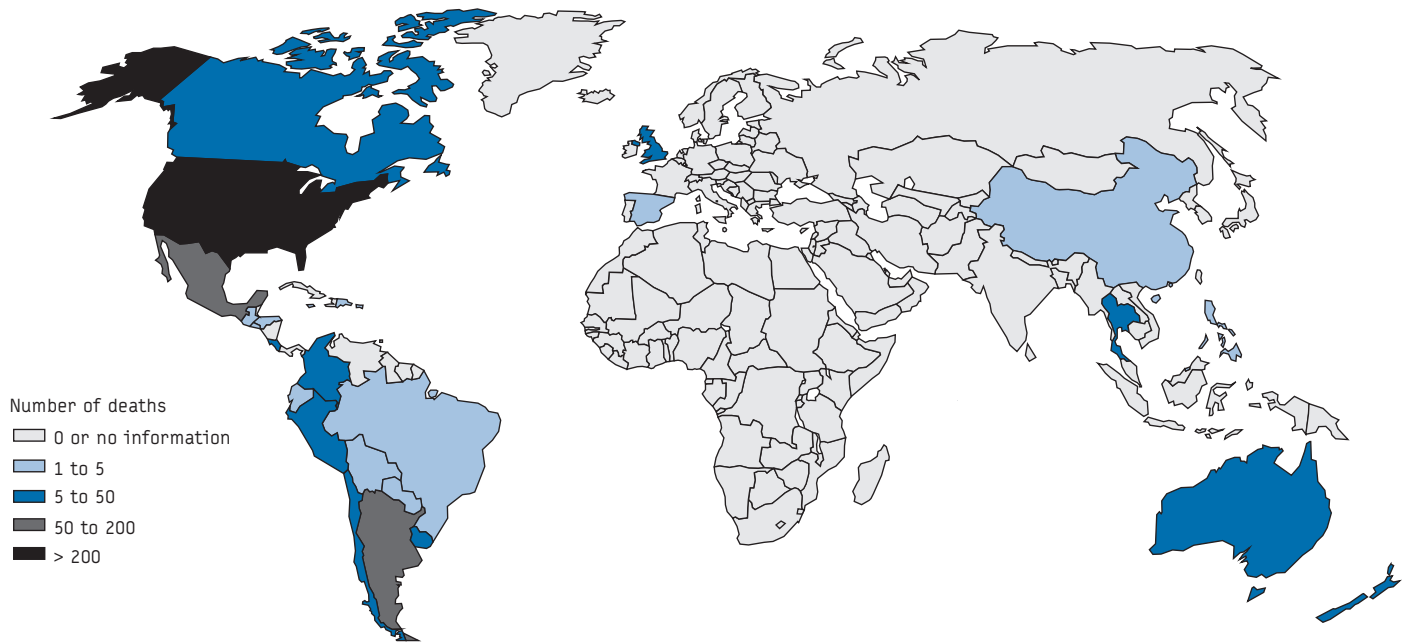
As of 16 July 2009, 16 women (10% of all individually documented female cases who died and 30% of the 20-39 year-old women who died) were pregnant or had delivered at the time of their death. Among these 16 women, at least eight had documented underlying health risks (obesity, heart disease or a respiratory disease such as asthma or tuberculosis). No information was available as to the underlying health status of the eight remaining women who died.

Underlying disease

A sub-analysis examined the 354 cases (241 cases with individual data and 113 with aggregated data) who died and were also documented for underlying disease and for sex and/or age (Figure 2). Presence or absence of underlying disease was documented for 241 of 449 (53% of the 449 cases with individual data) of deaths with individual data. Of these, 218 (90%) had documented underlying disease and 23 (10%) had documented absence of underlying disease. A further sub-analysis was conducted

FIGURE 1

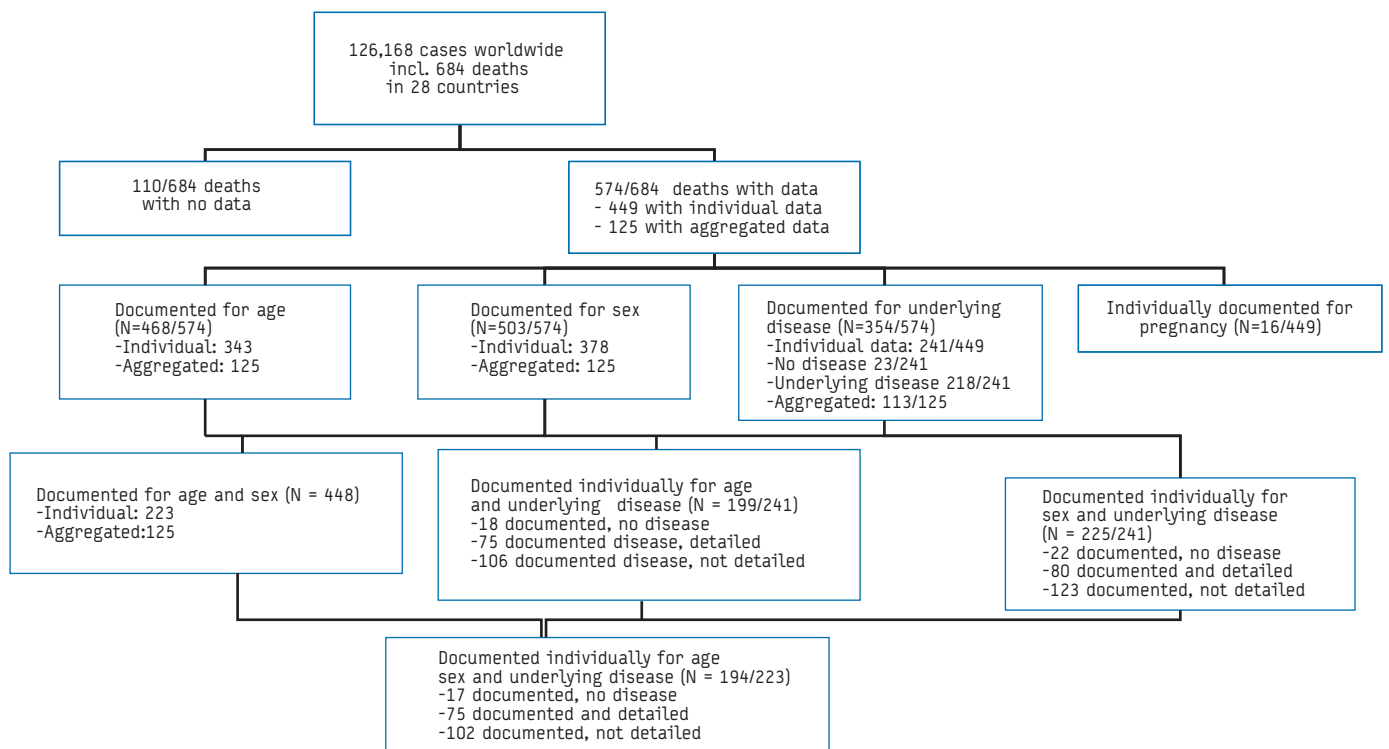
Deaths associated with pandemic H1N1 influenza 2009 reported officially worldwide as of 16 July 2009



Source: Ministries of Health, local or national public health authorities, European Centre for Disease Prevention and Control, United States Centers for Disease Control and Prevention, World Health Organization.
Map drawn with Philcarto (free software available from: <http://philcarto.free.fr/>)

FIGURE 2

Breakdown of fatal case counts used in our analysis



on 102 cases of known sex (80 with detailed underlying disease and 22 without disease) and 93 cases of known age (75 with detailed underlying disease and 18 without disease) (Figure 2). Underlying disease (or its absence) was equally distributed between the sexes, but understandably not among age groups (Figure 4). A high proportion of young children (27% of the 0-9 year-olds) and young adults (22% of the 20-29 year-olds) had no documented underlying disease, while 60% of people over the age of 60 years had heart or respiratory disease. Diabetes and obesity were the most frequently identified underlying conditions (Figure 5) and were found in fatal cases over the age of 20 years (the World Health organization defines "obesity" as a body mass index equal to or more than 30, but as the reporting format differed between sources and no standard definition of childhood obesity is applied worldwide, we cannot be sure the same definition has been applied for all cases). In the 13 fatal cases with individual detailed data on metabolic conditions, seven cases had obesity, five cases had diabetes, and one case had both. The available data for the other cases did not specify whether the metabolic condition included obesity only, diabetes only, or both.

Discussion and conclusions

Most cases described during the three pandemics of the 20th century and during seasonal influenza involve transient illness not requiring hospitalisation. Most deaths are described in the very young or the elderly or those with underlying disease. The 1918-1919 pandemic, however, was characterised by a high mortality rate in healthy young adults and an estimated CFR of 2-3% [5]. Even with a low CFR, seasonal influenza epidemics cause significant morbidity and mortality with an estimated three to five million cases of severe illness and about 250,000 to 500,000 deaths worldwide [6].

To date, the CFR attributable to the current H1N1 pandemic has been estimated at around 0.4%, based on surveillance data from Mexico and mathematical modelling [7]. This CFR is higher than that of average seasonal influenza but remains of the same order of magnitude. Whether this will change before the expected epidemic peak in the northern hemisphere in the autumn is unknown.

Evaluating CFR during a pandemic is a hazardous exercise. Aside from the issue of whether or not a death has been caused by

TABLE 1

Available individual and aggregated data on cases of pandemic H1N1 influenza 2009 and associated deaths worldwide, by country, as of 16 July 2009

Country	Data reported in official bulletins* to 16 July 2009				N deaths with individual data available**
	N deaths**	N confirmed cases	Computed CFR	Mortality per million inhabitants	
United States	211	37,246	0.6%	0.66	242
Argentina	137	3,056	4.5%	3.37	13
Mexico	124	12,645	1.0%	1.12	0
Canada	39	9,855	0.4%	1.15	41
Chile	33	10,491	0.3%	1.93	10
Thailand	24	4,057	0.6%	0.35	23
Australia	21	10,389	0.2%	0.98	31
United Kingdom	17	9,739	0.2%	0.27	17
Uruguay	15	550	2.7%	4.45	8
Costa Rica	10	428	2.3%	2.16	6
New Zealand	9	1,984	0.5%	2.09	10
Colombia	7	185	3.8%	0.15	4
Peru	6	2,082	0.3%	0.20	4
Brazil	4	1,027	0.4%	0.02	13
Paraguay	3	125	2.4%	0.46	4
Philippines	3	2,668	0.1%	0.03	4
Ecuador	3	277	1.1%	0.22	3
Salvador	3	404	0.7%	0.48	3
Bolivia	2	585	0.3%	0.20	2
Spain	2	1,099	0.2%	0.04	2
Guatemala	2	339	0.6%	0.14	2
Dominican Republic	2	108	1.9%	0.20	2
Jamaica	2	39	5.1%	0.73	1
Puerto Rico	1	20	5.0%	0.25	1
Brunei	1	334	0.3%	2.46	1
China	1	1,362	0.1%	0.00	1
Honduras	1	123	0.8%	0.13	1
Hong Kong (China)	1	1,389	0.1%	0.14	0
Total	684	112,606	0.6%	0.27	449

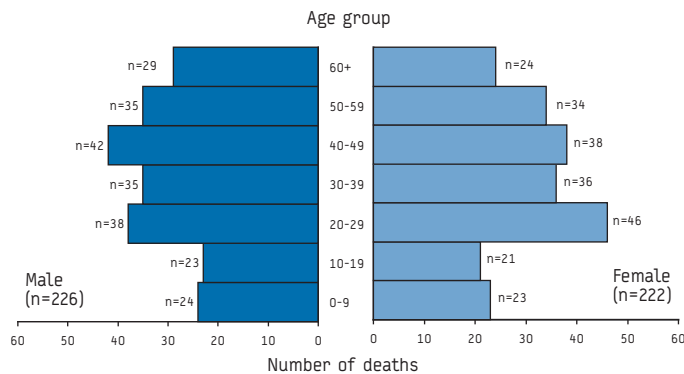
CFR: case fatality ratio.

* As per national bulletins, ECDC and WHO.

** For some countries, the N value in the first column is higher than in the third column due to a time lag for official reports.

FIGURE 3

Deaths associated with pandemic H1N1 influenza worldwide by age and sex, as of 16 July 2009* (n=448)



* Individual data, except from Mexico where aggregated data originate from the Ministry of Health.

the influenza infection, cases tend to be detected initially among severely ill patients with a higher probability of dying. This leads to an overestimation of the computed CFR at the beginning of an outbreak. The computed CFR subsequently evolves as the case reporting strategy is adapted to the situation. When the situation no longer requires exhaustive reporting of cases, the computed CFR will inevitably increase and grossly overestimate the true CFR.

Specific investigations or modelling allow for a more accurate estimation of the number of cases. As of 27 May 2009, there had been 820 confirmed cases in New York City, of whom two had died, resulting in a computed CFR of 0.2%. A telephone survey estimated that in fact 250,000 cases had occurred in that city of 8.3 million inhabitants, resulting in an estimated CFR of 0.0008% [8,9]. In the United Kingdom (UK), there were 28 deaths reported for a documented 10,649 cases as of 16 July 2009 and a computed CFR of 0.26%. However, health authorities estimated that the cumulative number in the UK on that date was 65,649 cases and 28 deaths, which corresponds to an estimated CFR of 0.04% [10].

The pandemic, however, is far from over, and deaths will unfortunately continue to occur. As in previous pandemics, available

TABLE 2

Deaths associated with pandemic H1N1 influenza 2009*, percentage and mortality rate (per million inhabitants), by age group and by country or continent, as of 16 July 2009 (n=468)**

Country or continent	Age group [years]								Total	Missing data
	0-4	5-9	10-19	20-29	30-39	40-49	50-59	60+		
Canada	0	3	2	1	2	6	4	10	28	13
%	0%	11%	7%	4%	7%	21%	14%	36%	100%	32%
Mortality rate	0.00	1.67	0.48	0.22	0.43	1.15	0.81	1.48	0.83	
USA	5	8	22	29	22	34	34	24	178	64
%	3%	4%	12%	16%	12%	19%	19%	13%	100%	26%
Mortality rate	0.23	0.38	0.51	0.65	0.52	0.76	0.81	0.42	0.56	
Mexico	11	8	5	30	25	22	17	7	125	0
%	9%	6%	4%	24%	20%	18%	14%	6%	100%	0%
Mortality rate	1.10	0.77	0.24	1.65	1.39	1.64	1.81	0.68	1.13	
Latin America	6	6	7	18	14	3	6	4	64	13
%	9%	9%	11%	28%	22%	5%	9%	6%	100%	17%
Mortality rate	0.17	0.16	0.09	0.25	0.23	0.06	0.16	0.10	0.16	
Europe	1	4	3	0	2	2	0	2	14	5
%	7%	29%	21%	0%	14%	14%	0%	14%	100%	26%
Mortality rate	0.17	0.70	0.25	0.00	0.13	0.12	0.00	0.08	0.13	
Asia	0	2	5	2	2	9	3	3	26	3
%	0%	8%	19%	8%	8%	35%	12%	12%	100%	10%
Mortality rate	0.00	0.13	0.17	0.07	0.08	0.44	0.20	0.21	0.16	
Oceania	1	1	1	4	5	6	7	8	33	8
%	3%	3%	3%	12%	15%	18%	21%	24%	100%	20%
Mortality rate	0.61	0.62	0.29	1.13	1.41	1.62	2.10	1.61	1.28	
Total	24	32	45	84	72	82	71	58	468	106
%	5%	7%	10%	18%	15%	18%	15%	12%	100%	18%
Mortality rate	0.26	0.34	0.24	0.46	0.43	0.54	0.57	0.36	0.40	

* Individual data, except from Mexico where aggregated data originate from the Ministry of Health.

** Latin America: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Paraguay, Peru, Dominican Republic, Salvador and Uruguay; Europe: Spain and United Kingdom; Asia: Philippines and Thailand; China is not included; Oceania: Australia and New Zealand.

data show that age groups are not equally affected. Compared to younger age groups, the elderly seem to be protected from infection to some extent, perhaps due to previous exposure to strains akin to influenza A(H1N1)v virus [11-13]. When infection does occur, however, the percentage of deaths in elderly cases seems to be higher than in others. Initial estimates available from Mexico for the period until 16 July 2009 showed that the risk of death in aged cases (over 50 years) was higher (6% deaths among cases) than in children (0-1% deaths among cases aged 0-19 years) and young adults (2-4% deaths among cases aged 20-49 years) [3].

There was documented underlying disease in at least 49% of documented fatal cases worldwide to date. Diseases most frequently associated with death were the same as those identified for death from seasonal influenza. Nevertheless, two risk factors are noticeable: pregnancy and obesity. Pregnancy is a well-documented risk factor for severe infection and death in seasonal influenza and in previous pandemics [14-16]. The role of obesity, however, remains to be further analysed in order to ascertain whether

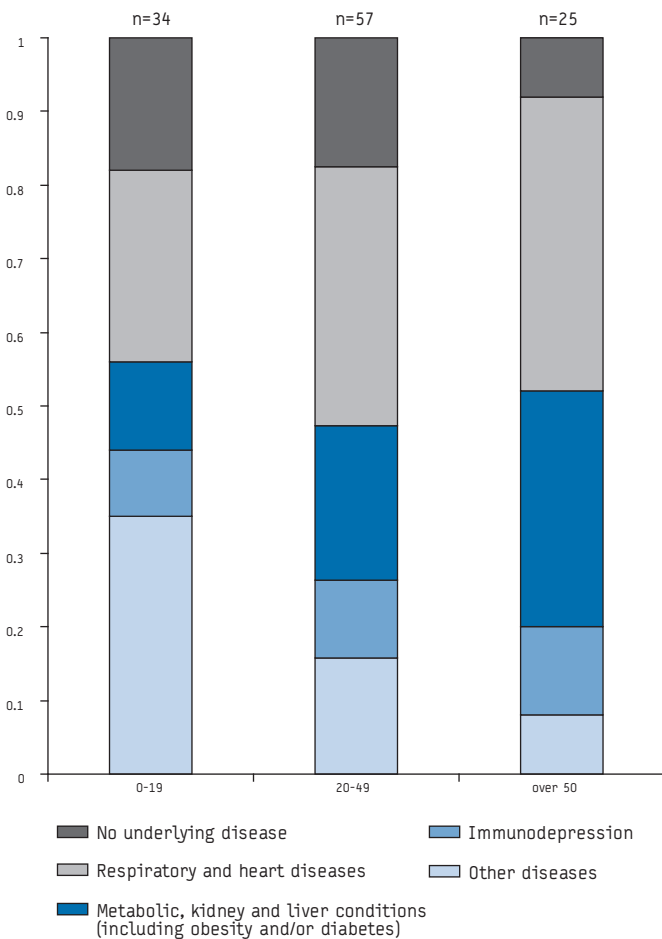
the risk is linked with complications of obesity during intensive care [17,18] or with a severe course of disease due to diabetes frequently associated with obesity [19], or whether obesity plays a specific role in the pathogenesis of severe influenza A(H1N1)v infection, for example by interfering with the host's immune responses, as has been shown in rodents [20].

All the data presented here were from official sources and were carefully documented. Yet they are to be interpreted cautiously due to the variable quality of data regarding underlying disease (especially for pre-existing respiratory disease), small numbers, incomplete reporting using different formats, a mixture of individual and aggregated data, epidemic dynamics within the population (epidemics initially affecting school children or travellers) and population structure. For instance, we found that deaths in Canada seem to have been especially frequent in elderly women. Finally, the difficulty in determining whether the cause of death is attributable to influenza A(H1N1)v infection or to associated factors remains a major limitation.

The proportion of deaths with documented underlying disease must be interpreted with care due to a significant amount of missing data. There may be an information bias which overestimates the proportion of underlying disease since its presence may be reported more readily than its absence.

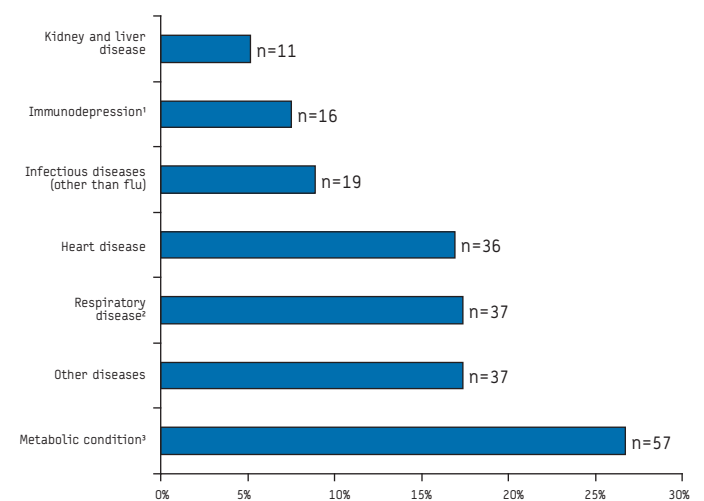
The analysis in this article is based on data collected only 10 weeks after the first international alert, and the pandemic is still in its very early phase. All evidence acquired so far remains to be completed and confirmed in the coming months, especially in view of the influenza epidemics currently ongoing in the southern

FIGURE 4
Distribution of underlying diseases in pandemic H1N1 influenza 2009-associated deaths by age, worldwide* as of 16 July 2009 (116 disorders documented in 93 fatal cases)



* Individual data, except from Mexico where aggregated data originate from the Ministry of Health.

FIGURE 5
Underlying diseases in pandemic H1N1 influenza 2009-associated deaths worldwide* as of 16 July 2009 (213 diseases documented in 193 fatal cases)



¹Including tumour (n=5), transplantation (n=2) and auto-immune disease (n=3)

²Including asthma (n=8)

³Including obesity (n=7), diabetes (n=5), obesity and diabetes (n=1) and obesity and/or diabetes (n=41 for whom only aggregated data were available)

* Individual data, except from Mexico where aggregated data originated from the Ministry of Health.

hemisphere. Surveillance of the progression of the pandemic H1N1 influenza 2009 will focus more and more on severe cases. A more reliable CFR could be estimated through specific surveys, mathematical modelling, syndromic surveillance of influenza-like illness and of reported deaths in the population. Encouraging reporting in a common international format would also be useful.

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PANDEMIC INFLUENZA A(H1N1)v IN NEW ZEALAND: THE EXPERIENCE FROM APRIL TO AUGUST 2009

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Following the detection of imported cases of pandemic influenza A(H1N1)v on 25 April 2009, New Zealand implemented containment measures that appeared to slow establishment of the pandemic during May. The pandemic accelerated markedly in June, reaching a peak within four to six weeks, and has been declining since mid-July. By 23 August there had been 3,179 recorded cases (97.8% reported as confirmed), including 972 hospitalisations, 114 intensive care admissions, and 16 deaths. Influenza-like illness (ILI) surveillance in general practice suggests that 7.5% (95% CI: 3.4–11.2) of the population of New Zealand had symptomatic infection, giving a case fatality ratio of 0.005%. Hospitalisations were markedly higher for Māori (age standardised relative risk (RR)=3.0, 95% CI: 2.9–3.2) and Pacific peoples (RR=6.7, 95% CI: 6.2–7.1) compared with Europeans and others. The apparent decline of the pandemic (shown by all surveillance systems) cannot be fully explained. New Zealand remains in the middle of its traditional influenza season, the influenza A(H1N1)v virus appears relatively infectious, and we estimate that only about 11% of the population have been infected by this novel agent.

Introduction

There has been considerable international interest in how the influenza A(H1N1)v pandemic might evolve during the southern hemisphere winter [1]. Initial reports from Australia showed an epidemic increase in influenza-like illness (ILI) reported by general practice (GP) sentinel surveillance from late May and peaking four to six weeks later in June [2]. Another southern hemisphere country, Peru, also observed an epidemic that accelerated rapidly in June, followed by an apparent decline [3]. Here we report the epidemiology of this pandemic in New Zealand based on the experience of the first four months, from late April to late August 2009.

Methods

New Zealand has multiple systems for surveillance of influenza, as listed below. Here we report on key surveillance findings, particularly from the first seven of these systems.

- **Notifiable disease surveillance:** 'Non-seasonal influenza A(H1N1)' was made a notifiable disease on 30 April 2008. Data are entered into a national web-based database (EpiSurv) operated

by the Institute of Environmental Science and Research (ESR) and are available for immediate analysis. This system also records hospitalised and fatal cases.

- **General practice (GP) surveillance:** Data on influenza-like illness (ILI) consultations with primary care medical practitioners are collected through two systems: the Sentinel GP Surveillance System (95 general practices covering about 10% of the New Zealand population) and HealthStat (84 computerised general practices with an additional 300 added in 2009, now covering about 40% of the New Zealand population). These systems provide weekly reports of ILI activity.
- **Laboratory-based surveillance:** Nasopharyngeal swabs are collected by practitioners contributing to the Sentinel GP Surveillance System, from a known number of patients seen with ILI every week. These influenza isolates are typed and tested for sensitivity to oseltamivir [4]. Specimens are also collected for diagnostic reasons from outpatients and hospitalised inpatients and as part of public health follow-up and investigation.
- **Healthline:** Reports on telephone calls regarding ILI made by the public to a national free-calling health information service are collated every week. This surveillance records daily counts of calls triaged for ILI, based on a wide set of key terms and clinical syndromes.
- **Hospital intensive care unit (ICU) utilisation:** This additional surveillance was established as part of the situation reporting system used by the Ministry of Health to support its ongoing pandemic management activities. It collects daily reports from all District Health Boards on a number of measures of healthcare utilisation including ICU influenza admissions, total occupancy, and ventilator capacity.
- **Population survey (Flutracker):** A cross-sectional survey was designed by the Ministry of Health and conducted by a market research company to measure the prevalence of ILI in the population and to assess the feasibility of using this form of surveillance on an ongoing basis. This survey used telephone interviewing. The pilot survey in June 2009 used a nationally representative sample of 629 people in 219 households. This full surveillance system was not continued because it was not considered necessary for the scale of the pandemic and was relatively expensive.

- **Mortality:** Data from death certificates and Coroner's reports are provisionally collated within days by the Ministry of Health (but final analysis and reporting of national data take about two years).
- **Hospital morbidity:** All publicly funded hospitals in New Zealand report hospitalisation data to the Ministry of Health with collated data available within three months (consequently these data were not available for this analysis, so notification data were used here to described hospitalisations).
- **Other influenza surveillance systems:** There are also regional systems for syndromic surveillance (based on one hospital emergency department in the capital city) and absenteeism surveillance (recording workplace and school absenteeism in one region of New Zealand).

Rates were calculated using 2008 mid-year population estimates except for ethnicity which used 2006 census data as the denominator. When calculating rates for ethnic groups we used prioritised ethnicity (where individuals record multiple ethnicities, Māori ethnicity takes precedence, followed by Pacific peoples, then Asian, with the remaining people included as European and other). Rates were age-standardised using the age distribution of the 2006 census.

Results Incidence

Up to 23 August 2009 there had been 3,179 notified cases of influenza A(H1N1)v in New Zealand, a rate of 74.5/100,000. Most cases were reported as confirmed (97.8%), with the rest (2.2%) classified as probable. Of the total cases, 972 (30.6%) were reported to have been hospitalised, 114 admitted to an ICU, and 16 to have died of pandemic influenza as the primary cause of death. Other possible pandemic-associated deaths are still being investigated by the Coroner's office [5].

Over the 11-week period that the pandemic strain has been circulating in New Zealand (from week 24, starting 8 June, to week 34, ending Sunday 23 August), the Sentinel GP Surveillance System detected a cumulative consultation rate of 1,906.2 ILI cases/100,000 population (i.e. 1.9%). During that same period, 382 influenza A(H1N1)v viruses were obtained from these sentinel practices, which was 19.0% of the swabs collected from patients with ILI. These data suggest a cumulative general practice consultation rate for influenza A(H1N1)v of 408.9/100,000, equivalent to a cumulative total of 17,672 patients across New Zealand.

Time course

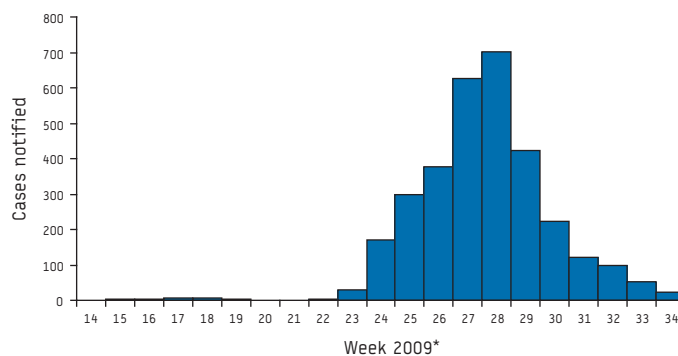
Epidemic curves for notifications, hospitalisations, ICU admissions and ILI cases (Sentinel GP Surveillance System, HealthStat, and Healthline calls) are shown in the figures below (Figures 1-7). The first known cases in New Zealand were detected on 25 April 2009 following arrival of a flight containing a school group who had travelled to Mexico. Containment efforts (case isolation, quarantine of contacts, and treatment with oseltamivir) appeared to have successfully prevented transmission from that group. No further cases of laboratory-confirmed disease were detected for about 4 weeks from 1 May until 31 May.

Following the end of May, a marked increase in influenza was detected by all surveillance systems starting in the first or second week of June (depending on the system). All surveillance systems showed that the epidemic reached a peak within four to six weeks (during the weeks starting Monday 27 June to 12 July).

Notifiable diseases

The first cases were notified in the week starting 27 April (student group from Mexico). There was a rapid rise in notified cases of influenza A(H1N1)v in week 23 (starting 1 June), with a peak six weeks later in week 28 (starting 6 July).

FIGURE 1
Influenza A(H1N1)v cases recorded on notifiable disease surveillance system by week, New Zealand, April-August 2009 (n=3,179)



* Week of onset, hospitalisation or reporting, whichever was earliest

FIGURE 2
Influenza A(H1N1)v cases hospitalised by week, New Zealand, April-August 2009 (n=972)

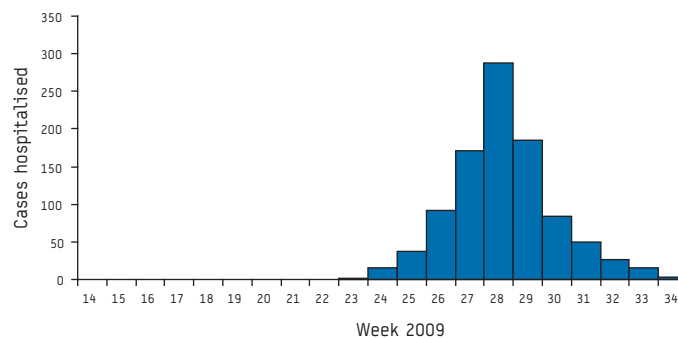
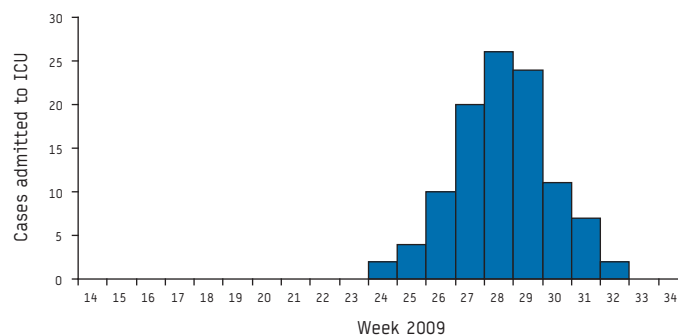
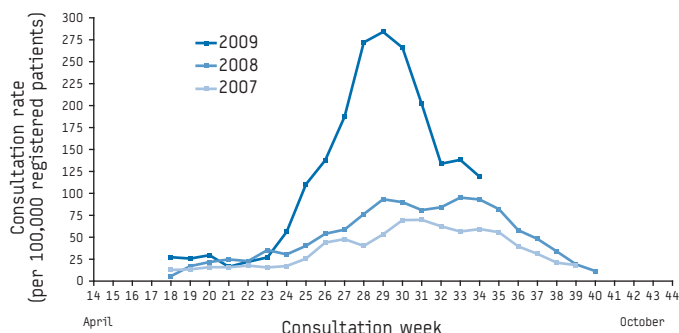


FIGURE 3
Influenza A(H1N1)v cases admitted to ICU by week, New Zealand, April-August 2009 (n=106*)



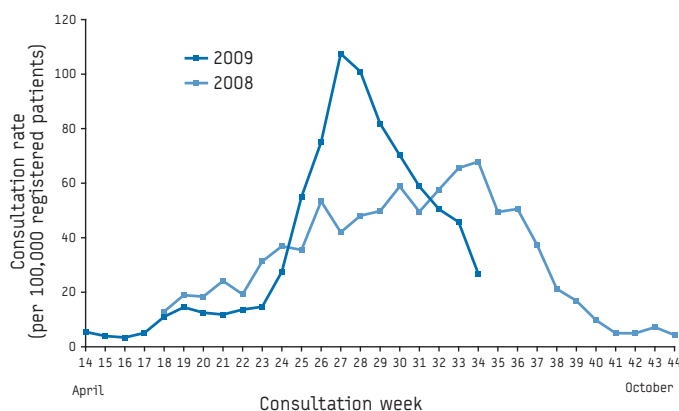
*excluding eight cases without reported admission dates

FIGURE 4
Weekly rate of ILI per 100,000 registered population, all ages, New Zealand, 2007–2009



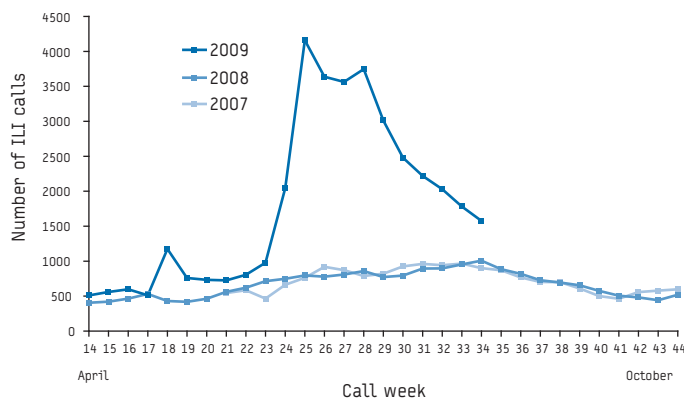
Source: Sentinel General Practice Surveillance System

FIGURE 5
Weekly rate of ILI per 100,000 registered population, all ages, New Zealand 2008–2009



Source: HealthStat General Practice Surveillance System
ILI: influenza-like illness

FIGURE 6
Weekly ILI calls to Healthline, New Zealand 2007–2009



ILI: influenza-like illness

Hospitalisations (subset of notifications)

The hospitalisation numbers showed the same pattern as the notifications. The first hospitalisations were in week 23 (starting 1 June), with a peak six weeks later in week 28 (starting 6 July).

Hospital intensive care admissions

New admissions to ICU followed a similar pattern to hospitalisations with the first admission in week 24 and a peak in week 28. About 12% of hospitalised cases were admitted to ICU.

FIGURE 7
Influenza viruses obtained from Sentinel GP Surveillance System by week, New Zealand, April–August 2009 (n=602)

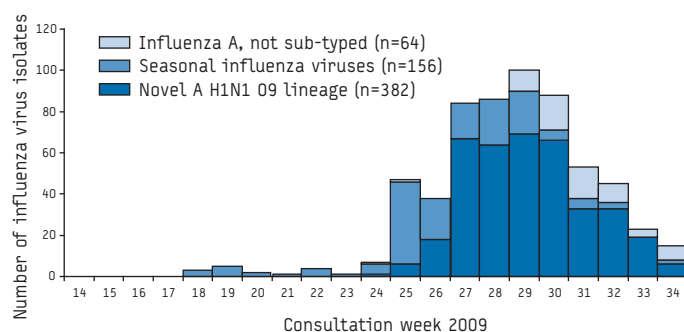


FIGURE 8
Rates of notified and hospitalised influenza A(H1N1)v cases by age group, New Zealand, cumulative rates for 2009

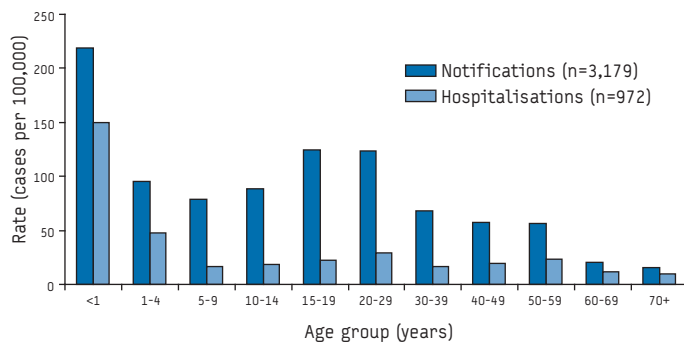
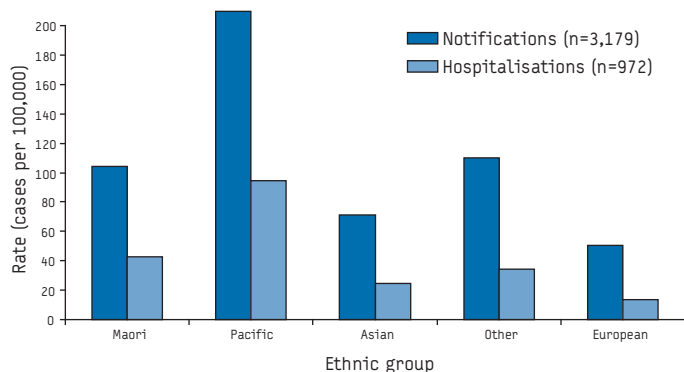


FIGURE 9
Rates of notified and hospitalised influenza A(H1N1)v cases by ethnic group, New Zealand, cumulative rates for 2009



Sentinel GP Surveillance

This system showed a rapid rise in ILI cases evident in week 24 (starting 8 June), with a peak six weeks later in week 29 (starting 13 July).

HealthStat GP Surveillance

This system showed a rapid rise in ILI cases evident in week 24 (starting 8 June), with a peak four weeks later in week 27 (starting 29 June).

Healthline calls

There was a rapid rise in ILI calls from the public evident from late in week 23 (starting 1 June). The calls peaked two weeks later in week 25 (starting 15 June).

Laboratory surveillance

Influenza A(H1N1)v was first detected by the Sentinel GP Surveillance System in week 24 (starting 8 June). It became the dominant circulating strain after four weeks (week 27 starting 29 June).

Population survey (Flutracker)

For the week of 22–28 June (week 26), ILI was reported by 2.0% (95% CI: 0.9–3.0) in a sample of 619 people. This was an ILI prevalence of 2,000/100,000 population (95% CI: 900–3,000). During that week the Sentinel GP Surveillance System reported a consultation rate of 137.7/100,000 (peaking two and three weeks later at a rate of 272.0 and 284.0/100,000). Also during that week, the expanded HealthStat GPs (n=384 GPs) reported a consultation rate of 80.7/100,000 (peaking one and two weeks later with a consultation rate of 112.0 and 119.6/100,000). Taking the average of these two rates for week 26 (109.2/100,000) implies that only one in 18.3 people with ILI consulted a GP and were also recorded by the ILI surveillance system (95% CI: 8.2–27.5).

Region

The intensity of the epidemic varied widely across New Zealand with some regions experiencing rates markedly higher than others. Across the 21 district health board regions, the cumulative hospitalisation rate ranged from 0.0/100,000 in Wairarapa to 52.9/100,000 in Hutt Health District (Wellington). The national average was 22.8/100,000.

Person characteristics

Notification data were analysed according to the age, sex, and ethnicity of notified and hospitalised cases (see Figures 8 and 9).

Rates of notified disease were highest in the under one year-olds (218.5/100,000) and the 15–29 year-olds (124.6/100,000), with the lowest rates in those over the age of 70 years (15.3/100,000). Hospitalisations showed a similar pattern with markedly higher rates in those under one year of age (149.8/100,000), but with rates falling to a relatively low level for all age groups over the age of five years. Hospitalisation rates for females (24.3/100,000) were slightly higher than for males (20.9/100,000).

Rates of notified disease were highest in Māori (age standardised relative risk (RR)=2.0, 95% CI: 1.9–2.1) and Pacific peoples (RR=4.0, 95% CI: 3.8–4.3), compared with Europeans and others. These inequalities were even more marked for hospitalisations (Māori RR=3.0, 95% CI: 2.9–3.2, Pacific peoples RR=6.7, 95% CI: 6.2–7.1).

Discussion

The virus

The pandemic influenza A(H1N1)v virus became the predominant circulating influenza virus in primary care settings in New Zealand within four weeks of its appearance [6]. It has been genetically very stable, based on testing conducted in New Zealand, and remains sensitive to oseltamivir [7]. The virology of this influenza epidemic was unique in that it was characterised by the co-circulation of three influenza A strains. As of 23 August 2009, there has been virtually no influenza B activity.

The pandemic

The pandemic in New Zealand has been characterised by relatively high transmissibility but low case fatality ratio (CFR). The reproduction number estimated for the early stages of the epidemic was 1.96 (95% CI: 1.80–2.15) [8]. The data from the Sentinel GP Surveillance System imply that about 17,672 patients infected with the pandemic strain have consulted a GP during the initial 11 weeks of the pandemic period. Given that the data from the cross-sectional survey (Flutracker) for week 26 imply that only one in 18.3 of the population with ILI are reported to this sentinel system, these data suggest that a cumulative total of 323,400 New Zealanders (7.5%, 95% CI: 3.4–11.2) have had symptomatic infection with the pandemic strain during this period. Experimental studies suggest about one third of seasonal influenza infections are asymptomatic [9], so these findings would be consistent with about 11% of the population having been infected with the pandemic strain. This result is broadly consistent with one other New Zealand estimate: Using capture-recapture methods and combining data from four sources it was estimated that 3.7% of the population of two Auckland regions (population 0.93 million) were symptomatically infected in a single month (July) [10].

Case fatality ratio

Calculating the CFR is highly dependent on estimates of the total number of people with symptomatic illness [11]. There have been 16 deaths with the pandemic influenza strain recorded as the principal cause (as of 23 August). Using the estimated denominator population of 323,400 symptomatic cases, this suggests a CFR of 0.005% (95% CI: 0.003–0.011). Interestingly, this estimate is in the range found for seasonal influenza in the population under the age of 65 years (according to data from the United States [12] and various assumptions [11]). This impact appears mild compared with the 1918 influenza pandemic in New Zealand, which killed 0.7% of the population [13] and which may have had a CFR of around 2.0% [14]. We can, however, speculate that those people admitted to ICU today (114 so far in New Zealand) would not have survived in 1918. On that basis, the comparable CFR estimate for the current pandemic would be considerably higher at 0.04%. Other interventions, such as use of antivirals (mainly oseltamivir), antibiotics to treat secondary bacterial pneumonia, and public communications have probably also contributed to lowering the CFR. Developing countries without access to such resources might, therefore, experience far more severe health impacts than those seen in a developed country like New Zealand.

Vulnerable groups

Some population groups appear more vulnerable to influenza A(H1N1)v infection than others. A distinctive epidemiological feature of pandemics is the shift in the age distribution to younger people [15], and this feature was clearly evident in New Zealand. In addition, there have been markedly higher rates of severe disease (as reflected by the number of hospitalisations) for Māori (cumulative age-standardised hospitalisation rate of 43.0/100,000)

and Pacific peoples (94.2/100,000) compared with Europeans and others (14.1/100,000). Similar ethnic inequalities between Māori and non-Māori were seen for fatalities in the 1918 influenza pandemic in New Zealand [16]. The reasons for these differences have not been established. However, Māori and Pacific peoples in New Zealand experience marked health inequalities, and these are also manifest for other infectious diseases [17]. Chronic health conditions have been commonly reported for hospitalised cases (notably respiratory disease, cardiac disease, diabetes, and immune suppression) along with some infections in pregnant women.

Impact of school holidays

There is some evidence that the start of the school holidays in New Zealand reduced influenza transmission and that the return to school slightly accelerated the epidemic. In New Zealand, the holidays for all schools lasted from Saturday, 4 July to Sunday, 19 July this year (weeks 28 and 29). It is difficult to identify what impact the start of the school holidays had as it coincided with what appears to have been the 'natural' peak of the pandemic. However, following the return to school on Monday 20 July, HealthStat GP consultation rates for school age groups (5–14 years) increased and remained elevated for three weeks (weeks 30–32) before continuing their downward trajectory in week 33. These relationships require further in-depth analysis, but the overall effect on the pandemic appears to have been small.

Public health response

New Zealand has a relatively well developed pandemic plan that includes 'keep it out', 'stamp it out', 'manage it', and 'recover' phases [18]. At the point of writing this article, the country is continuing with the management stage. The first two containment stages were applied from the first detection of imported cases on 25 April until 22 June, when New Zealand formally switched to the 'manage it' phase. The considerable interval without reported cases during May (before the epidemic accelerated in June) provides some suggestive evidence for the success of the containment measures, although this assessment requires further evaluation.

Impact on health care services

The pandemic resulted in a heavy demand for health services in those geographic areas where it was most intense. This demand was experienced by general practices, emergency departments, inpatient paediatric and adult medicine services, diagnostic laboratories, as well as public health services. The impact was particularly marked in ICUs because a relatively large proportion of hospitalised cases were admitted to these units and because many patients stayed there for a relatively long time. The demand on intensive care services peaked at 25% of national ICU occupancy. The health services were not overwhelmed, largely because of considerable additional time and effort by staff, postponing and cancelling of non-urgent work, and also because the numbers of infected people and the morbidity in this pandemic were lower than had been initially expected.

Surveillance

The notifiable disease surveillance system was useful during the containment stage for recording individual cases and supporting control measures aimed at interrupting spread of the disease. Once New Zealand moved into the management phase, this system ceased to provide a meaningful indication of the progression of the pandemic, mainly because routine laboratory testing of ILI patients was discouraged unless clinically indicated. However, this system has increasingly been used for recording hospitalisations and deaths, and the resulting dataset (EpiSurv) therefore provides

insights into the more severe end of the disease spectrum. The two GP surveillance systems have provided the most consistent data about the progression of the pandemic. The sentinel GP system with integrated epidemiological and virological surveillance has been particularly valuable in estimating the disease burden as it enables the contribution from different circulating influenza strains to be measured. The pilot testing of the Flutracker cross-sectional survey suggested that this system has good potential for surveillance of more severe pandemics which might overwhelm routine surveillance systems.

Limitations of this analysis

All of these surveillance systems have considerable limitations. The cross sectional survey (Flutracker) in particular was run as a pilot and consequently had a relatively small sample. Consequently, there is considerable uncertainty around the multiplier this study has suggested for estimating ILI in the population based on healthcare events (such as GP visits). It is reassuring that data from a cross-sectional telephone survey in New York City suggested a very similar multiplier (18.2) between physician visits and self-reported ILI (this calculation is based on an estimated emergency department multiplier of 60 and the ratio of 3.3 physician visits per emergency department visit reported in this study) [19]. Sentinel surveillance data themselves were affected by advice discouraging most patients with ILI from attending their GP, which would have lowered the consultation rates compared with previous years. Notification data include only a small proportion of all cases and are unlikely to be representative of influenza A(H1N1)v virus infections in the community. All of the findings presented here require more in-depth analysis based on finalised data following the end of the pandemic.

Persisting uncertainties

All surveillance systems currently show a consistent decline in pandemic disease rates in all areas of New Zealand. This decline cannot be fully explained. New Zealand is still in the middle of its traditional influenza season, the A (H1N1)v virus appears relatively infectious, and we estimate that so far only about 11% of the population have been infected by this novel agent. Similar patterns of a relatively short epidemic have also been reported in other countries in the southern hemisphere, notably Australia [2]. This pattern would be consistent with a range of potential explanations. The lower levels of infections in older age groups may be indicative of some existing immunity in the population. Certain changes in behaviour may also have contributed to reducing the effective reproduction number.

The largest uncertainties relate to the future development of this pandemic. Previous pandemics tended to cause multiple waves over periods between two and five years [15]. This present pandemic is causing widespread illness with low mortality, which would be consistent with the first wave seen in some previous pandemics. In other respects it could be seen as behaving like a typical seasonal influenza strain which usually infects 5–10% of the population over a period of about eight weeks every winter and then largely disappears. It would be prudent for health authorities to plan for a range of pandemic scenarios that might unfold over the months and years ahead. There is also a need to maintain existing surveillance systems and supplement these with an operational research programme including, for example, population sero-surveys to provide more accurate estimates of the pandemic impact to date

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INFLUENZA A(H1N1)v IN GERMANY: THE FIRST 10,000 CASES

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The analysis of the first 10,000 cases of influenza A(H1N1)v in Germany confirms findings from other sources that the virus is currently mainly causing mild diseases, affecting mostly adolescents and young adults. Overall hospitalisation rate for influenza A(H1N1)v was low (7%). Only 3% of the cases had underlying conditions and pneumonia was rare (0.4%). Both reporting and testing requirements have been adapted recently, taking into consideration the additional information available on influenza A(H1N1)v infections.

Introduction

After the first cases of influenza A(H1N1)v in the United States and Mexico became public, the Robert Koch Institute (RKI) established a case-based reporting of cases of influenza A(H1N1)v [1]. In the first weeks of the pandemic, data were reported to the national level by fax, phone and email in parallel with the routine electronic reporting system SurvNet [2]. Thereafter, this changed to exclusive electronic data reporting, including additional information relevant for the assessment of the epidemiological situation.

After the detailed examination of the first 100 cases in the early phase of the pandemic [1], we analyse here data of the first 9,950 cases in Germany, with a focus on information regarding the risk groups, hospitalisation frequency and other factors contributing to the impact this pandemic has on the healthcare system, in order to guide further public health measures.

Methods

As of 30 April 2009 the following information was collected through SurvNet with standardised free-text: classification of cases (possible, probable, confirmed, discarded case), in-country transmission, number of contacts (close as well as wider contacts), antiviral drug used. From 22 June 2009 onwards, the variables were changed in order to collect more detailed data on treatment (start of therapy, antiviral drug), risk groups, presence of pneumonia, hospitalisation and source of infection.

In order to take the age structure of the population into consideration, we calculated the incidence per 100,000 population per age group. From our data, we also calculated the time interval between date of symptom onset and diagnosis and start of therapy, respectively.

Categorical variables were presented as percentages with interquartile ranges when appropriate. Odds ratios were calculated including 95% confidence intervals where appropriate.

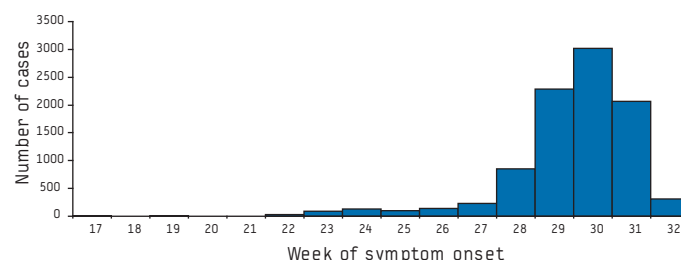
Results

As of 25 August 2009, 14,940 cases of influenza A(H1N1)v have been reported in Germany. For the detailed report below we analysed the first 9,950 cases that were reported to the RKI until 10 August 2009.

The date of symptoms onset of the first German case was 20 April 2009. The person had travelled to Mexico and had already become symptomatic while staying in Mexico. Until the end of May, only sporadic cases were notified, usually associated with travel to North America. Most secondary infections with influenza A(H1N1)v which occurred in this period could be traced back to returning travellers. In June, the number of new cases rose to approximately 10 to 50 cases per day. Since mid-July we saw a considerable increase in cases in Germany (Figure 1) with a peak of up to 500 cases per day and 3,000 cases per week at the end of July. Since then, the number of new cases per day has decreased.

From the 9,950 cases, 54% were male. The median age was 19 years (range: 0-89 years). The majority of cases (77%) were from 10 to 29 years old. Two per cent of the cases were younger than five years, 3% were between five and nine years old, 17% were between 30 to 59 years old and less than 1% of the reported cases were 60 years old and older.

FIGURE 1
Notified cases of influenza A(H1N1)v by week of symptom onset, Germany, April-August 2009, (n=9,275 cases with available information on symptom onset)



Looking at the incidence (Figure 2), the 15 to 19 year-olds were most affected, with 90 cases per 100,000 population, followed by the 20 to 24 year-olds (43/100,000). In children up to two years old, there were 5.5 cases per 100,000 population. Persons 60 years old and older had less than one case per 100,000 population. The proportion of incidence by age group over the weeks 28 to 32 showed a stable age distribution over this time period (Figure 3).

For 2,141 cases (22%), Germany was indicated as the most likely country of infection. In the first weeks of the pandemic (May and June), most travel-associated cases had been returning travellers from North America. Since the first week in July, the proportion of infections associated with travel to European countries has risen sharply. In July, 80% of travel-associated infections were seen in travellers returning from Spain, followed by the United Kingdom (6%), Bulgaria (3%) and North America (2%). From week

FIGURE 2
Incidence of notified cases of influenza A(H1N1)v, by age group, Germany, April-August 2009, (n=9,950)

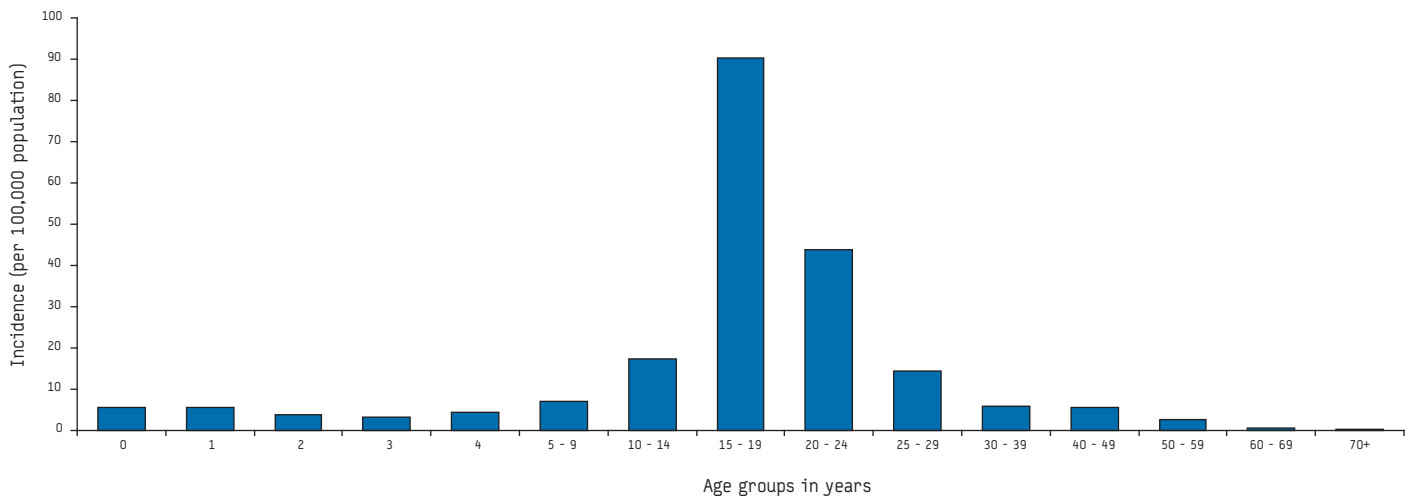
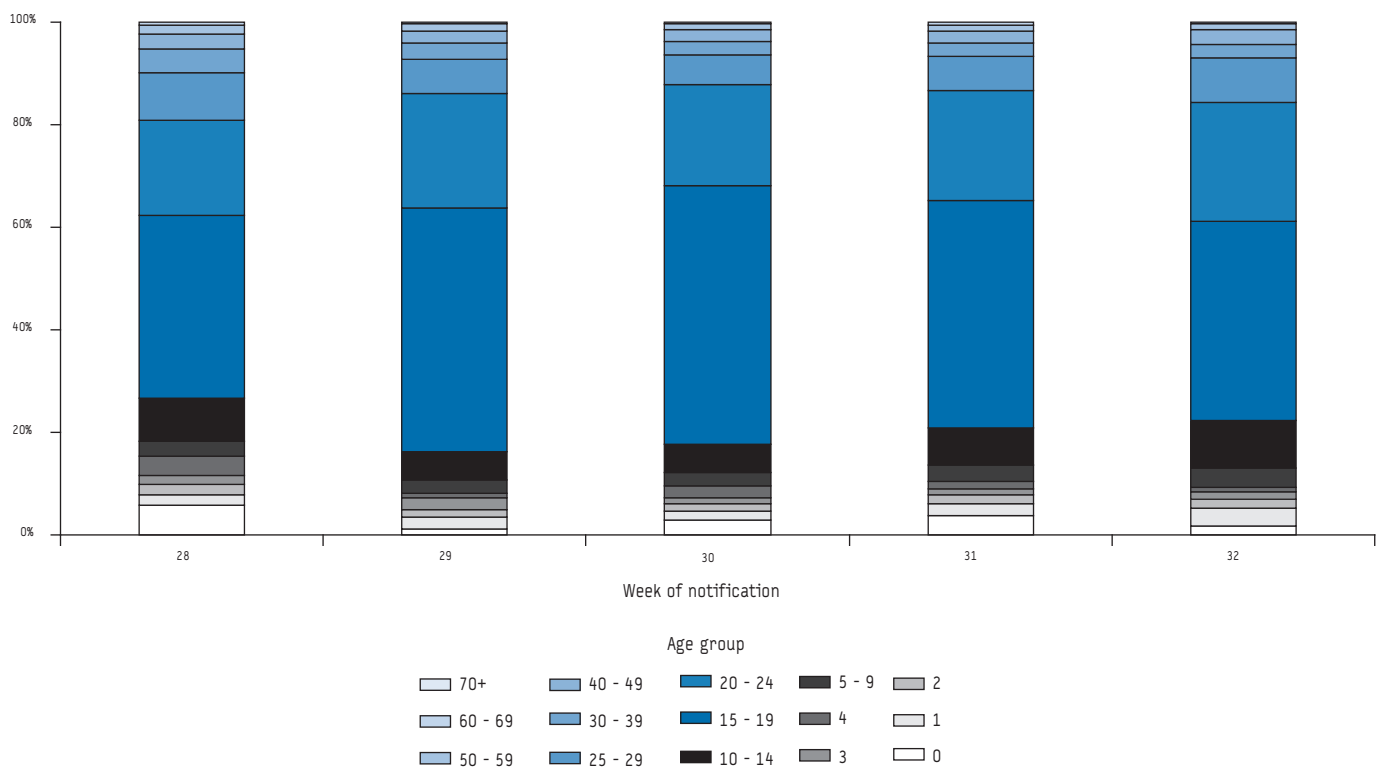


FIGURE 3
Proportion of incidences by age group and week of notification for notified cases of influenza A(H1N1)v, Germany, July-August 2009, (n=9,341)



29 to 32, the number of cases most likely infected in Germany rose steadily from 16% to 24%. For the cases without travel history, the proportion of infections without a known source increased between weeks 29 and 32 from 38% to 43% (n=1,039).

Symptoms were reported for all 9,950 cases. Cough was the most common symptom, present in 82% of the cases, followed by fever (78%).

Data were also collected on underlying health conditions and risk factors. The results are presented in the table.

The average time interval between date of symptom onset and diagnosis (n=7,955 cases for whom this information was available) was 3.6 days with an increasing trend from week 26 (2.4 days) to week 31 (3.8 days). The average time between date of symptom onset and start of therapy (n=1,810 cases for whom this information was available) was 2.2 days with a decreasing trend from week 28 (4.0 days) to week 32 (2.0 days). Cases with underlying conditions were more likely to receive treatment (72/134: 54%) than cases without underlying conditions (1,679/3,805: 45%; OR=1.44 [1.01; 2.07]). Information on presence of pneumonia at the time of notification was available for 6,460 cases. Pneumonia was reported for 26 cases (0.4%), out of which four belonged to a risk group (two had respiratory, two had unspecified risk factors) and eight were hospitalised.

From 3,630 cases for whom hospitalisation status was available, 263 (7%) persons were admitted to a hospital because of influenza, 122 cases (3%) were in hospital for other reasons, and for 42 cases (1%) the reason of hospitalisation was not known. The influenza hospitalisation rate changed from 11% in week 29 to 5% in week 31. We also looked for cases with information on their risk factors and their hospitalisation status (n=3,270). The proportion of people with risk factors who were hospitalised for influenza was 19% (20/108), while the proportion of people without risk factors that were hospitalised for influenza was 7% (220/3,162; OR = 3.04 [1.78; 5.16]). The median age was 19 years for both groups.

During the first phase of the pandemic, all contacts of cases in Germany were traced back by the local public health authorities

TABLE

Frequency of underlying health conditions for cases of influenza A(H1N1)v, Germany, April-August 2009, (n=5,885 cases for whom this information was available)

Underlying conditions*	Number of cases (%)	Proportion of all underlying conditions
No	5,690 (96.7%)	-
Yes	195 (3.3%)	-
Respiratory disease	87 (1.5%)	45%
Cardio-vascular disease	29 (0.5%)	15%
Diabetes	17 (0.3%)	9%
Obesity	11 (0.2%)	6%
Pregnancy	9 (0.2%)	5%
Immunsuppression	5 (0.1%)	3%
Others	34 (0.6%)	17%
Not specified	9 (0.2%)	5%

*Multiple answers were possible.

and the number of contacts was reported to the national level. The trace back was done for 2,635 cases. On average, three contact persons per case were identified (upper and lower quartile: 2 to 6 contacts, range 0 to 330 contacts).

Discussion

The analysis of the first approximately 10,000 cases of influenza A(H1N1)v in Germany showed that after some sporadic cases and a slow increase in June 2009, a significant increase of newly reported cases was seen starting with July. This trend was also reported from other countries in Europe [3]. There seems to be a downward trend now in Germany, even taking into account a reporting delay of approximately one week. Whether this decrease is a true decline in incidence is not yet clear. A change in health-seeking behaviour might also play a role. The first anxiety about the new infection might have made more people with respiratory symptoms seek medical advice and therefore might have brought the cases to the attention of the of the public health authorities. However, other European countries, like the UK, also report signs that the potential first wave of the pandemic might be coming to an end [4].

The cumulative number of cases by age group clearly shows that there is a peak in the age group 15 to 19 years . Many of these cases were high-school graduates who travelled to Spain in large groups at the end of the school year. The incidence in the under two year old children is relatively low (5/100,000). Data from the United States showed a much higher incidence (22.9/100,000) in children up to five years old [5]. The very low incidence in people over 60 years of age is consistent with other investigations [4-7]. It is still unclear if this is due to a partial immunity from former infections with H1N1 influenza viruses or if this is because the virus has not yet been sufficiently introduced in this subpopulation. Looking at the proportion of affected age groups over weeks, no shift to the older (>60 years) or younger (<5 years) age groups can be seen yet.

The high proportion of cases imported from Spain does not necessarily indicate a relevant epidemic activity there, but probably rather reflects the travel patterns of German holiday makers during summer. The German Federal Office for Statistics reported that from June to August 2008 approximately 1.1 million people travelled every month from Germany to Spain by air [8]. Additionally, there are many organised bus tours to Spain that are especially favoured by high-school students. Closer physical contact, sharing of drinks and special party settings were discussed as possible risk factors, but they need to be validated by further research. Besides the high number of cases in travellers, we could see an increasing proportion of cases that had no travel history and no known source of infection in the last weeks.

Most cases of influenza A(H1N1)v currently seem to have uncomplicated influenza-like illnesses. Our data show that the most common symptoms were cough and fever, similarly to reports from other countries [6-9]. This was one of the reasons why we specified the list of symptoms for the physicians to notify a patient to the local health authorities.

A particular interest for the public health authorities is the protection of the vulnerable groups. These are people with underlying conditions, such as chronic diseases, but also pregnancy, who have a higher risk of developing complications during an influenza infection. From all notified cases in Germany for whom the information was available, only 3% had underlying

conditions. Nearly half of them had chronic respiratory tract diseases. Pregnancy was not often reported among the confirmed cases. Pneumonia at the time of notification was also very rarely reported.

With increasing numbers of cases and laboratory diagnoses, the time interval between date of onset of symptoms and date of diagnosis has increased considerably. In the beginning, both transport of specimens and laboratory testing were done very fast. Now diagnostics have become more routine work and the high number of samples has caused a backlog of samples to be tested. The time interval between onset of symptoms and start of therapy decreased from four to two days. That means physicians start therapy as recommended before the laboratory confirmation of the influenza infection. Treatment is started on average within 48 hours from symptom onset, when the antiviral drugs are supposed to be most effective.

The hospitalisation rate changed considerably over the weeks. During the first weeks, the majority of cases were hospitalised due to infection control measures. Even though that might still be the case for some patients, hospitalisation is now considered as a proxy for the severity of the disease in patients. In the last couple of weeks, the hospitalisation rate due to influenza in the notified cases halved to 5% in week 32. This is a relatively low proportion and does not constitute a high burden for the hospitals at this stage of the pandemic. When we looked closer at those cases with reported underlying conditions we could see that they had a hospitalisation rate more than two times higher than in cases without underlying conditions. Here precaution could have contributed to the referral to a hospital, but it still shows that these known groups with underlying conditions will present an important group when dealing with the pandemic.

Conclusion

As of August 2009, the majority of influenza A(H1N1)v cases reported in Germany are mainly imported from other European countries. However, the proportion of cases with in-country transmission is increasing.

Several factors might influence the characteristics of notified cases in the near future. Firstly, as of 18 August 2009, physicians have to notify possible cases only if the patient presents with cough and fever, therefore it is assumed that the number of cases reported to the national level will decrease. Since 17 August 2009, the costs of the laboratory confirmation have been paid by the statutory health insurances only for cases with severe disease or cases with the risk to develop severe disease. Therefore, the percentage of laboratory-confirmed cases among the notified cases will decrease. However, as long as the sentinel surveillance in Germany does not give a signal, the assessment of the epidemiological situation must rely on routine surveillance.

The public health strategy has changed in Germany from containment (follow-up of all contact persons) to the protection of vulnerable groups. Now, only contact persons who have occupational contacts to persons with a high risk to develop severe disease are followed up (e.g.: healthcare workers).

Until now, no fatalities due to influenza A(H1N1)v have been reported in Germany, which may be partly due to these strategies.

Germany wants to continue the current reporting system until the number of respiratory infections increases significantly, as can be expected in autumn again. Then it is planned to stop the case-

based reporting by physicians and get the necessary information from the laboratory-based reporting of confirmed cases as it is done for seasonal influenza viruses and the sentinel surveillance.

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EPIDEMIOLOGICAL ANALYSIS OF THE INFLUENZA A(H1N1)v OUTBREAK IN BOLIVIA, MAY-AUGUST 2009

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The outbreak of pandemic influenza (H1N1) began in Bolivia on 25 May 2009. Between May and August, the National Center of Tropical Disease (CENETROP) analysed by RT-PCR 7,060 samples of which 12.7% were positive. A preliminary analysis of the 895 confirmed cases identified between May and August 2009 describes epidemiological and clinical characteristics. After the first imported cases from the United States and Peru, the locally acquired infections predominated (90%). The number of cases was highest in the age group of 10 to 29 year-olds, and 89.6% of cases were observed in people under the age of 40 years. Fever, cough, nasal discharge and headache remained the main symptoms.

Introduction

In response to the health emergency declared by the World Health Organization (WHO) on 29 April 2009, the Bolivian Ministry of Health activated a warning system to monitor the presence of influenza within its territory. An active surveillance system was established at all international airports and bus terminals (trains being of low importance in public transport in Bolivia). The current net of sentinel sites established throughout the country for virological surveillance of influenza and respiratory virus was alerted, as well as all other health centres on national territory, with the obligation to report all patients with fever and respiratory symptoms. A number of health facilities were prepared to receive suspected cases. In addition, the Bolivian authorities initiated an educative campaign in the media and distributed informative leaflets on measures to control the epidemic. A free telephone line was set up for health professionals and the public to report suspected cases or obtain information. The Immunology and Molecular Biology laboratory at the National Center for Tropical Diseases (CENETROP) was prepared for testing influenza A(H1N1)v as described by the United States Centers for Disease Control and Prevention (US CDC). All reagents and material for the real-time RT-PCR test were provided from CDC and WHO. This laboratory was the only laboratory in Bolivia accredited to perform this test.

This short report presents the epidemiological characteristics of the early stage of the influenza A(H1N1)v outbreak in Bolivia, from 5 May to 2 August 2009, on the basis of data collected by CENETROP.

Methods

A suspected case was defined as a person with sudden onset of fever (≥ 38 °C) and respiratory symptoms detected in any part of the Bolivian health system. Suspected cases were examined

at the nearest healthcare facility for clinical evaluation. Nasal samples were taken from symptomatic people and submitted to the CENETROP laboratory for testing, together with a case report form containing clinical and epidemiological data that were collected for all suspected cases. Nasal swabs were received from all suspected cases from 5 May until 31 July 2009. From 1 August, the protocol was changed and nasal samples were only taken from severe cases, following a WHO recommendation to that effect.

If the sample was PCR-positive for influenza A(H1N1)v and the clinical manifestations were severe, the patients were hospitalised and specific treatment was administered. In the beginning of the outbreak, antiviral drugs were given to all suspected cases and their contacts. From 1 August, antiviral drugs were given only to symptomatic high-risk groups.

Data collected by the Immunology and Molecular Biology laboratory at CENETROP were immediately entered in a database. Data from the samples registered until 31 July are analysed here with SPSS (Chi-square tests, Mann and Whitney tests and T-test).

Results

On 25 May 2009, the surveillance group of the Departmental Health Services (SEDES) in Bolivia identified the first two cases of influenza A (H1N1)v at Santa Cruz international airport by checking all arriving passengers, airplane personnel informing the healthcare staff at the airport about passengers with symptoms of fever, cough or others symptoms of respiratory disease. A woman in her late 30s returning from New York had symptoms of fever, cough and a sore throat. She was accompanied by her seven year-old child who was still asymptomatic. Nasal swabs of mother and child were taken at the airport and sent to the CENETROP laboratory. Both were placed under medical observation in a clinic especially organised to receive suspected cases from the airport, and the child subsequently developed symptoms. The RT-PCR was positive for both of them and treatment was administered in a second level reference hospital.

Between 29 May and 11 June 2009, six further cases were confirmed in Santa Cruz, La Paz and Montero, all with a history of international travel (to the United States (US), Peru and Argentina) or of contact with travellers returning from affected countries. On 12 June, the first case without travel history or known close contact with a suspected case was confirmed in Santa Cruz. From

FIGURE 1

Number of cases of influenza A(H1N1)v by week of disease onset analysed at CENETROP, Bolivia, 5 May-2 August 2009 (n=7,060 analysed samples)

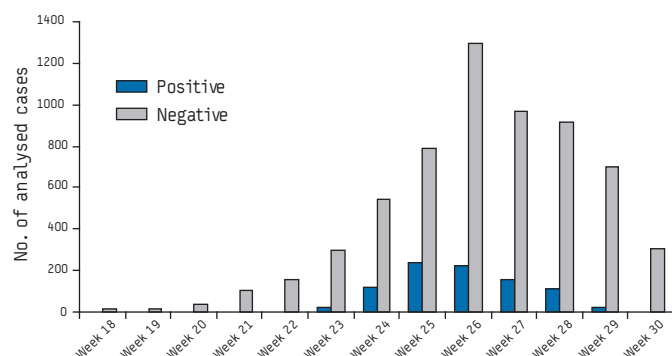
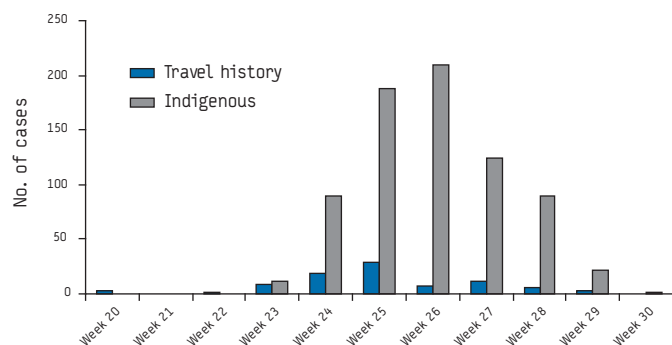


FIGURE 2

Number of laboratory-confirmed influenza A(H1N1)v infections by week of disease onset and travel history, Bolivia, 11 May-26 July 2009 (n=824*)



*for whom travel history was known

TABLE 1

Geographic distribution of influenza A(H1N1)v samples with known place of origin (n=7,018)

Department	Locality	Total	% Laboratory-confirmed for influenza A(H1N1)v
Santa Cruz	Santa Cruz	4,933	12.8
	Other	343	9.0
La Paz	La Paz/Alto	843	12.6
Beni	Trinidad	62	6.5
Chuquisaca	Sucre	60	10.0
Cochabamba	Cochabamba	351	20.2
	Other	153	3.9
Oruro	Oruro	67	17.9
	Other	6	0
Potosí	Potosí	41	24.4
	Other	19	10.5
Tarija	Tarija	92	6.5
	Other	48	14.6
Total		7,018	12.7%

15 June onwards, the number of cases increased greatly, mainly in Santa Cruz.

Between 5 May and 2 August 2009, CENETROP received 7,060 samples of suspected cases, of which 895 (12.7%) were confirmed by PCR as influenza A(H1N1)v virus. Thirteen patients (1.5%) died, two of them children under the age of five years, and six of them adults who suffered from chronic medical conditions (diabetes, Chagas disease, chronic respiratory disease) [1]. The temporal distribution of cases by week of onset of disease is presented in Figure 1. The average time between onset of symptoms and arrival of the samples at the CENETROP laboratory was 2.9 days. The weekly number of confirmed cases reached a peak between 22 June and 5 July (21.8% of cases), and decreased until the last week of July. From 1 August 2009, swabs were no longer systematically taken and sent to CENETROP.

Patients with recent history of travel to the US, Argentina, Brazil, Chile, Colombia, Cuba, Paraguay, Peru, Spain, Uruguay or Venezuela accounted for 9.9% of confirmed (n=89). The proportion of travel-related cases among all cases decreased after the end of June (week 26) (Figure 2).

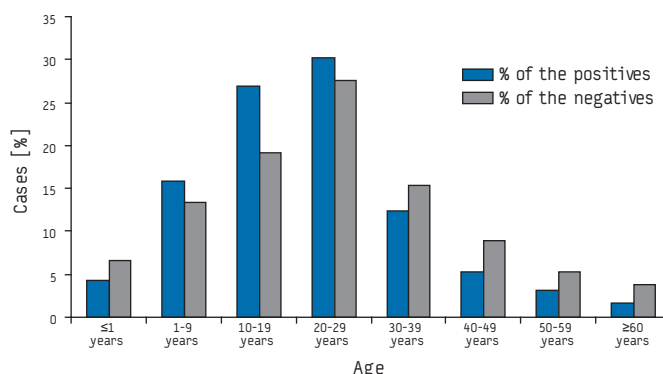
The majority of cases were recorded in the main cities of Bolivia like Santa Cruz (73.7%) and La Paz, Tarija and Cochabamba (Table 1). Other localities were either less affected or sent less samples to CENETROP. The proportion of laboratory-confirmed samples among suspected ones varied from one Department (Bolivia is divided into nine administrative Departments) to the other. By 2 August, cases had been reported in eight of the nine departments.

Of 7,060 specimens analysed, 3,462 were from men and 3,598 from women. The proportion of laboratory-confirmed cases was higher for men (13.6% male versus 11.7% female, P=0.017). The age ranged from one month to 80 years. The average age was 21.5±13.7 years, the median age was 20 years, and the age group most affected was the group of 10-29 year-olds (Figure 3). There was no difference in the mean age according to the sex (women: 21.9±13.6 years, men: 21.0±13.9 years, P<0,05).

The symptoms most frequently reported by confirmed influenza A(H1N1)v patients were fever (91.6%), cough (86.7%), nasal discharge (82,4) and headache (82,4 followed by sore throat,

FIGURE 3

Age distribution of suspected and laboratory-confirmed influenza A(H1N1)v cases, Bolivia, 5 May-2 August 2009 (n=7,060)



myalgia, and asthenia. Diarrhoea was rare as well as bronchitis and pneumonia. Symptoms that were found to be correlated with laboratory-confirmed samples are listed in Table 2 (P<0,01). Diarrhoea and pneumonia were negatively correlated. Nasal discharge and otitis were observed more frequently in women than in men (P<0,05). Fever and vomiting were observed more frequently in young people under the age of 15 years, while myalgia, headache, asthenia and short breath were observed more frequently in adults over the age of 15 years (P<0,05).

Discussion

By 25 May 2009, the new influenza A(H1N1)v virus had entered Bolivia from the US, Peru and Chile, one month after the first notification of the infection in Mexico, and two to three weeks after the neighbouring countries were affected [2-4]. Despite the fact that Bolivia continued to observe sporadic imported cases, mainly from Argentina (47/89), indigenously acquired infections predominated as a consequence of local transmission (90%). Indigenous cases in Bolivia had a rate of local transmission almost like the one observed in Peru (95.6 %) [2] and much higher than in Colombia (35.5 %) [3]. As soon as the new influenza virus arrived in the country, it spread rapidly in the major urban centres, particularly in Santa-Cruz. Geographical spread within rural Bolivia currently seems low, but unfortunately cannot really be estimated in this study, based on analyse of received suspected nasal swabs.

The distribution of cases by age and sex is similar to what is observed elsewhere [4-7], with young adults being mostly affected by the disease. However, in Bolivia men are slightly more affected than women, and the median age is at the higher end of the range observed worldwide. It is possible that the rapid spread of disease in Santa Cruz has enlarged the age range.

As of 2 August, CENETROP has confirmed only a small proportion of 12.7% influenza A(H1N1)v virus infections among the total of 7,060 samples analysed. Of the 81.7% of submitted

samples that matched perfectly the inclusion criteria, 13.8% were laboratory-confirmed). The remaining 18.3% analysed samples came from patients who had fever without respiratory symptoms (7.12% of those were confirmed) or respiratory symptoms without fever (8.2% of those were confirmed). Finally, six asymptomatic patients (tested as contacts) were confirmed to have influenza (H1N1)v virus infection. The low concordance between early clinical suspicion of influenza A(H1N1)v and laboratory confirmation may be partly due to the fact that other influenza viruses are currently circulating in Bolivia (apart from other virus such as dengue virus). Of 179 samples negative for influenza A(H1N1)v that were subsequently analysed for other respiratory viruses in La Paz, seven (3.9%) were positive for syncytial respiratory virus by indirect immunofluorescence test, 24(13.5%) were positive for seasonal influenza A by PCR, and 12(6.7%) were positive for influenza A by indirect immunofluorescence [1].

The low percentage of laboratory-confirmed samples also reflects the impact on healthcare services of the current H1N1 influenza pandemic. Between May and August 2009, an abundance of samples were sent to the national reference laboratory at CENETROP. It was partly a consequence of the high concern in the population, fed by the media in response to the increasing number of positive cases throughout the world. Symptoms are similar to those of seasonal influenza, and many people in Bolivia would not usually consult at healthcare facility for such symptoms. The volume of medical consultations has overwhelmed the CENETROP laboratory which succeeded in managing the extraordinary work load but experienced a shortage in reagents after only a few weeks. The drop in the epidemiological curve at the end of July is a reflection of this deficit in reagents, which are currently reserved for severe cases. At the same time, medical staff began to send fewer samples to CENETROP. Overall, this study also highlights the difficulty, with regard to local resources, of managing an epidemic surveillance system at a high level and for a long time.

TABLE 2

Clinical characteristics of patients with RT-PCR-positive and -negative result for influenza A(H1N1)v, Bolivia, 5 May-2 August 2009 (n=7,055*)

Symptoms	Total number with symptoms	% with symptoms		P value
		RT-PCR A(H1N1)v positives(n=895)	RT-PCR A(H1N1)v negatives(n=6,160)	
Asthenia	4,370	65.8	61.3	0.01
Bronchitis	1,144	19.4	15.7	0.005
Conjunctivitis	2,240	35.0	31.2	0.02
Cough	5,599	86.7	78.1	<0.001
Diarrhoea	964	10.6	14.1	0.004
Fever	6,078	91.6	85.2	<0.001
Headache	5,450	82.4	76.3	<0.001
Myalgia	4,812	74.2	67.2	<0.001
Nasal discharge	5,504	82.4	77.2	<0.001
Otitis	966	13,7	13.7	NS
Pharyngitis	5,183	77.9	72.7	0.001
Pneumonia	368	3.5	5.5	0.01
Vomiting	1,506	21.5	21.3	NS

NS: non-significant.

* for which information on symptoms was available.

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Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the National Minister of Health of Bolivia.

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ASSESSMENT OF SECONDARY ATTACK RATE AND EFFECTIVENESS OF ANTIVIRAL PROPHYLAXIS AMONG HOUSEHOLD CONTACTS IN AN INFLUENZA A(H1N1)v OUTBREAK IN KOBE, JAPAN, MAY–JUNE 2009

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This report describes the assessment of the secondary attack rate (SAR) and the effectiveness of post-exposure antiviral prophylaxis among household contacts in the first domestic outbreak of a novel influenza A(H1N1)v between mid-May and early June 2009 in Kobe city, Japan. Of the 293 subjects, 14 (4.8%) household contacts met the case definition and most secondary cases were probably infected around the time of symptom onset date of the respective index case. The SAR among household contacts who did not receive prophylaxis was 7.6%, similar to the rate of seasonal influenza, and the attack rate in siblings was significantly higher than that in parents. We conclude that it is important to establish routine infection control measures for households in order to prevent the spread of the virus among household contacts and, possibly, to the community. We could not conclude whether antiviral prophylaxis was effective or not. However, among close contacts with underlying disease who received prophylaxis, nobody developed a severe form of the disease.

Introduction

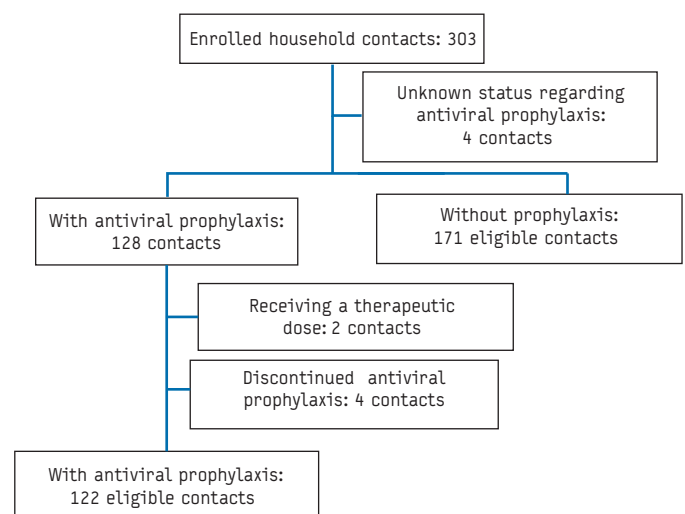
Between 16 May and 5 June 2009, 110 laboratory-confirmed cases of influenza A(H1N1)v, affecting mainly high school students, were reported from the Public Health Centre of Kobe City (PHCKC), Japan. The PHCKC provided post-exposure antiviral prophylaxis (oseltamivir or zanamivir) primarily to household contacts with underlying disease, in addition to implementing aggressive school closure throughout the city for one or two weeks from 16 May. The number of new laboratory-confirmed cases decreased in late May following the school closures [1], and community transmission was limited. No severe cases were reported during this period. We suppose that preventing the spread of influenza among household contacts effectively prevented the development of severe disease in each household and the transmission to the community. In this study, we assess the secondary attack rate (SAR) among household contacts who did not receive antiviral prophylaxis and the effectiveness of post-exposure antiviral prophylaxis in preventing the spread of influenza A(H1N1)v among household contacts in this particular outbreak.

Methods

Subjects and case definition

We included 303 household contacts from 97 households with the exception of three households with one person living alone. The median number of household members including index cases was four, ranging from two to eight. We defined an index case (IC) as the first person in each household who met the case definition described below according to the epidemiological investigation. The PHCKC followed up on these household contacts every day for approximately eight days either from the date when the ICs started antiviral therapy or from the date the PHCKC began to observe household contacts in case the ICs did not take antiviral therapy. In addition, household contacts were requested to stay

FIGURE 1
Flow diagram of enrolled household contacts, pandemic H1N1 influenza outbreak, Japan, May–June 2009



home but to avoid close contact with the patient in their household during the follow-up period. Household members with influenza-

like symptoms were instructed to wear face masks. Along with the PHCKC, we collected data on the symptoms and the use of antiviral prophylaxis. We excluded four contacts for whom information about antiviral prophylaxis was not available, four contacts who had discontinued antiviral prophylaxis and two contacts who were receiving a therapeutic dose (oseltamivir, 150 mg/day, or zanamivir, 20 mg/day; for five days). Overall, our study subjects comprised 122 household contacts receiving and 171 not receiving antiviral prophylaxis (Figure 1)..

Cases were confirmed by using the following case definition for household contacts, which is similar to the definition established by the Ministry of Health, Labour and Welfare at that time [1]:

Suspected case: a person who displayed high fever of $\geq 38^{\circ}\text{C}$ or at least two acute respiratory symptoms (nasal obstruction/

TABLE 1

Demographic data for index cases, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=97)

Total no. of index cases		97
Sex	Women, no. (%)	40(41)
	Men, no. (%)	57(59)
Age, median (range)		17(1-53)
<20 years-old, no. (%)		87(90)
Cases with antiviral medication, no. (%)		89(92)
Interval from symptom onset to treatment, median days (range)		1(0-7)

TABLE 2

Demographic data for household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=293)

Total no. of subjects		Without prophylaxis	With prophylaxis			P-value*
			Total	Oseltamivir	Zanamivir	
		171	122	100	22	
Sex	Women, no. (%)	80(47)	65(53)	53(53)	12(55)	P=0.33**
	Men, no. (%)	91(53)	57(47)	47(47)	10(45)	
Age, median (range)		39(0-83)	45 (2-85)	48 (2-85)	14(7-41)	P<0.05***
Age unknown, no.		14	8	8	0	
Relationship to index case, no.						
Parent		85	73	71	2	
Sibling		64	31	11	20	
Child		4	3	3	0	
Spouse		2	2	2	0	
Grandparent		11	11	11	0	
Other		5	2	2	0	
Underlying disease, no.		n=167	n=122			
Asthma		0	9	7	2	
Hypertension		0	13	13	0	
Cardiovascular disease		1	2	2	0	
Diabetes		0	2	2	0	
Neoplasm		0	1	1	0	
Rheumatism		0	4	4	0	
Total		1	31	29	2	P<0.01**
The interval from symptom onset of index cases to prophylaxis, median day (range)			4 (0-8)	4(1-8)	3.5(0-8)	
0			3	0	3	
1			7	7	0	
2			21	19	2	
3			27	21	6	
4			23	20	3	
5			17	13	4	
6			3	2	1	
7			12	10	2	
8			9	8	1	

* Comparing total household contacts receiving prophylaxis to those not receiving prophylaxis
 ** Chi-square test
 *** Wilcoxon rank-sum test

rhinorrhoea, sore throat, cough, fever of ≥ 37 °C), excluding individuals with negative RT-PCR for influenza A(H1N1)v virus;

Confirmed case: a suspected case with laboratory-confirmed influenza A(H1N1)v infection as tested by RT-PCR.

TABLE 3

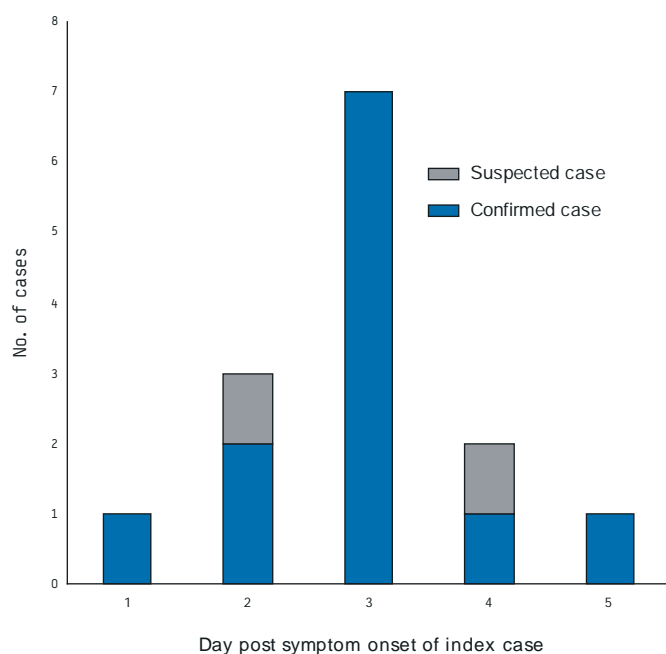
Demographic data for confirmed and suspected cases, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=14)

No. of cases		Confirmed case	Suspected case	Total
		12	2*	14
Sex	Women, No. (%)	7 (58)	1 (50)	8 (57)
	Men, No. (%)	5 (42)*	1 (50)	6 (43)
Age, years				
0-9		2	2*	4
10-19		8	0	8
40-49		1	0	1
50-59		1	0	1
Relationship to index case				
Parent		2	0	2
Sibling		10	1*	11
Child		0	1	1
Spouse		0	0	0
Grandparent		0	0	0
Other		0	0	0
Underlying disease		0	0	0

* Including one case who received antiviral prophylaxis

FIGURE 2

The interval from symptom onset of index cases to symptom onset of household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=14)



Antiviral prophylaxis

Either oseltamivir (75 mg/day for adults or 2mg/kg/day for children*) or zanamivir (10 mg (two inhalers)/day) was administered household contacts for a period of 7–10 days, provided that they had underlying diseases (e.g. asthma or diabetes).

Statistical analyses

We calculated the secondary attack rate (SAR) among household contacts who did not receive antiviral prophylaxis. We also compared the attack rate among siblings and parents who did not receive antiviral prophylaxis in households where the ICs were under 20 years-old. We further compared the attack rate among household contacts receiving and not receiving antiviral prophylaxis to assess its effectiveness. Inter-group comparisons were made using Chi-square test or Fisher's exact test.

Results

Of the 97 ICs, 89 (92%) were treated with antiviral medication (Table 1) and 80 (82%) ICs began antiviral therapy within two days of symptom onset (e.g. nasal obstruction/rhinorrhoea, sore throat, cough or fever of ≥ 37 °C); 87 (90%) ICs were under 20 years-old.

Zanamivir was prescribed particularly to household contacts in their teens (Table 2), because there are concerns about the association between oseltamivir and abnormal behaviour in this age group in Japan [2].

The gender distribution of household contacts was not significantly different between the groups receiving and not receiving antiviral prophylaxis. However, the household contacts receiving prophylaxis were significantly older ($P < 0.05$, Table 2).

Of the 293 subjects, 14 (4.8%) in 13 households (representing 13 ICs) met the case definition: 12 confirmed cases (4.1%) and two suspected cases (0.7%) (Table 3). All 13 ICs took antiviral medication within two days of symptom onset. The median interval from symptom onset of ICs to symptom onset of the 14 contacts was three days (range: 1–5 days; Figure 2).

Only one suspected case (female, under five years old) had a history of receiving prophylaxis during this outbreak. The interval from symptom onset of her IC to the administration of antiviral prophylaxis was two days. The SAR in household contacts who did not receive antiviral prophylaxis was 7.6% (13/171)*.

In those households in which the ICs were under 20 years-old, 10 (16.4%)* cases in siblings and two (2.4%)* cases in parents met the case definition. The attack rate in siblings was significantly higher than that in parents. The odds ratio (OR) was 7.84 (95% confidence interval (CI): 1.52–54.2; Table 4).

The difference in the attack rate between household contacts who had received prophylaxis and those who had not was statistically significant. However, the household contacts receiving prophylaxis were significantly older, so we stratified household contacts according to age (≥ 20 years-old or < 20 years-old). After that, there was no statistical significance in either group (Table 5).

Discussion

The United States Centers for Disease Control and Prevention (US CDC) have estimated that the incubation period of influenza A(H1N1)v could be between one and seven days, but more likely

between one and four days [3]. Our investigation showed that the median interval from symptom onset of ICs to symptom onset among the 14 cases in the household contacts was three days (range: 1–5 days). These results indicate that most secondary cases were probably infected around the time of symptom onset of the ICs. Therefore, routine infection control measures for each household should be established because it is sometimes difficult for public health authorities to intervene in affected households immediately after ICs develop symptoms.

The World Health Organization (WHO) reported that the current estimate of the SAR of influenza A(H1N1)v was 22–33%, and the SAR of seasonal influenza was 5–15% [4]. Our investigation showed a SAR of 7.6%. This rate was lower than that for influenza A (H1N1) v reported by WHO and similar to the rate of seasonal influenza. The PHCKC and the mass media actively provided information to the public about influenza A(H1N1)v and emphasised the importance of infection control measures (such as hand washing, cough etiquette including wearing masks) at home during the outbreak period. These measures or social pressure might have been effective in reducing the number of secondary cases.

We could not conduct sero-epidemiological examinations in this investigation. Therefore, mild or asymptomatic cases that did not

meet the case definition were possibly overlooked, and the SAR may have been underestimated. This issue requires further investigation.

The attack rate among siblings was significantly higher than the attack rate for parents, indicating greater contact between siblings or that infection control measures might not have been satisfactorily practiced by the younger household contacts. We conclude that it is necessary to effectively convey infection control advice among young household members, as well as to their parents, to prevent the virus from spreading in the household and, possibly, to the community. Both the public health sector and the mass media can play an important role in this responsibility.

Antiviral prophylaxis for seasonal influenza among household contacts has been shown to be effective [5–8]. Our data indicated no significant difference in the SAR in households stratified by age and age was considered to be a confounding factor. However, only one contact who had received antiviral prophylaxis met the case definition, so it was impossible to conclude whether antiviral prophylaxis was effective or not. Moreover, because no severe cases were reported among these households, we think that post-exposure antiviral prophylaxis can be given to close contacts at high risk for developing influenza complications, as recommended by the European Centre for Disease Prevention and Control (ECDC) and the US CDC [9,10]. The effectiveness of antiviral prophylaxis warrants further study and discussion, regarding its potential to prevent severe cases and the cost-benefit relationship.

Conclusion

From the results of this study, we conclude that it is important to establish routine infection control measures for households in order to prevent the spread of the virus among household contacts and, possibly, to the community. In future outbreaks, educating young household contacts on infection control measures through public notification and the media may be effective in controlling the outbreak. The effectiveness of prophylaxis for household contacts was not determined. However, close contacts with underlying disease who received prophylaxis did not develop a severe form of the disease.

TABLE 4

Comparison between the secondary attack rate in siblings and parents, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=143)

	Cases	Not cases	Total	OR(95%CI)	P-value
Siblings	10	51	61	7.84	<0.01*
Parents	2	80	82	(1.52–54.2)	
Total	12	131	143		

CI: confidence interval; OR: odds ratio.
*Chi-square test

TABLE 5

Comparison between household contacts receiving antiviral prophylaxis and those not, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=293)

	Cases	Not cases	Total	OR(95%CI)	P-value
With prophylaxis	1	121	122	0.10	<0.05*
Without prophylaxis	13	158	171	(0–0.75)	
Total	14	279***	293		
With prophylaxis < 20 years-old	1	23	24	0.15	0.09**
Without prophylaxis < 20 years-old	11	39	50	(0.01–1.30)	
Total	12	62	74		
With prophylaxis ≥ 20 years-old	0	90	90	0	0.50**
Without prophylaxis ≥ 20 years-old	2	105	107	(0–4.86)	
Total	2	195	197		

CI: confidence interval; OR: odds ratio.

* Chi-square test

** Fisher's exact test

*** Including 14 without prophylaxis and eight with prophylaxis for whom the age was not known.

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*Authors' correction: On request of the authors, the two percentages in this sentence were corrected on 4 September 2009. Further, the sentence "The SAR in household contacts was 7.6%." was changed to read "The SAR in household contacts who did not receive antiviral prophylaxis was 7.6% (13/171)" on 7 September 2009 on request of the authors, information on oseltamivir dosage was added ("75 mg/day for adults or 2mg/kg/day for children"), and the percentage of confirmed male cases in Table 3 was corrected to read 5(42).

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DETECTION OF INFLUENZA A(H1N1)V VIRUS BY REAL-TIME RT-PCR

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Influenza A(H1N1)v virus was first identified in April 2009. A novel real-time RT-PCR for influenza A(H1N1)v virus was set up *ad hoc* and validated following industry-standard criteria. The lower limit of detection of the assay was 384 copies of viral RNA per ml of viral transport medium (95% confidence interval: 273-876 RNA copies/ml). Specificity was 100% as assessed on a panel of reference samples including seasonal human influenza A virus H1N1 and H3N2, highly pathogenic avian influenza A virus H5N1 and porcine influenza A virus H1N1, H1N2 and H3N2 samples. The real-time RT-PCR assay for the influenza A matrix gene recommended in 2007 by the World Health Organization was modified to work under the same reaction conditions as the influenza A(H1N1)v virus-specific test. Both assays were equally sensitive. Clinical applicability of both assays was demonstrated by screening of almost 2,000 suspected influenza (H1N1)v specimens, which included samples from the first cases of pandemic H1N1 influenza imported to Germany. Measuring influenza A(H1N1)v virus concentrations in 144 laboratory-confirmed samples yielded a median of 4.6 log RNA copies/ml. The new methodology proved its principle and might assist public health laboratories in the upcoming influenza pandemic.

Introduction

Influenza A(H1N1)v virus was identified in humans in Mexico and the United States (US) in April 2009 [1] and has since spread worldwide [2]. The World Health Organization (WHO) declared pandemic alert stage 6 on 11 June 2009, indicating an ongoing influenza pandemic [3]. The transmissibility of the influenza A(H1N1)v virus was estimated to be higher than that of seasonal influenza viruses [4]. Influenza A(H1N1)v infections have been primarily seen among young and previously healthy adults suggesting that they are most vulnerable to infection. It remains speculative whether older people might have some level of cross-protection from pre-existing antibodies [4]. Clinical presentation and severity remains unclear, but with the exception of cases in Mexico, most confirmed cases have been characterised by mild influenza-like illness [5]. However, a considerable proportion of

patients reported vomiting or diarrhoea which is unusual in seasonal influenza [5]. To limit community or hospital transmission, as well as to initiate antiviral therapy in time as recommended by the WHO, the rapid detection of the virus in suspected cases remains crucial [6].

After the emergence of the H1N1 influenza pandemic no specific or well-validated diagnostic test was available. Rapid antigen-based tests for seasonal influenza seem to be compatible with pandemic H1N1 influenza, even though anecdotal reports exist on false-negative test results [1]. In the clinical diagnosis of influenza, nucleic acid testing by RT-PCR has widely replaced traditional virus culture due to shorter turnaround times and increased sensitivity [7]. Broadly reactive RT-PCR assays are indeed capable of detecting influenza A(H1N1)v virus [1], but they may lack sensitivity and cannot differentiate between contemporary influenza A viruses and influenza A(H1N1)v virus [8].

Immediately after the recognition of the new virus, sequence information was made publicly available by the Global Initiative on Sharing Avian Influenza Data (GISAID) [9]. We used this information to design and distribute a real-time RT-PCR assay specific for influenza A(H1N1)v [10,11]. In parallel, a published screening assay was evaluated for its ability to detect both influenza A(H1N1)v and seasonal influenza A virus [12]. This second assay served as a confirmatory test for pandemic H1N1 influenza, as well as for discriminating seasonal influenza from influenza A(H1N1)v infection. Pre-validated and quality-confirmed sets of oligonucleotides for both assays were centrally distributed within a large network of laboratories within Germany, covering most university hospitals and many public health institutions [13,14].

On 27 April 2009, samples from the first imported case of pandemic H1N1 influenza in Germany were received before specific assays for pandemic H1N1 influenza became available. The diagnosis was therefore confirmed overnight by sequencing of initial amplification products from an assay not specific for

pandemic H1N1 influenza [8]. The second imported case in Germany occurred on the evening of 28 April, the day the assay was first distributed. This case was diagnosed primarily with the new assays within three hours of receipt of the specimen. Here we report technical and clinical performance of the novel set of diagnostic tests on a large panel of samples.

Methods

Patient samples from the H1N1 influenza pandemic

At the beginning of the pandemic, 106 samples from 106 individual patients with acute onset of respiratory symptoms accompanied by fever and a recent travel history to countries with sustained human-to-human transmission of pandemic H1N1 influenza were analysed with the novel pandemic H1N1 influenza real-time PCR assay as well as the general influenza A (matrix gene) screening assay. These samples were collected and analysed in Bonn, Freiburg, Hamburg, Marburg and Regensburg. One of these samples was from an imported laboratory-confirmed case of influenza A(H1N1)v infection (Patient 1), and one from the first patient with hospital-acquired influenza A(H1N1)v infection in Germany (Patient 2). Patient 1 was diagnosed in Hamburg. Patient 2 was from Regensburg and had been infected by the first imported case to Germany [8].

A further 1,838 suspected cases were analysed at Bonn University Medical Centre later in the pandemic, until 30 July 2009. Of those, 211 cases were laboratory-confirmed pandemic H1N1 influenza. A selection of 144 pandemic H1N1 influenza-positive samples were used to determine virus concentrations in respiratory samples.

Specimens included nasopharyngeal swabs in viral transport medium, sputum, broncho-alveolar lavage fluid, throat washes, as well as cell culture medium containing reference virus strains. Viral nucleic acid was extracted using the Viral RNA mini kit (Qiagen).

Pandemic H1N1 influenza-specific real-time RT-PCR assays

Real-time RT-PCR oligonucleotides for influenza A(H1N1)v virus targeting the haemagglutinin (HA) gene were designed with Primer Express version 2 (Applied Biosystems) software. GenBank Accession number FJ966082 served as the template sequence. Several primer-and-probe combinations were evaluated experimentally to determine the most efficient combination.

A PCR reaction (One-step RT-PCR kit, Qiagen) of 25 µl for the pandemic H1N1 influenza specific assay contained: 5 µl of RNA extract, 1x reaction buffer, 400 µM of each dNTP, 40 ng/µl bovine serum albumine, 400 nM of primer H1SWS (CATTTGAAAGGTTTGAGATATTCCC; GenBank Accession Number FJ966082, nt 380-404), 400 nM of primer H1SWAs (ATGCTGCCGTTACACCTTTGT; nt 457-437), 200 nM of probe H1SWP (FAM-ACAAGTTCATGGCCAATCATGACTCG-BBQ; nt 409-435) and 1 µl of Enzyme Mix. All primers and probe were synthesised by TIB Molbiol, Berlin, Germany. Thermal cycling was done on a LightCycler 2.0 (Roche Diagnostics) instrument under the following conditions: 30 min at 50 °C; 15 min at 95 °C; 45 cycles of 15 s at 94 °C; and 30 s at 60 °C.

The same protocol can be run on a Lightcycler 480 system (Roche Diagnostics) without loss of sensitivity (data not shown). No other commercial test kits were evaluated in this study.

General influenza A (MA) real-time RT-PCR

Published real-time PCR primers targeting the matrix (MA) gene of influenza A virus were used [12]. A PCR reaction (One-step RT-PCR kit, Qiagen) of 25 µl for the matrix assay contained 5 µl of RNA extract, 1x reaction buffer, 400 µM of each dNTP, 40 ng/µl bovine serum albumine, 400 nM of primer M_InfA F (AAGACCAATCCTGTACCTCTGA; GenBank Accession number CY038773; nt 175-197), 400 nM of primer M_InfA R (CAAAGCGTCTACGTCGAGTCC; nt 269-248), 200 nM of probe M_InfA TM (FAM-TTTGTGTTCACGCTACCGT-BBQ; nt 215-234) and 1 µl of Enzyme Mix. Thermal cycling was done on a LightCycler 2.0 (Roche Diagnostics) instrument under the following conditions: 30 min at 50 °C; 15 min at 95 °C; 45 cycles of 15 s at 94 °C; and 30 s at 60 °C.

As above, the same protocol can be run on a Lightcycler 480 system (Roche Diagnostics) without loss of sensitivity (data not shown).

Construction of in vitro-transcribed RNA controls

A partial HA gene fragment from the virus isolated from Patient 1 was amplified using primers HA_InfA_CaF1 (CAACAGACACTGTAGACACAG; GenBank Accession number FJ966082; nt 86-106) and HA_InfA_CaR1 (TTCCATTGCGAATGCATATCTCGG; nt 825-802) and cloned into a pJET12 plasmid vector (Fermentas). The complete MA gene from the same virus was amplified using primers Matrix_CaL_F (TAACCGAGGTCGAAACGTACG; GenBank FJ969513; nt 11-31) and Matrix_CaL_R (TTACTCTAGCTCTATGTTGAC; nt 982-902) and ligated and cloned as described above. Plasmids were transcribed into RNA by means of a MEGAScript T7 *in vitro* transcription kit (Ambion) as described [15]. RNA *in vitro* transcripts were purified and quantified spectrophotometrically. Sequence integrity was checked by sequencing on an ABI 3100 automated sequencer (Applied Biosystems).

Determination of lower limit of detection

Initial experiments were done with RNA extracted from nasopharyngeal specimens of Patient 1. To exactly determine the lower limit of detection (LOD) of both real-time RT-PCR assays, different concentrations of HA RNA transcript as well as MA RNA transcript were spiked into viral transport medium, and RNA was extracted using the viral RNA mini kit (Qiagen). Influenza-negative swabs to account for patient derived matrix effects were not used since possible PCR inhibitors will most likely be efficiently diluted by the viral transport medium. Five replicates of each concentration were processed and analysed by the pandemic H1N1 influenza (HA RNA transcript) and the screening (MA RNA transcript) real-time RT-PCR, respectively. Fractions of positive results for each concentration were subjected to probit regression analysis using the Statgraphics software package (Manugistics).

Quantitative results for pandemic H1N1 influenza

Nasal and throat swabs from a selection of 144 cases of pandemic H1N1 influenza (see above) were used to determine influenza A(H1N1)v virus RNA concentrations in the H1N1 influenza-specific (HA) real-time assay using *in vitro*-transcribed RNA as described [15]. An external curve was generated and cycle threshold values were transformed into log RNA copies/ml.

Results

Pandemic H1N1 influenza-specific (HA) real-time RT-PCR assays

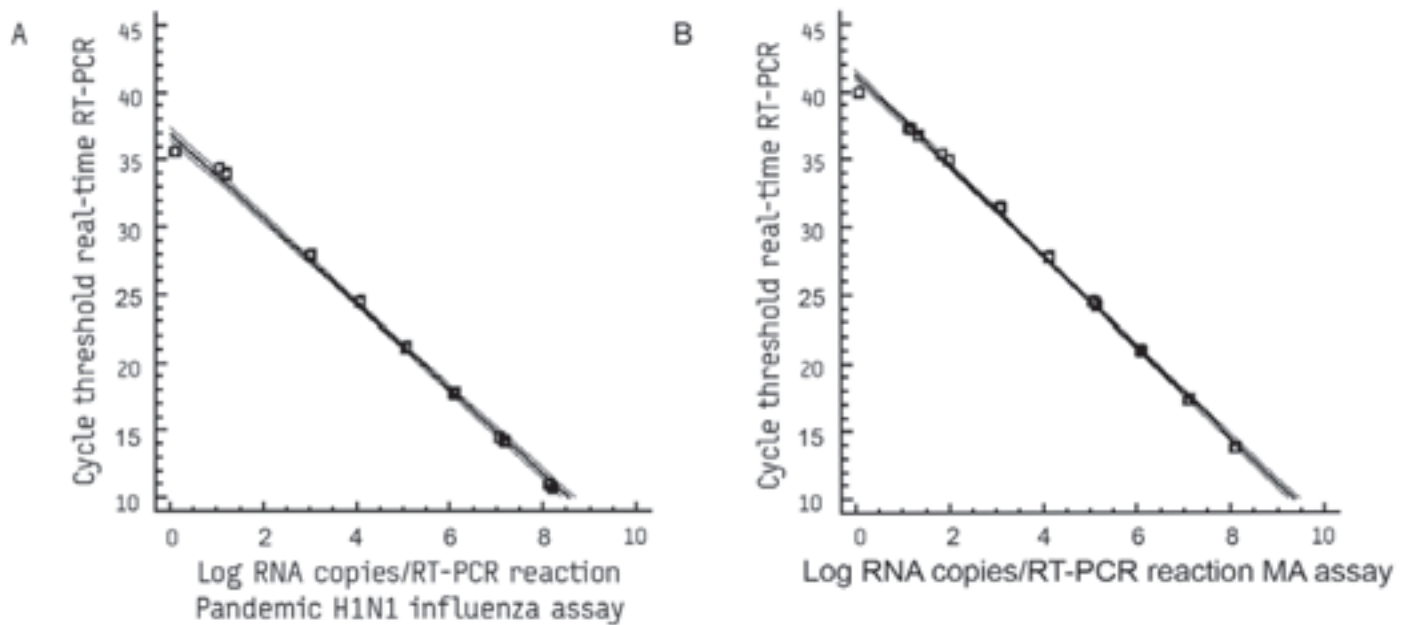
Tenfold serial dilution series of *in vitro*-transcribed HA RNA were tested in duplicates in the pandemic H1N1 influenza (HA)

RT-PCR (Figure 1A) and the general influenza A (MA) screening RT-PCR (Figure 1B), in order to determine the linear range of both real-time RT-PCR assays. The resulting end-points of detection in

the pandemic H1N1 influenza (HA) RT-PCR were 1 and 5 RNA copies/ μ l in different experiments. A linear correlation between the

FIGURE 1

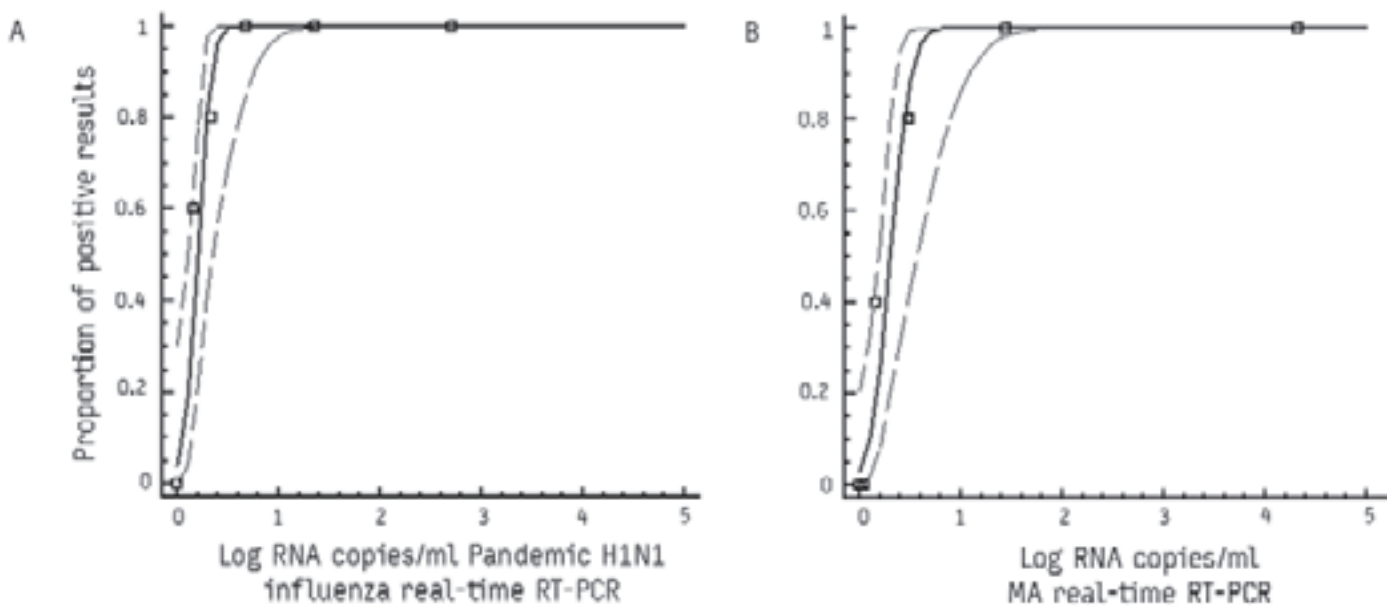
Linear range of pandemic H1N1 influenza (HA) real-time RT-PCR and general influenza A (MA) screening real-time RT-PCR



HA: haemagglutinin gene; MA: matrix gene. Observed cycle thresholds are plotted against log RNA concentration (square points). Thick centre lines represent the prediction line, thin lines the 95% confidence intervals.

FIGURE 2

Probit analysis of pandemic H1N1 influenza (HA) real-time RT-PCR and general influenza A (MA) screening real-time RT-PCR



HA: haemagglutinin gene; MA: matrix gene. Depicted are the observed proportion of positive test results in parallel experiments (square data points), as well as the derived predicted proportion of positive results (line) at a given input concentration of RNA. The centre line denotes the prediction, thin broken border lines are 95% confidence intervals.

log starting copy number and threshold cycle was achieved from 2.67 x 10² RNA copies/μl to at least 2.67 x 10⁸ RNA copies/μl.

TABLE 1

Serial tenfold dilutions of RNA extracted from Patient 1 tested by the MA broad-range assay as well as the pandemic H1N1 influenza-specific real-time RT-PCR

	Log ₁₀ dilution series RNA, Patient 1					
	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷
MA assay	+	+	+	+	-	-
Pandemic H1N1 influenza assay	+	+	+	+	-	-

MA: matrix protein gene.
+ indicates a positive result, - denotes a negative result.

TABLE 2

Specificity testing of influenza specimens of porcine and human origin by MA broad-range assay and pandemic H1N1 influenza-specific assay

Influenza virus specimen		Real-time RT-PCR result	
		MA assay	Pandemic H1N1 influenza assay
1	A/Swine/Hannover/1/81(H1N1)	+	-
2	A/Swine/Germany/2/81 (H1N1)	+	-
3	A/Swine/Italy/21599-3/03 (H1N1)	+	-
4	A/Swine/Borkum/1832/00 (H1N2)	+	-
5	A/Swine/Italy/30019-2/07 (H1N2)	+	-
6	A/Swine/Italy/65260-11/06 (H3N2)	+	-
7	A/Bayern/7/95 (H1N1)	+	-
8	A/Beijing/262/95 (H1N1)	+	-
9	A/Brazil/11/78 (H1N1)	+	-
10	A/Moscow/10/99 (H3N2)	+	-
11	Influenza A clinical samples 2008-9 (n=120)*	+	-
	Influenza quality assessment samples		
12	A/Fukushima/141/06 (H1N1)	+	-
13	A/New Caledonia/20/99 (H1N1)	+	-
14	A/Brisbane/10/07 (H3N2)	+	-
15	A/Brisbane/59/07 (H3N2)	+	-
16	A/California/7/04 (H3N2)	+	-
17	A/Wisconsin/67/06 (H3N2)	+	-
18	A/duck/Vietnam/TG24-01/05 (H5N1)	+	-
19	A/whooper swan/Germany/R65-2/06 (H5N1)	+	-
20	B/Florida/4/06**	-	-
21	B/Malaysia/2506/04**	-	-
22	B/Shanghai/361/02**	-	-

MA: matrix protein gene.
+ depicts a positive, - a negative result.
*All 120 samples tested positive in the MA and negative in the pandemic H1N1 influenza assay.
**All influenza B samples tested positive in an influenza B- specific RT-PCR (data not shown).

The slope was calculated as 3.15 for the pandemic H1N1 influenza (HA) assay. Based on the slope value, PCR efficiency was calculated to be 1.0 (according to the PCR amplification formula $E=10^{(1/\text{slope})}-1$; E being the PCR efficiency), indicating 100% efficient PCR amplification.

The 95% LOD was determined next. This common technical specification indicates the concentration down to which an assay will detect the analyte with at least 95% probability. To generate defined reference material that mimics clinical samples, different concentrations of *in vitro*-transcribed RNA were spiked into viral transport medium in which swabs are routinely received in the laboratory. Each analyte concentration was tested in five replicate reactions in each RT-PCR assay and yielded a 95% LOD of 384 RNA copies/ml (95% CI: 273-876 RNA copies/ml) for the pandemic H1N1 influenza (HA) assay (Figure 2A).

General influenza A (MA) real-time RT-PCR

For confirmation of influenza A virus detection, oligonucleotides from several published and evaluated RT-PCR assays were checked against the genome sequence of influenza A(H1N1)v virus. One assay developed by Ward et al. [12], was targeted against the MA gene. This assay had been recommended by the WHO for general influenza A virus screening, including avian influenza A virus (H5N1), matched the influenza A(H1N1)v virus sequence except for one base pair mismatch (C-T) 13 nucleotides from the 3'-end of the plus strand primer [16]. This mismatch was considered uncritical. The assay was optimised in order to comply with the same cycling conditions as the pandemic H1N1 influenza (HA) assay, so that both assays could be run in parallel in one LightCycler instrument. Serial dilution series of patient RNA were tested with both assays. As shown in Table 1, both assays were equally sensitive.

Using *in vitro*-transcribed MA RNA, the MA assay yielded an end-point dilution sensitivity of 13 RNA copies per μl . The linear range extended from 1.28x10² RNA copies/ μl to at least 1.28x10⁸ RNA copies/ μl . The slope was calculated as 3.35, and PCR efficiency was 0.99 (Figure 1). In a probit analysis as described above, the MA-based broad range assay showed a 95% LOD of 570 RNA copies/ml (95% CI: 397-1,232 RNA copies/ml) (Figure 2).

Specificity of the pandemic H1N1 influenza (HA) assay

Specificity of the H1-based pandemic H1N1 influenza assay was confirmed on a panel of 21 stored clinical samples containing adenovirus (n=1), respiratory syncytial virus (RSV)-A (n=5), RSV-B (n=2), human coronavirus OC43 (n=1), human coronavirus 229E (n=3), human coronavirus NL63 (n=1), human metapneumovirus (n=1), parainfluenzavirus 3 (n=1) and entero-/rhinovirus (n=6) as assessed by xTAG Respiratory Viral Panel (Luminex; authors' unpublished data). As expected, none of these pathogens reacted with the pandemic H1N1 influenza real-time RT-PCR indicating its high specificity. The MA-based broad range assay was not evaluated on this panel but demonstrated its specificity as described. [12].

Because of the porcine origin of pandemic H1N1 influenza [17], the assay was also tested on cell culture supernatants containing porcine influenza A virus reference samples (Table 2, rows 1-6).

To exclude cross-reactivity with human influenza viruses, we tested cell culture supernatants of human influenza virus strains (Table 2, rows 7-10) as well as 120 original clinical samples from patients with seasonal influenza A virus infection from the 2008-9 season, including H1N1 and H3N2 viruses (Table 2, row 11). All of these were negative in the pandemic H1N1 influenza (HA) assay and positive in the MA-based broad-range assay (shown in Table 2).

In addition, 30 stored samples from recent quality assessment tests for influenza virus detection were evaluated (Table 2, rows 12-22). None of these materials, which included various dilutions of contemporary human influenza A(H1N1, H3N2) as well as avian influenza A(H5N1) and influenza B virus samples yielded a positive result with the pandemic H1N1 influenza (HA) assay. All influenza A samples were positive in the general influenza A MA-based assay.

Clinical evaluation

A preliminary clinical evaluation was done in five public health and university laboratories in Germany. By mid-May 2009 samples from 106 individual patients suspected on clinical and epidemiological grounds to have acquired influenza A(H1N1)v infection had been analysed with the new assays. Of these 106 samples, 102 gave negative results in both assays. Three of the four

remaining samples tested positive in the MA-based assay, but were negative in the HA-based pandemic H1N1 influenza assay. After to further confirmatory testing, these three samples turned out to be human seasonal influenza A virus infections (data not shown).

The last sample was positive in both assays. This patient (Patient 1) was preliminary classified as having acute influenza A(H1N1)v infection. She had a recent travel history to Mexico and sought medical treatment for fever and acute respiratory symptoms in Hamburg on 28 April 2009. Influenza A(H1N1)v infection was confirmed by the National Influenza Reference Centre at the Robert-Koch Institute (RKI), Berlin.

Material from another confirmed case (Patient 2) was provided retrospectively for testing with both assays. This patient had not reported a recent travel history but shared a hospital room with the first imported case of pandemic H1N1 influenza in Germany [8]. The patient had only very mild symptoms. Both assays reacted clearly positive.

Later in the pandemic, further samples of suspected influenza A(H1N1)v infection were analysed with the new assay at Bonn University Medical Center, so far 1,838 samples. Among those, 221 confirmed cases of pandemic H1N1 influenza have been identified as of 30 July.

Quantitative results for pandemic H1N1 influenza

Viral RNA concentrations were measured in samples from 144 laboratory-confirmed cases of pandemic H1N1 influenza for whom RNA preparations were available at Bonn University Medical Center. A median of 4.6 influenza A(H1N1)v virus log RNA copies per ml of viral transport medium was determined in the pandemic H1N1 influenza-specific (HA) assay (range 2.1-7.9 log RNA copies/ml), indicating rather low virus concentrations.

Discussion

A real-time RT-PCR specific for influenza A(H1N1)v virus was set up immediately after first sequence information became available, and evaluated thoroughly from a technical and clinical point of view.

In the currently evolving influenza pandemic, rapid and reliable case identification remains crucial to limit extensive transmission and to initiate therapy [18]. The performance of antigen-based tests for pandemic H1N1 influenza has not been extensively evaluated so far, but anecdotal reports do exist of false negative test results in confirmed cases of pandemic H1N1 influenza [19]. A further issue with antigen-based tests is the fact that they do not discriminate between seasonal influenza A virus strains and influenza A(H1N1)v virus strains. The concurrence of the first wave of the pandemic H1N1 influenza and regular seasonal influenza in the southern hemisphere poses a risk of intra-human reassortation, making it highly relevant to discriminate between viruses by laboratory testing [20].

Real-time RT-PCR has proven highly effective in the detection of seasonal human influenza [21]. First reports on clinical cases in which influenza A(H1N1)v virus was detected by real-time RT-PCR have become available, but the assays used so far had not been validated thoroughly from a technical point of view [19,22,23]. Our study presents the first fully validated real-time RT-PCR for pandemic H1N1 influenza. Its LOD at 384 RNA copies/ml (95% LOD, probit analysis) is comparable to that of commercial test kits [21,24]. Specificity was proven on a comprehensive panel of

120 clinical samples containing contemporary human influenza A and B viruses, on reference specimens from an external quality assurance study, and on a panel of selected swine influenza viruses. Clinical applicability was demonstrated on the first imported cases of pandemic H1N1 influenza in Germany, and by testing more than 200 confirmed cases later in the pandemic without any false positive or negative results. Interestingly rather low virus concentrations were measured by the pandemic H1N1 influenza-specific real-time RT-PCR, compared to viral loads seen in seasonal influenza [25,26]. It remains unclear if this is related to the host or propensity of the virus itself.

We have also shown in this study that a broad-range influenza A assay recommended by WHO and based on the MA gene had the same high sensitivity as the HA-based pandemic H1N1 influenza-specific assay and can be used for simultaneous detection of influenza A(H1N1)v virus and seasonal strains [12]. It can thus serve as a confirmatory test and for discriminating influenza A(H1N1)v virus from seasonal strains. Both assays were developed to allow for parallel testing on a single real-time PCR instrument, reducing the time of turnover significantly [27]. Use of the combined assays facilitates decentralised testing in clinical laboratories, which is necessary when the demands for testing will exceed the capacities of reference laboratories during the upcoming pandemic [20,28]. In this respect, it is important to mention that the validation data presented in this report have been generated by five different laboratories that had obtained the assays in form of protocols and pre-evaluated oligonucleotides. Recent experiences during the epidemics of severe acute respiratory syndrome (SARS) and chikungunya disease have demonstrated that rapid provision of pre-formulated diagnostic assays can facilitate immediate diagnostic capacity building [13,14,29].

To conclude, we could demonstrate that the testing algorithm proposed here is a feasible approach and might assist public health laboratories in the upcoming influenza season.

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ECONOMIC CONSEQUENCES TO SOCIETY OF PANDEMIC H1N1 INFLUENZA 2009 – PRELIMINARY RESULTS FOR SWEDEN

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Experiments using a microsimulation platform show that vaccination against pandemic H1N1 influenza is highly cost-effective. Swedish society may reduce the costs of pandemic by about SEK 2.5 billion (approximately EUR 250 million) if at least 60 per cent of the population is vaccinated, even if costs related to death cases are excluded. The cost reduction primarily results from reduced absenteeism. These results are preliminary and based on comprehensive assumptions about the infectiousness and morbidity of the pandemic, which are uncertain in the current situation.

Introduction

In cooperation with the epidemiological unit at the Swedish National Board of Health and Welfare, researchers at the Swedish Institute for Infectious Disease Control and the Royal Institute of Technology micro-modelled the effects of a possible future scenario of an outbreak of pandemic H1N1 influenza in Sweden, projected for the autumn of 2009. An executable simulation model [1] was used together with registry data from Statistics Sweden (Statistiska centralbyrån, SCB) [2] to link the entire Swedish population together in a large spatially explicit social network. The overall aim of developing the model has been to allow for the simulation of the spread of infection in a population in a realistic manner, and examine the effects of applying different policy strategies. Individuals in the stochastic model go to kindergarten, schools, work, healthcare facilities, and travel to places where they may

be exposed to the risk of infection. Since all places have explicit coordinates, the geographical spread can be studied.

Method

The simulations were run with the following assumptions (see detailed description in the Annex at the end of the article): The outbreak of pandemic influenza in Sweden starts on 1 September 2009, and is mild. The infection rate produces an R0-value of approximately 1.4, but here only cases from the first waves of the epidemic (first 180 days) and not from the whole outbreak are reported. Children and adolescents are assumed to be more susceptible and more infectious than adults. For all ages, the following allocation of morbidity holds: 16% are asymptotically ill (i.e. show no symptoms), 34% are mildly ill, 40% display a typical illness, while 10% have a severe form of illness. The latter category includes patients referred to specialised care at a hospital, which does not necessarily entail hospitalisation. One adult in the household stays home from work for as many days as a child younger than 12 years is sick.

The 90% coverage scenario amounts to mass vaccination, since 10% of the population are assumed to be impossible to vaccinate. Each simulation covered 180 days and began with 50 randomly selected individuals infected on day 0. Each scenario was simulated five (or ten for the most likely scenarios of 50%, 60%, or 70% vaccination coverage) times with different random seeds to obtain

TABLE

Distribution of the level of immunity. Simulation of pandemic H1N1 influenza in Sweden.

Level of immunity after dose 1	Proportion of vaccinated	Proportion of individuals with 40% immunity after dose 2	Proportion of individuals with 60% immunity after dose 2	Proportion of individuals with 80% immunity after dose 2	Proportion of individuals with 100% immunity after dose 2
100%	15%				100%
80%	20%			40%	60%
60%	25%		40%	40%	20%
40%	20%	10%	40%	35%	15%
30%	15%	40%	35%	25%	0%
10%	5%	40%	35%	25%	0%

robust results and to examine variability. Vaccination started after 30 days (on 1 October). The doses were delivered weekly at a rate that gave all people time to be vaccinated with two doses over 14 weeks. For immunity, the following assumptions were made: Dose 1 gives partial immunity, which is then increased through the second dose (Table 1). For example, an individual who after the first dose gained 40% immunity (i.e. risk of getting the infection reduced by 40%) will after the second dose stand a 10% chance of staying at the same level, a 40% chance of increasing the immunity to 60%, a 35% chance of reaching 80% immunity, and finally a 15% chance of obtaining full immunity (i.e. being no longer susceptible). If a vaccinated individual is infected, the disease will be milder and the infectivity lower than that of an unvaccinated individual.

To compare the societal costs of the six scenarios, the following cost estimations — obtained from health economists at the Swedish Ministry of Health and Social Affairs — were used:

- Cost of one-day absence from work per employee: SEK 2,000 (this includes average daily salary of SEK 1,500 and secondary costs (taxes, overhead) of SEK 500).
- Cost of treatment by a doctor in primary care: SEK 2,000.
- Cost of one-day inpatient care: SEK 8,000.
- Cost of vaccine and administration of vaccination per person: SEK 300.

For all scenarios, the SEK 300 vaccine costs are based on the assumption that the entire population is vaccinated (a total of 18 million doses), split evenly between vaccine cost and vaccine administration. This means that no savings on vaccine administration are attributed to a lower number of vaccinated than 90%. The model presupposes absent workers to take care of sick children, and thus the event of sick children does not produce the SEK 2,000 cost in a family where a parent is already ill. The inpatient care does not include expensive specialist care, but is based on the average cost of one day in inpatient care (SEK 8,119, according to figures from 2007, obtained from: <http://sjvdata.skl.se>).

Direct costs related to death cases are considered, using the figure of SEK 22 million per deceased (as employed by the Swedish Institute for Transport and Communications Analysis), but the case fatality rate (CFR) is hard to assess. Since the CFR for pandemic H1N1 influenza is still unknown [3], one way to proceed is to use a best estimate. Three scenarios were used for the present analysis, motivated by the early figures from New Zealand: 0.005%, 0.010%, and 0.050%. The first of these is considered the most likely scenario [4]. A similar cost assessment could be made regarding those suffering permanent health damages from the disease, but this is not reported here. Finally, neither deaths resulting from vaccination, nor import infections (i.e. cases of infected individuals travelling to Sweden from abroad) have been included in the model.

Results

For the scenario in which no policy interventions are made, the outbreak reaches its peak in weeks 16-20 in the five simulations run, each with over 100,000 newly infected in that peak week (Figure 1). More than a third of the individuals were infected at home (Figure 2). The neighbourhood is an aggregate of all contacts in geographical and social proximity, outside the home. That schools play a relatively important role in spreading a new infection is in

FIGURE 1

The number of infected persons per week during five simulations of the scenario without intervention. Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.

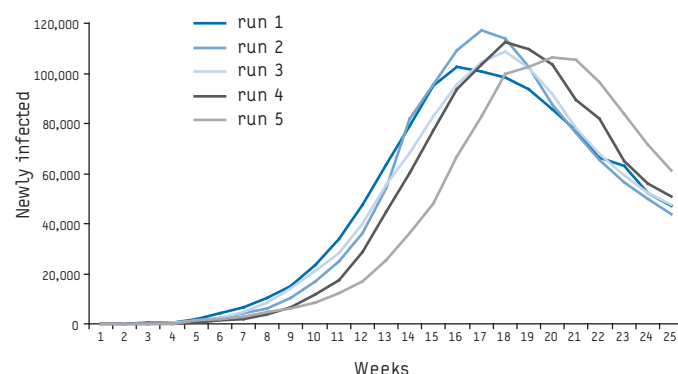
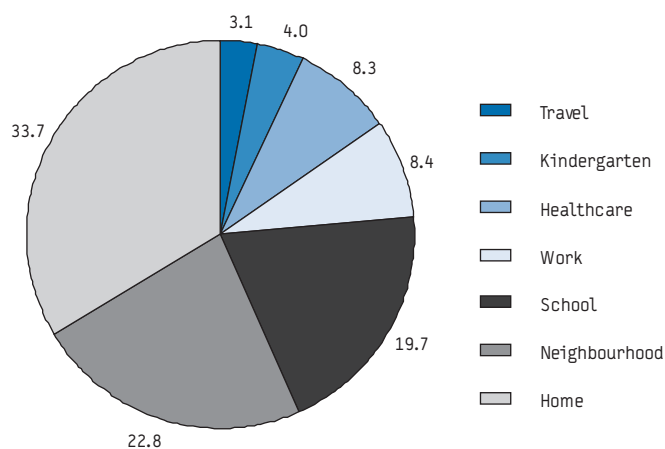


FIGURE 2

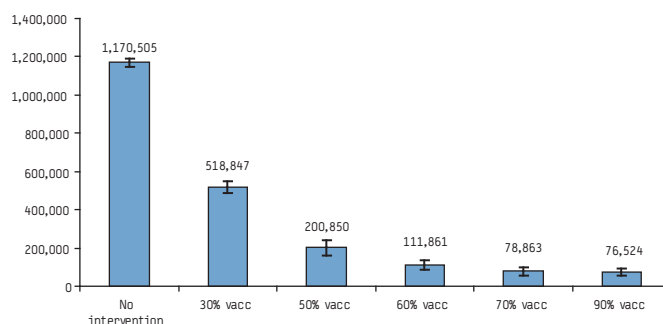
The place distribution of infected individuals, for the scenario without intervention. Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.



Note: Numbers denote percentages, averaged over the five runs of this particular scenario.

FIGURE 3

The total number of infected individuals (y axis), for all runs. The error bars indicate one standard deviation of uncertainty. Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.



part a result of the assumption of increased infectiousness in the young population.

In Figure 3, the total numbers of infected individuals are presented, for all runs. The age distribution is not presented here, but is largely consistent with reports from actual spread, with an overrepresentation of the youngest and an underrepresentation of the oldest individuals.

The societal costs have been computed for four levels of CFR, including a baseline zero risk scenario depicted in Figure 4 (total costs) and Figure 5 (costs broken down into five categories). The two figures do not include the vaccine cost for the baseline scenario, even though it should be noted that Sweden has already ordered 18 million doses, putting the baseline scenario out of step with the actual fact. This fact notwithstanding, the scenario without

interventions proves the most costly, and Figure 5 makes it evident that the mounting costs related to sick leave is the dominating factor. Including costs related to death cases provides even more evidence for the preliminary result that a vaccination level of at least 60% should be recommended (Figure 6). Figure 7 provides a simple sensitivity analysis, where the cost related to the deceased become the major cost as the most plausible CFR (0.005% of infected individuals) is increased by a factor of ten.

Discussion

There are many reasons to be careful when interpreting the results of these simulation experiments, since the assumptions made might not reflect the actual characteristics of the current pandemic. However, as the effects of the pandemic are being assessed, new assumptions and new sensitivity analyses can relatively easily be made, following the same methodology as described here. And, we believe, that the overall conclusion stands, namely that given an outbreak of pandemic H1N1 influenza of the size contemplated here, vaccinating at least 60% of the Swedish population is recommended, from an economic perspective. When the actual doses arrive in Sweden, they will be distributed among the counties based on county population: the more people, the more doses. In Sweden, vaccination will be voluntary, but for the purpose of these simulation experiments it was assumed, somewhat unrealistically [5], that everyone offered vaccination will accept it. A recent survey, conducted on behalf of the National Board of Health and Welfare, on attitudes towards vaccination in Sweden, found a 72% willingness-to-vaccinate. The survey was conducted between July 27 and August 23, and consisted of 2,000 interviews.

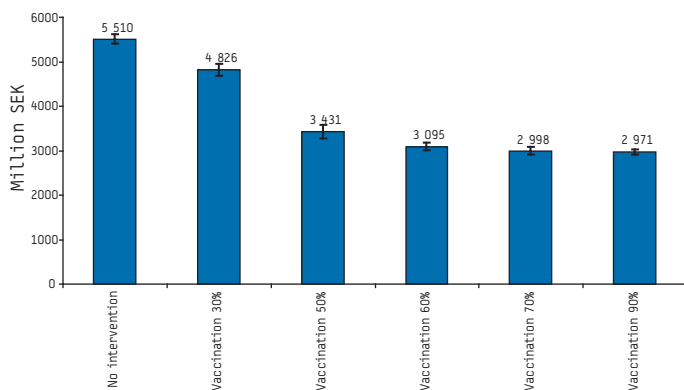
The time to reach the peak of an outbreak in these simulation experiments was more than two weeks longer than what has been reported for the actual outbreaks in the southern hemisphere. This is likely to favour immunisation. Our hypothesis is that the relatively rapid, especially in view of the R0 values reported, peaks in Australia and New Zealand could be explained by the earliest cases going unrecognised, and a constant influx of new cases from abroad. In the model presented here, all cases are recognised, including the earliest asymptomatic cases, pushing back the start date of the epidemic. The fact that cases from abroad were not included can to some extent be justified by the relatively small number of people travelling to Sweden in the early fall.

A recent study [6] suggests that vaccinating school children and their parents leads to a reduction of spread, in large part thanks to herd immunity [7]. The MicroSim model is highly suitable for investigating the efficiency of such policies, since the social network allows for identifying the parents, and a replication study is under way.

Acknowledgements

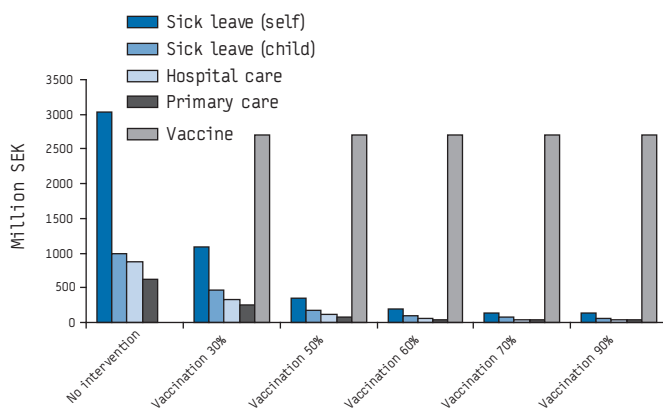
Model assumptions have been scrutinised by both The Swedish National Board of Health and Welfare (SoS), and by the panel of experts employed in the project which includes Anders Tegnell, Annika Linde, Åke Örtqvist, and Fredrik Elgh. Information on supplies and effectiveness of vaccines is based on information from GlaxoSmithKline AB, Hillar Kangro. Simulation model developed at SMI, by Lisa Brouwers, Martin Camitz, Baki Cakici, and Kalle Mäkilä. The programming of interventions was done mainly by Baki Cakici. Analysis and reporting is the responsibility of Lisa Brouwers, with technical assistance from Magnus Boman.

FIGURE 4
Total costs for the six scenarios, averaged over all runs. Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.



Note: Case fatality rate is here set to zero. The “no intervention” scenario acts as a base line with zero cost for vaccination, while the other five scenarios all have actual cost for vaccination (SEK 2.7 billion). Error bars denote the standard error of the mean.

FIGURE 5
Detailed costs for the six scenarios. Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.



Note: Case fatality rate is set to zero.

FIGURE 6

Detailed costs for the six scenarios, including the costs related to the deceased, where the CFR is set to 0.005%. Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.

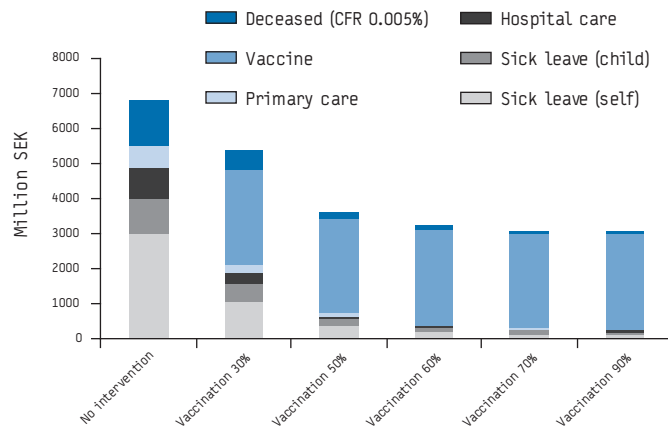
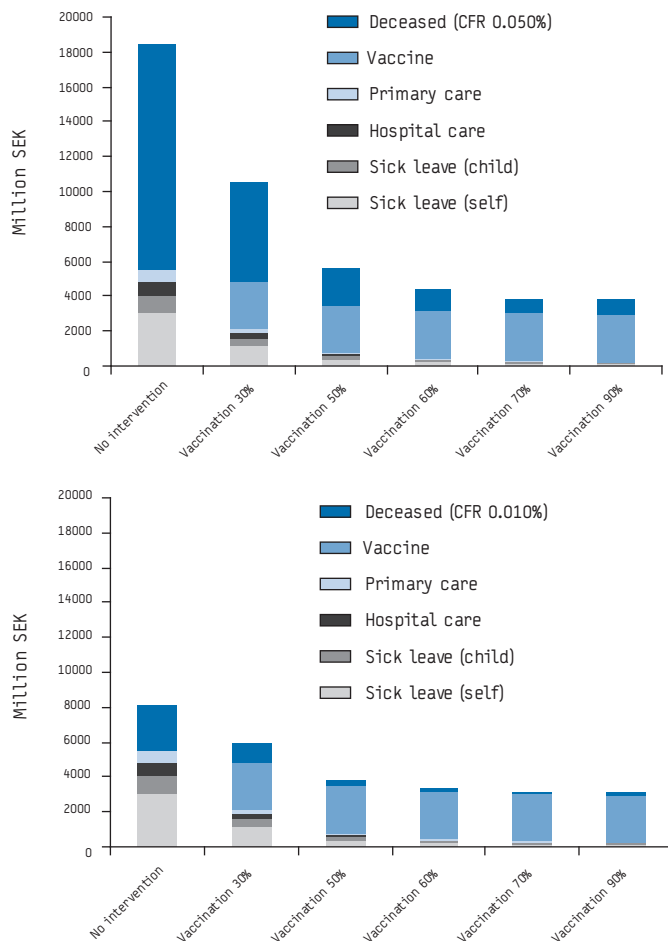


FIGURE 7

Detailed costs for the six scenarios, including the costs related to the deceased, where the CFR is set to 0.050% (top) and 0.010% (bottom). Estimation of costs of pandemic H1N1 influenza 2009 for Sweden.



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Annex: Assumptions prior to the experiment

1. Introduction of infection

On the first day of simulation, 50 individuals are randomly selected to be the initially infected.

$$R_0 = \frac{-\ln\left(\frac{A}{B}\right)}{1 - \frac{A}{B}}$$

2. R0 value

R0 is defined as the average number of individuals a typical person infects under his/her full infectious period, in a fully susceptible population. Here parameter values were used that, on average, cause outbreaks with R0-value 1.4. This value was calculated using the following formula:

B: Total number of susceptible individuals before the outbreak

A: Total number of susceptible individuals after the outbreak

Note that 7,978,105 out of 8,861,388 individuals in Sweden belong to the giant component, that is to say, they are connected to the social contact network. We use this lower value instead of the total population for the “susceptible before” value in the calibrations in order to avoid overestimating the infectiousness.

To reach the required R0-value, we adjusted the amplitude of the epidemic profiles. We used a factor 0.997 as the escape probability to obtain the required R0-value (4,000,080 infections).

3. Infectiousness profiles

We use different infectiousness profiles for different disease severities. Additionally, we assume that children are both more infectious and more susceptible. The infectiousness is the risk of transmission through personal contact, i.e. when an infectious and a susceptible person meet (during a period of eight hours). See Annex Figures 1 through 4 below for the corresponding profile graphs.

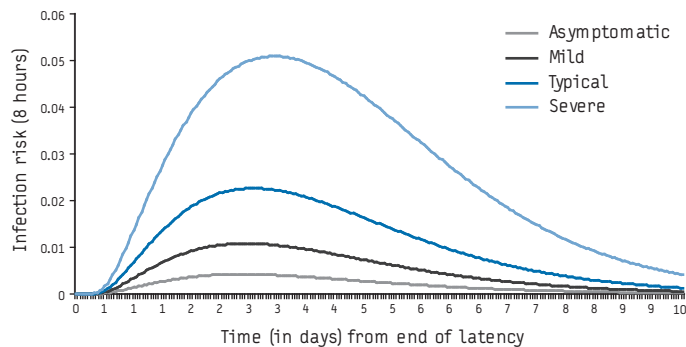
The infectiousness profiles are adapted from Carrat et al. [8], where a static latency period is included. We chose to remove this latency period from the Carrat profiles and instead introduced a varying latency period (12 to 60 hours), generated from a Weibull distribution with scale parameters 1.1 and 2.21 [9,10].

4. Disease profiles

In the experiments, all infected individuals are assigned a certain disease profile with the following proportion: asymptomatic (16%), mild (34%), typical (40%) and serious (10%). The infected individuals display different levels of illness depending on their disease profile (Annex Figure 5).

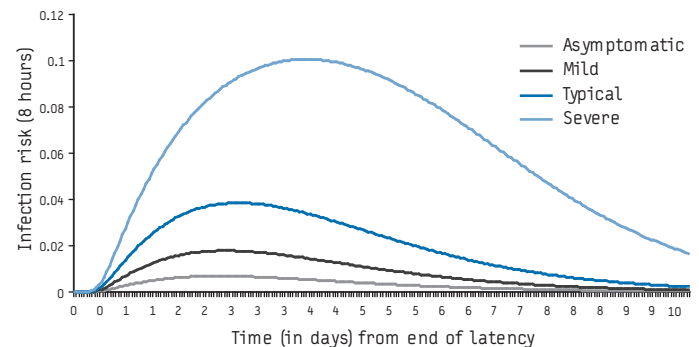
ANNEX: FIGURE 1

Infectiousness profiles adult -> adult



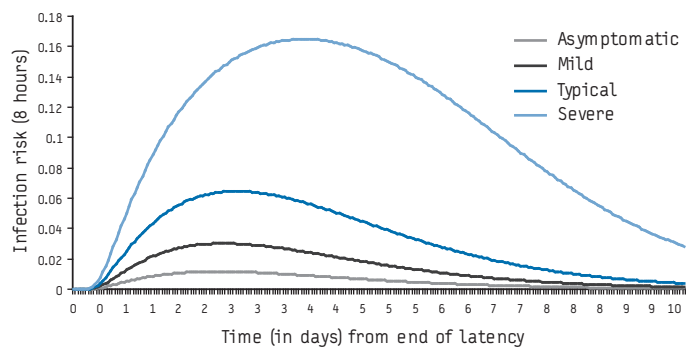
ANNEX: FIGURE 3

Infectiousness profiles child -> adult



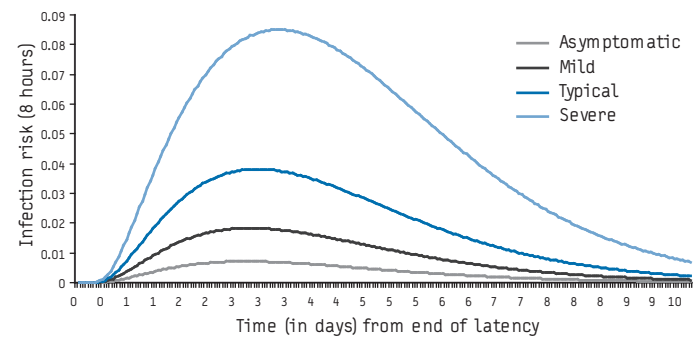
ANNEX: FIGURE 2

Infectiousness profiles child -> child



ANNEX: FIGURE 4

Infectiousness profiles adult -> child



The number of deaths was calculated externally, after the simulations, due to the uncertainty of case fatality rates. We multiplied the number of infected individuals by the CFR 0.005% estimated in another study [4].

5. Choice of place according to disease level

Depending on their disease level, the individuals spend their day in different settings (Annex Figure 6). The choice of place is determined randomly. Persons with the same disease level can spend the day in different settings: one stays at home from work, another is at work, and a third person visits the emergency room. Disease level 0 represents all individuals who are not infected, as well as those infected without symptoms.

Settings in the model extracted from register data

By using different SCB (Statistics Sweden) register data [2] individuals have been linked to their workplaces and their residences. Individuals are also linked together in their families.

In the model, each person object contains the family identifier, birth year, gender, coordinates for the family residence (indicated at the level of 100 x 100 meter squares), and workplace identifier. Workplace representations include the workplace identifier, county, and coordinates of the workplace. The workplace identification

number is used to connect the person and the workplace. Place objects include a list of members; for residences this list contains the family members and for workplaces it contains employed individuals.

Unit size

We have decided on a maximum number of persons, x, to belong to any one unit. This means that an individual is in close contact with a maximum of x other individuals at his/her workplace, school, nursery centre, etc.

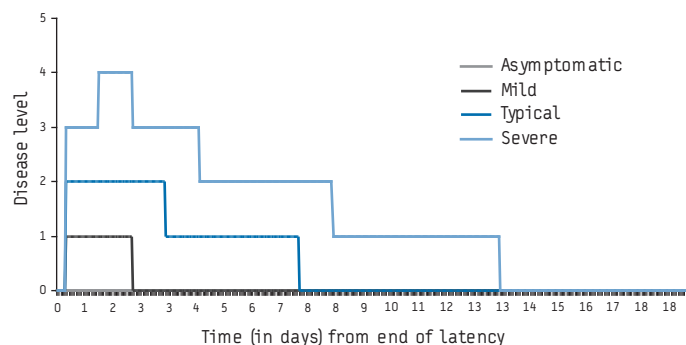
At large places, it is also possible to transmit infection between units.

Since the individuals in the model lack memory, it is possible for them to visit primary care one day, go to work the next day and visit primary care again on the third day. To avoid this issue, we created a place choice rule to limit emergency room visits to one.

The number of visits to emergency rooms and primary treatment are based on information gathered by the Swedish Association of Local Authorities and Regions (SALAR) in 2006 [11]. This database is also the source of the costs for 24 hours of inpatient care, as noted in the paper.

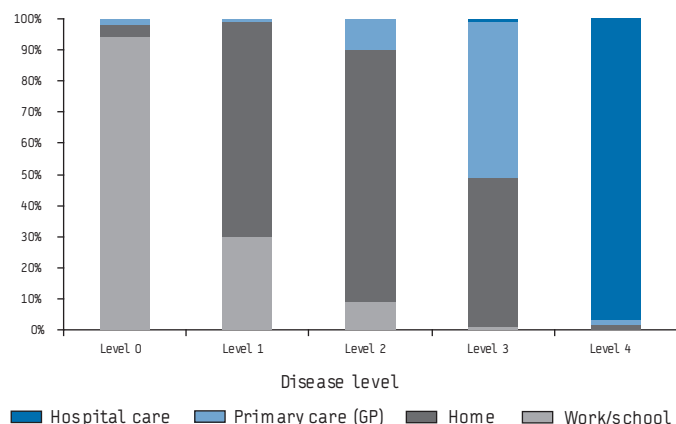
ANNEX: FIGURE 5

Disease levels



ANNEX: FIGURE 6

Place distribution by disease level



ANNEX: TABLE 1

Maximum size of places

Type of place	Maximum size of unit/group
Kindergarten	no unit division
School	25
Office	25
Emergency room	no unit division
Infectious diseases clinic	no unit division

ANNEX: TABLE 2

Number of outpatient visits

Visits to general practitioners (excluding antenatal and paediatric care)	25,238,500
All other visits (including day care treatment)	34,131,400
Total:	59,369,900
Per day:	162,657

ANNEX: TABLE 3

Number of infected individuals

Scenario	Number of infected	Standard deviation	Number of runs
No interventions	1,170,505	45,345	5
Vaccination coverage 30%	518,847	63,742	5
Vaccination coverage 50%	200,850	40,653	10
Vaccination coverage 60%	111,861	52,219	10
Vaccination coverage 70%	78,863	45,586	10
Vaccination coverage 90%	76,524	37,307	5

In the model, the daily risk of visiting primary care (for an individual with disease level 0) has been determined to be 0.0184 (162,657/8,860,000).

The estimates of daily probability of staying home from work due to illness or for other reasons at disease level 0 are based on data from SCB [2] and the Swedish Social Insurance Agency [12]. The absence, as indicated in the data, varies over time depending on changes in compensation levels and regulations. We use 4%, a relatively low level, for the current model.

6. Ad hoc contacts

In addition to contacts within the social network, we include two additional place types to represent ad hoc contacts: neighbourhood and travel. Neighbourhood infections are used to represent infections in an individual's geographical vicinity, while travel indicates infectious spread between Sweden's 81 regions.

Neighbourhood

Infection transmission in the neighbourhood occurs in two steps for each region:

- 1) Calculate the total number of new infections for each region:
N = Current number of infected in region
C = Number of contacts (=10, for the current model)
R = Risk of infection: the mean value of the four disease profiles

$$I = N \times C \times R$$

The number of individuals infected in the neighbourhood decreases over time, as described by multiplying the right-hand side of the above equation by the fraction S/T, where S is the number of susceptible individuals and T is the total number of individuals.

- 2) Choose the individuals to be infected

We pick an infectious person at random from the list of infectious individuals in the region, and search for a susceptible person within a radius of 15km to infect. If no susceptible individuals are found, we increase the radius and try again.

Travel

The daily number of travellers from one region to another has been estimated using statistics about travel [13]. This number is used to calculate the new infections that will occur as a result of infected individuals travelling within the country.

7. Vaccine availability

We assume that 346 boxes of vaccine arrive in Sweden every week. Each box contains eight cases, and each case contains 500 doses. Vaccination can be initiated three days after the boxes' arrival. One to two days are needed to administer 346x8x500 doses of vaccine. After 14 weeks we will have received 19 million doses, which is enough to vaccinate the entire population using two doses for each individual.

8. Total number of infected individuals

The table below presents the total number of infected individuals, averaged over all 180 day runs, for the six scenarios, with their standard deviations (Figure 3 in the article above).

SUB-OPTIMAL HAND SANITISER USAGE IN A HOSPITAL ENTRANCE DURING AN INFLUENZA PANDEMIC, NEW ZEALAND, AUGUST 2009

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The hand hygiene behaviours of the public in response to the current H1N1 influenza pandemic 2009 (or other pandemics) have not previously been described. An observational study was undertaken to examine hand hygiene behaviours by people passing a hand sanitiser station in the foyer of a public hospital in New Zealand in August 2009. Of the 2,941 subjects observed, 449 (18.0%, 95% confidence interval: 16.6, 19.6) used the hand sanitiser. This is a far from optimal result in response to the health promotion initiatives in the setting of a pandemic. These findings suggest the need for more effective health promotion of hand hygiene and also provide baseline measurements for future evaluation of hygiene practices.

New Zealand surveillance and research efforts have described various aspects of the influenza A(H1N1)v pandemic in 2009. This work has covered the descriptive epidemiology of the pandemic [1-3], key epidemiological parameters [4], and characteristics of the virus [5]. However, there has been no analysis to date on the behavioural responses of the public to the pandemic in this country – including in the area of hygiene behaviour. Here we describe an observational study to measure hand sanitiser use at the entrance to the Wellington Regional Hospital in New Zealand (the main hospital in the capital city) in August 2009.

Pandemic influenza intervention recommendations from the World Health Organization state that ‘handwashing (...) should be routine for all and strongly encouraged in public health messages; such practices should be facilitated by making hand-hygiene facilities available’ [6]. There is strong evidence to indicate that good hand hygiene is effective in reducing the spread of infection [7]. Alcohol-based sanitisers (e.g. Sterigel™) are as effective as hand washing (with soap and water) for not visibly soiled hands [8-10]. The convenience of alcohol-based sanitisers increases hand washing compliance and reduces healthcare-associated infection rates [6,7].

Methods

Starting in July 2009 and continuing to the present (mid-September 2009), Wellington Regional Hospital had a hand sanitiser station placed in the middle of the entrance foyer (approximately 8 m from the entrance). This station included two

Sterigel™ pump dispensers positioned at a height of 1 m, an A3 laminated sheet recommending respiratory hygiene and a large banner stating ‘please CLEANSE your hands when entering and leaving’. The Capital and Coast District Health Board (CCDHB) responsible for this hospital state that their goal in providing the sanitiser station was to create an environment where public and staff would cleanse their hands going into and out of the hospital.

In this study, people were observed entering and leaving the hospital foyer using the main entrance as the reference point. An initial data set was collected over four hours by two observers (one hour per day for four days), one noting the number of people who passed in and out of the hospital entrance and the other counting those who used the hand sanitiser. This allowed an estimation of the proportion of people who used the hand sanitiser.

A further phase of the study involved observation with the collection of additional demographic data (gender and estimated age-group), direction (entering or leaving), and an assessment on whether the person was a member of the public or hospital staff (identified as wearing a uniform or identity tag). We observed 30 min periods in the morning, midday and afternoon of a single day.

Data were analysed using Microsoft Office Excel 2003 and OpenEpi. Inter-observer variation was measured by two observers individually recording hand sanitiser use and demographics over an additional 30 min observation period. Cohen’s kappa scores were then calculated.

Results

Data from all observations showed the proportion of people using hand sanitiser in the foyer of Wellington Regional Hospital was 18.0% (95% confidence interval (CI): 16.6%-19.6%) (Table). Use of hand sanitiser on entering the hospital was significant higher than use when leaving (risk ratio (RR) = 4.8, 95% CI: 2.8 to 8.1). It was also significantly higher for adults than for children and teenagers (Table). However, no difference was identified with regards to gender or time of day.

Comparison of the individual data from the two observers showed variation only in the category of people entering or leaving the hospital. The kappa score for this activity was calculated as 0.84,

indicating high levels of chance-corrected agreement between the two observers.

Discussion

Key findings and interpretation

A level of hand sanitiser use of 18% in a hospital entrance and during an influenza pandemic is clearly far from optimal. Unfortunately there is no comparative data, as hand sanitisers are not routinely promoted to the public in New Zealand hospitals in non-pandemic situations. The fact that no signage for the hand sanitiser was visible to people exiting the hospital may explain the even lower usage rate (5%) for those exiting through this doorway. The reason for higher sanitiser use by adults compared to children and teenagers is not obvious but may reflect the fact that the dispenser is psychologically aimed at adults due to the signage and table height and that adults are more aware of the need for infection control.

Study validity and limitations

This observational study showed that it is feasible to systematically observe hand sanitiser use in a hospital setting (indeed, this is the first such study that we know of). The kappa score of 0.84 indicates it is unlikely there was substantive inter-observer variation.

Nevertheless, the single location and restricted time of data collection mean that the results may not be truly representative of hand-sanitising activity in the hospital, or may not hold external validity for other parts of New Zealand. Also, other opportunities to practice hand hygiene in the hospital setting (e.g. hand sanitisers on some of the wards) may have contributed to the lower proportion of people using the sanitiser in the entrance hall when leaving the hospital. Another issue was a possible Hawthorne effect, as we suspect that some people were aware of being observed and this may have increased sanitiser usage. Finally, it was not possible to reliably distinguish staff from members of the public through observation.

Policy implications

Changes to the design and location of the hand sanitiser station would probably increase compliance. Such measures could include: positioning the station closer to the door, targeting signage and visual promotional material to both inflowing and outflowing traffic, ensuring that prompts are multi-lingual and simple, life-size posters depicting 'model behaviour' (e.g. of a nurse using the sanitiser) and, to encourage even higher compliance, having an official hospital worker present overseeing sanitiser use.

Part of the New Zealand Ministry of Health's response to the pandemic was to increase public awareness in the area of good

TABLE

Hand sanitiser use in a hospital entrance by activity, gender, age-group and time of day, Wellington Regional Hospital foyer, August 2009

Characteristics	Used hand sanitiser		Passed hand sanitiser		Risk Ratio (95% confidence interval)
	Number	Number	Number	%	
All observations (5.75 hours)	449	2,492		18.0 (95% CI: 16.6-19.66)	
Observation period with additional data collection					
Direction of movement*					
Entering the hospital	90	407		20.1	4.8 (2.8-8.1)
Leaving the hospital	15	324		4.6	Reference (1.0)
Total	105	731		14.4	
Gender**					
Male	43	287		15.0	1.1 (0.7-1.5)
Female	55	386		14.2	Reference (1.0)
Age group**					
Child (<12)	0	14		0.0	
Teenager (12-18)	0	12		0.0	
(Child/Teenager Combined)	(0)	(26)		0.0	Undefined
Adult (>18)	98	647		15.1	Undefined (p=0.031)***
Time of day**					
Morning (08:20-08:50h)	23	179		12.8	1.0 (0.6-1.7)
Mid-day (12:50-13:20h)	46	263		17.5	1.4 (0.9-2.1)
Afternoon (15:55-16:25h)	29	231		12.6	Reference (1.0)
Total**	98	673		14.6	

CI: confidence interval

* Total of 1.75 hours of observation with data excluded from those 'milling around' (i.e. those who had no clear direction of movement) and using the hand sanitiser.

** Total of an additional 1.5 hours of observation with data included from those 'milling around' and using the hand sanitiser.

*** Result was statistically significant (p=0.031) using Fisher exact test, 2-tailed.

hand hygiene practices through a televised mass media campaign. As hand hygiene during a pandemic has not, to our knowledge, been measured before, we cannot draw conclusions on the effectiveness of such media campaigns. Our findings could, however, be used as baseline measurements to allow for future campaign evaluation.

Research implications

Further research, be it observational or interventional, could aim to capture staff versus public activity, eliminate possible Hawthorne effects and capture additional data on children and teenagers. The possible occurrence of 'clustering effects' could also be studied: The observers noticed that people were more likely to stop and sanitise if they saw another person using the hand sanitiser. For the design of more effective hygiene promotional material, an interventional study could be undertaken investigating the effect of depicting authority figures role-modelling appropriate hygiene behaviours in hospital settings.

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OSELTAMIVIR SUSCEPTIBILITY IN SOUTH-WESTERN FRANCE DURING THE 2007-8 AND 2008-9 INFLUENZA EPIDEMICS AND THE ONGOING INFLUENZA PANDEMIC 2009

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The recent emergence of seasonal influenza A(H1N1) strains resistant to oseltamivir makes it necessary to monitor carefully the susceptibility of human influenza viruses to neuraminidase inhibitors. We report the prevalence of the oseltamivir resistance among influenza A viruses circulating in south-western France over the past three years: seasonal influenza A(H1N1), seasonal influenza A(H3N2), and the influenza A(H1N1)v viruses associated with the ongoing 2009 pandemic. The main result of the study is the absence of oseltamivir resistance in the pandemic H1N1 influenza strains studied so far (n=129).

Introduction

Even if yearly vaccination remains the best way to prevent influenza, antiviral drugs have proven their efficacy in preventing and treating acute influenza. The adamantanes (amantadine and rimantadine) were the first available influenza antiviral medications. They are associated with severe adverse effects and high levels of resistance among influenza A viruses [1]. This resistance may occur in the absence of antiviral drug use and also emerge rapidly under treatment. Fortunately, neuraminidase inhibitors (NAIs) have been designed to expand the therapeutic possibilities. Presently two anti-influenza drugs are commercially available: oseltamivir and zanamivir [2], which selectively inhibit the neuraminidase of both influenza A and B viruses. Oseltamivir is preferred over zanamivir because it is administered by the oral route [2]. NAIs have been prescribed worldwide since 1999 [3]. In France, their use was limited before the influenza pandemic 2009.

Until recently, the level of resistance to NAIs among circulating influenza A viruses was low [3,4]. However, surveillance studies revealed the sudden emergence of seasonal A(H1N1) strains resistant to oseltamivir in 2007-2008 in Europe where NAIs are used sparsely [5]. From the last quarter of 2007 until June 2008, the highest rate of resistance was reported in Norway (67%). France had the second highest rate with 47% of seasonal A(H1N1) viruses resistant to oseltamivir [6].

Mutations implicated in NAIs resistance were found to be subtype-specific in the neuraminidase active site: The mutations R292K and E119V (in N2 numbering) predominate in the influenza A(H3N2) subtype. R292K induces a resistance to both NAI, whereas E119V leads to oseltamivir but not to zanamivir resistance. H274Y (in N2 numbering) predominates in the seasonal influenza A(H1N1) subtype and confers a high level of resistance to oseltamivir, but these strains remain sensitive to zanamivir [7].

During the season 2007-8, the predominant influenza subtype circulating in south-western France was A(H1N1), while influenza A(H3N2) viruses were the paramount subtype in the 2008-9 winter season. In April 2009, the new influenza A(H1N1)v virus emerged, which has the potential for rapid spread [8]. In the present study, influenza A viruses were collected during two consecutive seasons, 2007-8 and 2008-9, and during the current ongoing influenza pandemic (May to mid-September 2009) for surveillance of oseltamivir resistance using sequence analysis.

Methods

Respiratory samples of patients with influenza-like illness were obtained from Bordeaux Hospital and through a sentinel surveillance network of 21 general practitioners in south-western France. These clinical samples were nasal swabs, bronchoalveolar lavage fluids and nasopharyngeal secretions and were screened by real time RT-PCR in order to determine the virus strain. Primers and probes for the seasonal influenza strains were designed 'in house', those for influenza A(H1N1)v viruses were developed and provided by the two French National Reference Centres for influenza viruses (North and South). None of the patients from whom respiratory specimens were obtained had been treated with NAI before.

The influenza A virus isolates were screened for mutations known to confer resistance to oseltamivir by sequencing of the neuraminidase gene. A multiple sequence alignment was done of influenza A neuraminidase sequences available in Genbank, in order to choose specific RT-PCR primers that would recognise most of the influenza A(H1N1) and A(H3N2) seasonal strains and the pandemic influenza A(H1N1)v. Three primer pairs were designed, targeting the following regions: nucleotide positions 684 to 1,021 of the N1 gene for seasonal influenza A(H1N1) and 692 to 930 for pandemic influenza A(H1N1)v, and nucleotide positions 153 to 1,078 of the N2 gene for seasonal influenza A(H3N2). The target regions were amplified by RT-PCR and sequenced.

The epidemiological features of the ongoing influenza H1N1 pandemic in south-western France were studied following specific instructions from the French Ministry of Health. The target populations were: patients coming from endemic countries (mainly South America and the United States), patients with severe influenza infection, clustered cases of influenza in the community or at school and work place, or pregnant women, children under the age of five months and healthcare workers who had influenza-like symptoms.

Results

In this surveillance study we could amplify sequences for 21 seasonal influenza A(H1N1) viruses in the 2007-8 influenza season, for 97 seasonal influenza A strains (92 H3N2 and five H1N1) in 2008-9, and for 173 pandemic influenza A(H1N1)v viruses collected during the ongoing pandemic. The neuraminidase genes of all 21 seasonal influenza A(H1N1) viruses detected in south-western France during the 2007-8 influenza season were successfully sequenced, and 47.6% of them (10/21) contained a mutation associated with oseltamivir resistance. During the 2008-9 season, none of the 92 seasonal influenza A(H3N2) virus samples contained the E119V or the R292K mutation in the neuraminidase N2 sequence, but all five co-circulating seasonal influenza A(H1N1) viruses had the H274Y mutation in the neuraminidase N1 gene. Since the beginning of the pandemic in late April 2009, 173 confirmed cases of pandemic influenza A(H1N1)v have been found in south-western France. Only 129 of those isolates have been genotyped so far. According to their neuraminidase sequence, all

129 were found to be sensitive to oseltamivir (Table 1). Currently, influenza A(H1N1) 2009 incidence is increasing worldwide including in south-western France (Table 2). As already described, young adults (19-34 years) seem to be particularly sensitive to A(H1N1) 2009 infection (Figure).

Discussion

As we had no phenotypic data in this study, we could not observe potential new mutations leading to resistance. Therefore, this study is limited to previously described resistance mutations that can be shown by sequencing. We report the results of a surveillance study for NAIs susceptibility among influenza A viruses isolated in south-western France during the last two influenza seasons and the current 2009 pandemic. Results obtained in the 2007-8 and 2008-9 influenza seasons are in accordance with the World Health Organization's Global Influenza Surveillance Network data. The recent emergence of oseltamivir-resistant influenza A(H1N1) strains during 2007-8 season in western Europe may appear surprising in view of the small proportion of treated patients [9]. This could have dramatic consequences if resistance were to emerge also among avian influenza A(H5N1) viruses or pandemic influenza A(H1N1)v strains. To date, only 12 oseltamivir-resistant influenza A(H1N1)v viruses have been detected worldwide, namely in Canada, China, Denmark, Hong Kong, Japan, Singapore and the United States [10]. Oseltamivir has been recommended since the beginning of the influenza pandemic 2009 for treatment and prophylaxis. Monitoring the susceptibility of pandemic influenza viruses to oseltamivir is important to identify cases in which zanamivir should be used as an alternative drug.

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TABLE 1

Oseltamivir resistance in influenza A isolates collected since 2007 in south-western France (n=247)

	Number of samples genotyped	Number of oseltamivir-resistant samples
2007-2008	21 A(H1N1) seasonal	10
2008-2009	5 A(H1N1) seasonal	5
	92 A(H3N2) seasonal	0
1 May - 15 September 2009	129 A(H1N1) 2009 pandemic	0

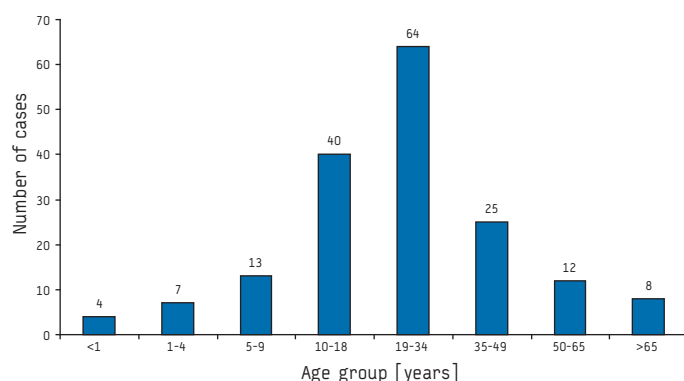
TABLE 2

Prevalence of pandemic influenza A(H1N1)v prevalence in south-western France, 1 May to 15 September 2009 (n=173)

	May	June	July	August	Sept.	Total
Number of samples tested	31	36	93	410	302	872
Number of influenza A(H1N1)v cases	3	9	8	113	40	173
Positive ratio (%)	9,7	25,0	8,6	27,6	13,2	19,8

FIGURE

Age distribution of cases of pandemic influenza A(H1N1)v, south-western France, 1 May - 15 September 2009 (n=173)



ENHANCED SURVEILLANCE OF INITIAL CASES OF PANDEMIC H1N1 2009 INFLUENZA IN IRELAND, APRIL - JULY 2009

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From 28 April to 18 July 2009 there were 156 cases of pandemic H1N1 2009 influenza confirmed in Ireland. During this time, Ireland was in containment phase, and detailed case-based epidemiological information was gathered on all cases presenting in the community and acute health care setting. Active case finding was performed among contacts of cases. Eighty percent of cases were in people under the age of 35 years, and 86% were imported. The most frequent symptoms were fever, sore throat, myalgia and dry cough. Nine people were hospitalised, no fatalities occurred.

Background

In late April 2009, a novel influenza virus led to human infection in Mexico. A public health emergency of international concern was declared by the World Health Organization (WHO) on 25 April 2009 [1]. Over the following weeks the virus spread rapidly to all regions of the world. Consequently WHO declared a phase 6 pandemic on 11 June 2009 due to evidence of community-level transmission in multiple countries globally [2].

In Ireland the National Pandemic Plan was implemented from 25 April; existing surveillance systems were augmented and pandemic H1N1 2009 influenza and enhanced surveillance commenced. On 28 April 2009, the first case of pandemic H1N1 2009 influenza was confirmed in Ireland.

Prior to April 2009, a number of surveillance systems were in place in Ireland to monitor influenza and clusters of influenza-like illness (ILI). These systems included year round surveillance by sentinel general practitioners (GPs), virological surveillance (sentinel and non-sentinel), hospital sentinel surveillance and statutory reporting of outbreaks of ILI and influenza under the Infectious Diseases Regulations [3].

Baseline seasonal ILI rate thresholds were set for the Irish population in 2008 based on surveillance of ILI between 2001 and 2008 [4]. New systems implemented in April 2009 included:

- enhanced case-based reporting of all cases of pandemic H1N1 2009 influenza using the national electronic reporting system, (Computerised Infectious Diseases Reporting system, CIDR);
- increased virological surveillance by the GP sentinel influenza surveillance scheme (number of samples to be taken by GPs increased from two to five per week);
- recruitment of additional sentinel GPs;

- expanded hospital sentinel surveillance;
- augmented mortality surveillance to identify excess all-cause deaths, excess pneumonia and influenza deaths; and
- surveillance of influenza-related calls to out-of-hours GP services.

We report on the enhanced case based surveillance of the first 156 confirmed cases of pandemic H1N1 2009 influenza up to 18 July 2009, when the strategy changed from containment to mitigation, and detailed case based surveillance of all cases ceased.

Methods

GPs and hospital clinicians reported all suspect cases of pandemic H1N1 2009 influenza to local departments of public health who in turn contacted and interviewed them. Public health staff completed case-based enhanced surveillance forms with information from these interviews. In order to facilitate active case finding for enhanced surveillance, the European Union case definition of 30 April 2009 was adopted [5]. As evidence emerged internationally in individual countries that they were experiencing community transmission (either by reporting of large numbers of cases, or by the country itself stating that community transmission was occurring), they were added to the list of countries where a travel history would be relevant for the clinical assessment. Staff from departments of public health contacted all persons who fit the criteria of the EU case definition for a case under investigation. They had a swab (nose and throat) that was submitted to the National Virus Reference Laboratory (NVRL) for testing. Samples from all cases under investigation for pandemic H1N1 2009 virus tested at the NVRL were confirmed with reverse-transcript PCR (RT-PCR).

Contact tracing of cases was undertaken and some additional cases were identified through this mechanism. Health authorities collated information on any clusters/outbreaks identified including the number of people involved and the type of outbreak. An outbreak of ILI was defined as three or more cases of ILI arising within a 72 hour period which met the case definition above and where an epidemiological link was established.

Enhanced surveillance data and laboratory results were entered into the CIDR to allow real-time exchange of information between the NVRL, regional departments of public health and the Health Protection Surveillance Centre (HPSC).

HPSC analysed the enhanced surveillance data to describe pandemic H1N1 2009 influenza in terms of age, sex, pre-existing

medical conditions of infected cases, presenting features and complications associated with the infection, as well as source, timing and clusters/outbreaks of disease.

Results

During the period 28 April to 18 July 2009, 156 confirmed cases of pandemic H1N1 2009 influenza were reported; 80 female (50.9%) and 76 male (49.1%). The median age of cases was 25.0 years (range: 0-73 years). Eighty percent of cases were in people under 35 years of age. Table 1 shows the number of confirmed cases by sex, five-year age group and age-specific incidence rate per 100,000 population.

After the first case of pandemic H1N1 2009 influenza on 28 April 2009, sporadic cases occurred until the middle of June, after which case numbers began to increase, with more than six new cases per day by early July (Figure). One hundred and thirty four (86%) cases were imported, 14 (9%) were infected in Ireland by an imported case and two (1%) were infected in Ireland without any identifiable travel association, information was missing for six (4%) cases.

Complete information on clinical symptoms was available for 106 (68%) cases (Table 2). For these, fever or history of fever ($\geq 38^\circ$) was reported in 95%. Sore throat, dry cough, myalgia and headache were frequently reported symptoms. Most cases reported mild to moderate illness similar to seasonal influenza. Sixteen percent reported diarrhoea. Six cases (4%) were reported as having developed pneumonia due to pandemic H1N1 2009 influenza, all of whom recovered.

Nine people were hospitalised with pandemic H1N1 2009 influenza (hospitalisation rate 5%). Of these cases, four were children under 5 years of age, four were in the age group between five and 64 years and one aged 65 years. Data on pre-existing medical conditions and pregnancy was collected on all hospitalised

cases. Two of the five adults had pre-existing medical conditions such as chronic respiratory disease, chronic heart disease, immunosuppression and diabetes mellitus. There were no pre-existing medical conditions reported in the paediatric cases. All hospitalised cases recovered, no fatalities occurred.

Twelve outbreaks of pandemic H1N1 2009 influenza were identified, involving a total of 38 people. One outbreak was in travelling companions while other outbreaks occurred within families and extended families. The number of people affected per outbreak ranged from two to six. All contacts of cases were offered chemoprophylaxis.

For three outbreaks information was available on attack rates which were 20%, 33% and 74% respectively. Surveillance of influenza-like illness (ILI) and respiratory illness in general showed little change from the baseline threshold for winter seasonal influenza activity.

GP sentinel surveillance over the eleven week period studied showed a small increase in ILI consultation rates, with a rate of 13.1 per 100,000 population being reported in the week ending 13 July, which was an increase in comparison to the rate of 8.8 per 100,000 population reported during the week ending 6 July. Six (4%) of cases of pandemic H1N1 2009 influenza were identified through this sentinel system. Sentinel hospital influenza surveillance found no increases in respiratory admissions up to 18 July. Analysis of all cause, and influenza- and pneumonia- related deaths showed no excess mortality compared with the same period in previous years and no outbreaks of non-pandemic influenza were notified up to 18 July.

Discussion

The epidemiology of the initial cases of pandemic H1N1 2009 influenza in Ireland was similar to that seen in other countries [6-13]. The majority of cases were children and adults under 35 years. Similar numbers of males and females were affected.

TABLE 1

Pandemic H1N1 2009 influenza cases by sex, age and age-specific incidence rates per 100,000 population, Ireland, 28 April - 18 July 2009 (n=156)

Age group [years]	Male cases (age-specific incidence rate)	Female cases (age-specific incidence rate)	Total cases (age-specific incidence rate)
0-4	11 (7.1)	6 (4.1)	17 (5.6)
5-9	3 (2)	3 (2.1)	6 (2.1)
10-14	2 (1.4)	3 (2.2)	5 (1.8)
15-19	9 (6.1)	11 (7.7)	20 (6.9)
20-24	15 (8.7)	14 (8.2)	29 (8.5)
25-29	7 (3.7)	16 (8.7)	23 (6.2)
30-34	5 (2.3)	5 (2.9)	10 (2.9)
35-39	6 (3.7)	5 (3.2)	11 (3.4)
40-44	6 (4)	3 (2)	9 (3)
45-49	2 (1.4)	3 (2.2)	5 (1.8)
50-54	2 (1.6)	4 (3.3)	6 (2.4)
55-59	5 (4.4)	2 (1.8)	7 (3.1)
60-64	1 (1.1)	2 (2.2)	3 (1.7)
65+	2 (1)	3 (1.2)	5 (1.1)
Total	76 (3.6)	80 (3.8)	156 (3.7)

The majority of infected experienced a mild self-limiting illness with fever, cough, sore throat and myalgia being the predominant symptoms. As with seasonal influenza, some people experienced more severe disease requiring hospitalisation. However, in contrast to seasonal influenza there was an under-representation of infection in older people.

The surveillance activities undertaken in the initial weeks of the pandemic had several strengths and weaknesses that should be borne in mind. The case definition adopted for pandemic H1N1 2009 influenza in the first few months of the pandemic was very specific with strict clinical and epidemiological criteria, particularly the epidemiological requirement to have travelled to an affected area, to have had contact with a confirmed case or to work in a laboratory testing cases. This was important when the numbers

of cases were very small and anxiety in relation to the disease was very high, but it resulted in the vast majority of presentations for suspected pandemic H1N1 2009 influenza being due to other viruses or no virus being detected. The use of a highly specific case definition ensured that public health and laboratory resources and public health control activities were targeted at people likely to have the disease and that those unlikely to have the disease were not treated and isolated, or their contacts quarantined unnecessarily. However, the disadvantage of this specific case definition was that a number of people with the disease may have been missed. For example, several samples that tested positive for pandemic H1N1 2009 influenza virus in Greece, where clinicians were allowed more discretion in testing people for influenza, were from people who did not fit the EU case definition [12]. However, because of the statutory system under which all outbreaks of disease, including ILI, are notifiable [3,14] it is unlikely that clusters of indigenous pandemic H1N1 2009 influenza were missed in Ireland.

A challenge with the epidemiological criteria of the case definition was the speed at which countries were becoming affected. In the first few weeks of the pandemic, spread of disease to different countries was rapid and revision of the case definition to include countries where community transmission was occurring proved difficult. This in turn resulted in a lag time between an area being classified as an affected area and people with travel to that area being investigated which may have led to under-identification of cases. A challenge with the clinical criteria of the case definition was that fever was required and subsequent reports from other countries presently indicate that fever is present in a smaller proportion of cases than previously believed and this could further have reduced case identification [11,12].

Our hospitalisation rate of 5% must be interpreted with caution for two reasons. Firstly, in the early phase of the pandemic, in

FIGURE

Confirmed cases of pandemic H1N1 2009 influenza by source of infection and week of laboratory confirmation, Ireland, 28 April - 18 July 2009 (n=156)

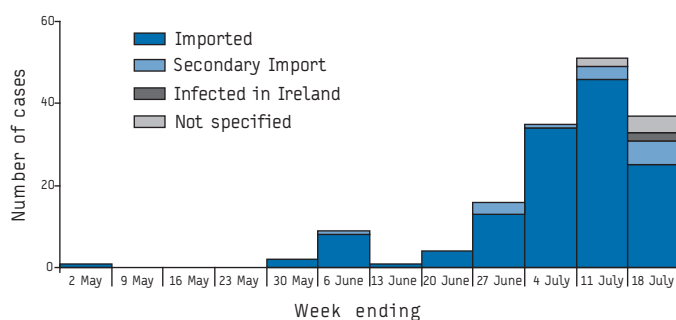


TABLE 2

Clinical symptoms in confirmed cases of pandemic H1N1 2009 influenza for whom information is available, Ireland, 28 April - 18 July 2009 (n=106)

Symptoms	Number of cases	%
Fever or history of fever	101	95
Sore Throat	64	60
Dry cough	58	55
Myalgia	56	53
Headache	48	45
Rhinorrhoea	36	34
Sneezing	20	19
Diarrhoea	17	16
Arthralgia	16	15
Nausea	15	14
Dyspnoea	14	13
Productive cough	14	13
Vomiting	14	13
Pneumonia	5	5
Altered consciousness	3	3
Conjunctivitis	3	3
Nose bleed	1	1
Seizures	0	0

Ireland, as in other countries [12,15,16], there may initially have been a low threshold for admitting patients with pandemic H1N1 2009 influenza. Reasons for this included concerns as to how the clinical course of patients with a novel disease would progress and for the administration of antivirals to young children, however no patient was admitted purely for infection control. As the pandemic has progressed in other countries there has been a move to hospitalising patients with severe disease only and this has led to much lower hospitalisation rates in those countries [17-19]. Even though there was active follow-up of known cases and their contacts, it is likely that some people with pandemic H1N1 2009 influenza only experienced mild symptoms and thus did not seek medical care which lead to an under-representation of mild cases and hence an over-estimation of hospitalisation rates.

The CIDR surveillance system is the principal infectious disease surveillance system in Ireland and combines clinical and laboratory surveillance data [20]. It was developed to provide high quality timely data and to be flexible to deal with new information and diseases. Once the public health emergency of international concern was declared the system was quickly adapted to include case based and cluster reporting of pandemic H1N1 2009 influenza which was implemented nationally. This was possible because the CIDR system was already functioning well for surveillance of other notifiable diseases. All regions in the country but one had implemented CIDR and surveillance experts in these regions were competent in its use. The CIDR allowed for real-time collection and sharing of data between laboratories, departments of public health and HPSC and enabled real-time analysis of the spread of pandemic H1N1 2009 influenza in the community.

Regional departments of public health undertook contact tracing and collected enhanced surveillance information on all cases under investigation, tasks for which their staff were well experienced as these are often part of processes required to control infectious diseases in the community. This meant that the public health system could respond very quickly to this outbreak. However, the public health workforce is small in Ireland and capacity was stretched to its maximum in responding to the containment phase of the pandemic H1N1 2009 influenza. Ireland moved from containment to mitigation phase on 16 July following advice from the WHO [21]. Once the mitigation phase started, this relieved public health authorities from the burden of intensive contact tracing, and allowed them to focus efforts on case-based surveillance of more severe i.e hospitalised cases and investigation of clusters of disease. At this time there was also a continued focus on increasing public awareness of pandemic H1N1 2009 influenza and encouraging activities to prevent spread of influenza.

While it is impossible to predict how pandemic H1N1 2009 influenza will progress in Ireland, based on other countries' experience and the continuing rise in case numbers in Ireland, it is possible that we will experience a large increase, corresponding to the first wave of a pandemic, in the autumn.

Experience to date internationally has shown that prolonged stays in intensive care units (ICU), for the small proportion of persons needing specialised treatment, have been the main cause of pressure on health services. Currently, enhanced surveillance is being carried out on all hospitalised cases and an ICU enhanced surveillance system is being developed, to monitor those most at risk of developing severe disease. High quality data on hospitalised cases and cases requiring ICU admission is essential to guide

health service planning and response to pandemic H1N1 2009 influenza.

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RESIDUAL IMMUNITY IN OLDER PEOPLE AGAINST THE INFLUENZA A(H1N1) – RECENT EXPERIENCE IN NORTHERN SPAIN

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The 2009 pandemic influenza A(H1N1) virus has a higher incidence in children and young adults, a pattern that has also been reported in seasonal influenza caused by the influenza A(H1N1) virus. We analysed age at infection in symptomatic patients with influenza in the Basque Country (northern Spain), reported through the sentinel influenza surveillance system which monitors 2.2-2.5% of the population. Between September 1999 and August 2009, influenza A(H3N2) or seasonal influenza A(H1N1) was detected in 941 patients, and from April to August 2009, pandemic influenza A(H1N1) was detected in 112 patients. The H3/H1 seasonal influenza ratio was between 3.3 and 3.4 in the under 60 year-olds, but 9.8 in older individuals, suggesting that people born before 1950 have residual immunity against the influenza A H1N1 subtype (both seasonal and pandemic).

Introduction

In 1957, the *Asian influenza* pandemic was caused by influenza A(H2N2) virus, which circulated until 1968 when it was displaced by the influenza A(H3N2) virus which was responsible for the *Hong Kong* pandemic. Before 1957, direct descendants of the influenza A(H1N1) virus that had caused the 1918 pandemic (*Spanish flu*) had circulated. In 1977, an influenza A(H1N1) strain re-emerged, which, together with the dominant influenza A(H3N2) strain, has been the cause of seasonal human influenza for more than three decades [1]. Despite the prolonged co-circulation of both subtypes, few studies have analysed their ability to affect distinct age groups.

The current pandemic influenza A(H1N1) virus, influenza A(H1N1)v, which emerged in the spring of 2009, has spread throughout the world. The aim of this study was to compare the distribution in distinct age groups of infections caused by the two subtypes of seasonal influenza in the past 10 seasons and relate this to recent infections due to influenza A(H1N1)v.

Methods

The virological study was performed in the Microbiology Department of Hospital Donostia, which is the Reference Laboratory for influenza infections in the Basque Country and part of the Spanish influenza surveillance system. The sentinel physicians in

this system attend to 2.2%-2.5% of the 2.1 million inhabitants of the region. The age and sex of subjects to be monitored represent the normal distribution of people in our region.

Samples (pharyngeal swabs with viral transport medium) were obtained from patients with symptoms of influenza according to the International Classification of Primary Care (ICPC) definition (code 487). This definition includes four (in epidemic seasons) or six (in non-epidemic seasons) of the following criteria: sudden symptom onset, fever of >38 °C, cough, chills, general malaise, muscle and joint ache, upper respiratory tract involvement, or contact with an infected person. We included patients between week 40 of one year and week 20 of the following year in the seasons from 1999 to 2008. The 2008-9 season was extended until 31 August 2009 due to the pandemic.

In the study period, influenza vaccination was recommended for individuals older than 65 years (ca. 65% coverage was reached during the study period) and individuals with risk factors. Seasonal influenza viruses were identified through virus culture and/or detection of two or more viral genes in a reverse transcriptase-polymerase chain reaction (RT-PCR) assay directed at the matrix and nucleoprotein genes [2], and positive samples were further subtyped by PCR as H1 or H3 [3]. RT-PCR assays were also done for the nucleoprotein [4], haemagglutinin and M2 matrix protein (Influenza A/H1N1 Detection Set®, Roche) of the pandemic influenza A(H1N1)v strain.

Results

A total of 1,106 laboratory-confirmed influenza A virus infections were detected in the 2,801 symptomatic patients who had consulted a physician of the surveillance network. Of these 1,106 infections, 994 were caused by seasonal influenza A viruses (733 H3, 208 H1 and 53 not subtyped) and 112 by the pandemic influenza A(H1N1)v virus. The distribution of the two seasonal influenza subtypes (H1 and H3) according to age is shown in Table 1.

The ratio between the subtypes H3 and H1 (total numbers) was 3.5. In people under and over the age of 60 years, it was 3.4 and 9.8, respectively (chi-squared test=4.29, p=0.038).

The results according to year of birth are shown in Table 2.

The first case of pandemic influenza A(H1N1)v infection was detected in the Basque Country on 26 April 2009. Of 263 patients suspected to have pandemic influenza who were studied by the influenza surveillance system between that date and 31 August 2009, 112 were laboratory-confirmed as influenza A(H1N1)v cases. These 112 infections affected mainly children and young adults (see Table 1), similar to a further 219 influenza A(H1N1)v infections that were not detected as part of the influenza surveillance system and are not included in this study.

Among the seasonal influenza patients, there were 55 vaccination failures, 47 cases of A(H3N2) and eight cases of A(H1N1) infection. The ratio was 4.5 (27 H3N2 and six H1N1) and 10 (20 H3N2 and two H1N1) in people under and over the age of 60 years, respectively (Fisher 0.45, non significant).

Discussion

Only two (1.8%) of the 112 patients with 2009 pandemic H1N1 influenza who were included in this study were older than 59 years. This percentage was 4.1% (9/219) among patients with

a 2009 pandemic H1N1 influenza infection not detected through the sentinel surveillance system. The low proportion of people born before 1950 who are infected with this virus has also been observed in other parts of the world [5,6].

Among the symptomatic cases of seasonal influenza who consulted a physician and were detected by the sentinel surveillance system in the Basque Country in the past 10 seasons, symptomatic infections caused by the H3 subtype were 3.5 times more frequent than those caused by the H1 subtype. This H3/H1 ratio was seen in all age groups until the age of 59 years, but in older individuals the ratio tripled (from 3.4 to 9.8), with 91% of the over 60 year-old patients infected with H3 strains.

That the two subtypes are not equally distributed in different age groups was initially reported in the 1980s [7,8] and more recently in a study from the United States and Oceania based on strains sequenced in the past 15 years (1995-2008) [9]. Unlike earlier studies reporting that the H1 subtype rarely affected people older than 30 years [7,8], the present study found that approximately one third of the patients with influenza A(H1N1), both pandemic and seasonal, were between 30 and 59 years-old, suggesting that young adults today do not have the residual immunity of persons

TABLE 1

Seasonal influenza A subtypes detected in the seasons from 1999 to 2009 (n=941*) and pandemic influenza A(H1N1) virus detected from 26 April to 31 August 2009 (n=112) in the Basque Country Influenza Surveillance System, by age group

Age group (years)	Seasonal influenza A			Pandemic influenza
	A(H3N2)	A (H1N1)	Ratio H3/H1	A(H1N1)v
0 a 4	110	31	3.5	4
5 a 9	105	33	3.2	7
10 a 14	92	26	3.5	31
0 to 14	307	90	3.4	42
15 a 19	52	15	3.5	15
20 a 24	48	15	3.2	16
25 a 29	60	16	3.8	14
15 to 29	160	46	3.5	45
30 a 34	40	9	4.4	3
35 a 39	46	17	2.7	5
40 a 44	48	15	3.2	3
30 to 44	134	41	3.3	11
45 a 49	38	11	3.5	7
50 a 54	27	10	2.7	4
55 a 59	28	6	4.7	1
45 to 59	93	27	3.4	12
60 a 64	11	0	-	1
65 a 69	8	1	8	0
70 a 74	8	1	8	0
60 to 74	27	2	13.5	1
>74	12	2	6.0	1
Total	733	208	3.5	112
Mean age	25.2	23.6		23.2

* 53 isolates were not subtyped and are not included.

of the same age in previous decades. Since this study included 10 influenza seasons, data by birth year gave a clearer indication of residual immunity than age in years.

Vaccination failures due to the influenza H3 subtype were six times more frequent than those due to H1, suggesting greater genetic variability of the H3 subtype. The antigenic drift proceeds at a slower pace in the H1 haemagglutinin gene than in the H3 gene [10]. This greater variability of the influenza A(H3N2) virus could also explain the greater frequency and severity of infections caused by this subtype [7].

Residual immunity against seasonal and pandemic influenza A(H1N1) virus in people born before 1950 is probably due to the lower capacity for drift of the H1N1 subtype, combined with the wide circulation of this virus between 1918 and 1957.

TABLE 2

Seasonal influenza A subtypes detected in the seasons from 1999 to 2009 (n=941) in the Basque Country Influenza Surveillance System, by year of birth

Year of birth	Seasonal influenza A		
	H3	H1	Ratio H3/H1
2005-2009	32	11	2.9
2000-2004	94	30	3.1
1995-1999	104	22	4.7
1995-2009	230	63	3.7
1990-1994	80	23	3.5
1985-1989	57	22	2.6
1980-1984	54	16	3.4
1980-1994	191	61	3.1
1975-1979	43	13	3.3
1970-1974	53	11	4.8
1965-1969	44	18	2.4
1965-1979	140	42	3.3
1960-1964	47	18	2.6
1955-1959	39	7	5.6
1950-1954	26	9	2.9
1950-1964	112	34	3.3
1945-1949	23	4	5.8
1940-1944	8	0	-
1935-1939	11	2	5.5
1935-1949	42	6	7.0
1930-1934	6	0	-
1925-1929	7	0	-
1920-1924	0	1	0.0
1920-1934	13	1	13.0
1900-1919	5	1	5.0
Total	733	208	3.5
Mean age	25.2	23.6	

Chi-squared test=4.55 in persons born before and after 1950; p=0.033; odds ratio 2.23 (95% confidence interval: 1.04 to 5.49).

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EARLY ESTIMATES OF 2009 PANDEMIC INFLUENZA A(H1N1) VIRUS ACTIVITY IN GENERAL PRACTICE IN FRANCE: INCIDENCE OF INFLUENZA-LIKE ILLNESS AND AGE DISTRIBUTION OF REPORTED CASES

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In the end of August 2009, an unusually elevated level of influenza-like illness (ILI) activity was reported to the French Sentinel Network. We quantified the observed excess in ILI cases in France during summer 2009 and characterised age patterns in reported cases. An excess of cases has been observed since 5 July, with a time increasing trend. The cumulated estimated excess number of ILI cases was 269,935 [179,585; 316,512], corresponding to 0.5% French population over the period. Compared to the same period in the past years, relative cumulated incidence was greater among young subjects and lower among subjects over 65 years-old. Compared to past epidemics, the relative cumulated incidence was greater in children less than five years-old. This excess of cases may reflect the current spread of the A(H1N1) virus in France, subject to the following limitations: estimates were based on clinical cases consulting a GP; large media coverage may have led to a non specific increase in consultation rates.

Background

Cases of infection with the 2009 pandemic influenza A(H1N1) virus have been reported in France since May 2009, with first evidence of local secondary transmission in July 2009.

By the end of August, an unusually elevated level of influenza-like illness (ILI) had been reported to the French Sentinel Network (FSN), an epidemiological surveillance system based on general practitioners (GPs) and operating since 1984 in France.

The objective of the present study was to quantify the excess in ILI cases in France during the 2009 summer and to examine age patterns in the reported cases using, for comparison, data reported to a long-running routine surveillance system.

Method

Sentinel network and estimation of ILI incidence

Sentinel GPs report ILI cases to the FSN in real time. The ILI case definition is sudden onset of fever (39°C or above) with myalgia and respiratory signs [1]. Weekly ILI incidence is estimated

using the average number of ILI cases reported by GPs, and then extrapolated to national ILI incidence using the ratio of all French GPs to participating sentinel GPs [2]. Characteristics of the GPs in the Sentinel Network are similar to those of all French GPs as regards the regional distribution, the proportion of GPs in rural practice and the type of practice [3].

Expected and excess ILI cases

Starting on 1 June 2009, the expected ILI incidence was calculated for each week as the average of weekly ILI incidences reported in the preceding, current and following weeks in the period 1985 to 2008 [4]. A 90% confidence interval was derived from the 5th and 95th percentiles of these values (Q_5 and Q_{95} , respectively) for each week.

For a given week, an excess in ILI incidence was defined when the observed incidence was above Q_{95} . The number of excess cases was calculated as the difference between the observed and expected incidences. The inferior bound (respectively superior bound) of this excess was calculated as the difference between the observed incidence and Q_5 (respectively Q_5).

Relative cumulated incidence according to age

Incidence according to age was determined by apportioning extrapolated cases according to the age distribution in reported cases, using the following age groups: <5 years, 5-17, 18-49, 50-64 and ≥ 65 years. However, it is difficult to compare directly these incidences with past epidemics as the A(H1N1) pandemic is still in its early phase. Therefore, we extracted the age pattern of reported cases by computing relative incidence rates as the ratio of incidence in an age group to incidence in the whole population. Relative incidences larger than 1 indicate that the corresponding age class experienced larger incidence than the population as a whole.

The relative cumulated incidence rates according to age of ILI cases were calculated for: a) the current period, b) the

same weeks in the past years and c) the past seasonal epidemic periods, as determined by the FSN and d) the 1986-7 and 1988-9 seasonal epidemics during which influenza A(H1N1) virus was the predominant circulating influenza virus [5].

Results

As shown in Figure 1, the current estimated ILI incidence has been in excess of expected incidences of ILI cases in France since week 28 of 2009 (6 to 12 July), with an increasing time trend.

Weekly estimated excess of ILI cases (90% CI bounds are presented in brackets) increased from 6,805 [654; 10,076] cases

in week 29, to 92,505 [72,563; 101,456] cases in week 37, the time of writing this article (Table). Overall, the cumulated excess number of ILI cases between week 28 and week 37 of 2009 was 269,935 [179,585; 316,512] (323,420 reported ILI cases minus the expected 53,485 over the period).

The median age of ILI reported cases was 26 years (range: 1-103 years), and 48% were male. Compared to weeks 28 to 37 of past years since 1985, age group-relative incidence rates of ILI between weeks 28 and 37 of 2009 were greater among subjects less than 18 years-old and smaller in those older than 65 years (Figure 2A).

Compared to past epidemic periods and A(H1N1) epidemics, age group-relative incidence rates of ILI between weeks 28 and 37 of 2009 was higher among subjects less than 5 years of age and lower among subjects aged 5 to 17 years (Figure 2B).

Discussion

An excess of 270,000 ILI cases has been reported to the French Sentinel Network since 1 July 2009, with a specific age pattern, compared to cases usually reported at this time of year. Compared to the past seasonal epidemics, (including those with predominant A(H1N1) circulating), the excess in ILI cases was largest among children less than 5 years-old.

In the past 24 years of surveillance, upper respiratory tract infections have been uncommon in summer, making the last weeks exceptional. Besides the pandemic influenza A(H1N1) virus, no unusual circulation of an infectious agent, nor seasonal influenza viruses have been reported in France since 1 June 2009 [6]. The recent excess of ILI cases must therefore reflect the developing pandemic in France.

Some pitfalls arise in the interpretation of this increasing incidence. First, cases reported by GPs are based on a clinical definition without virological confirmation. This case definition had positive predictive value for approximately 40% influenza virus infections in the past seasonal epidemics [1]. It has been in use

FIGURE 1
Estimated and expected incidence rates and their confidence interval, pandemic influenza A(H1N1) 2009, France

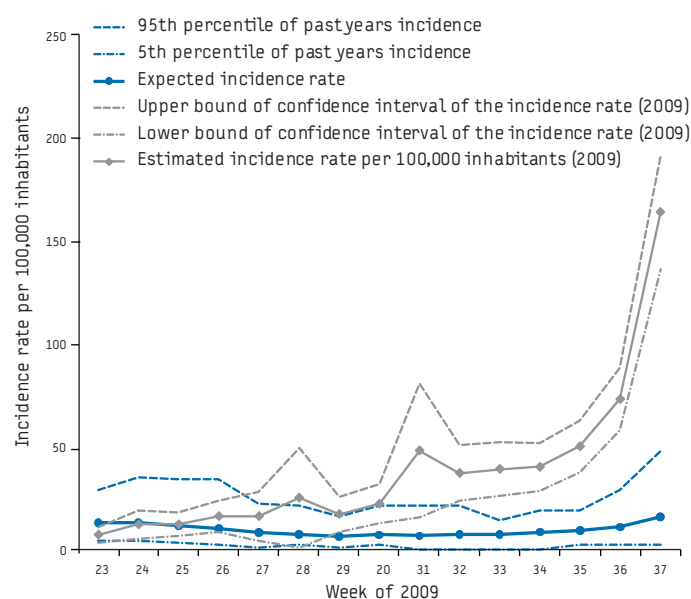


TABLE
Estimated and expected number of cases of influenza-like illness and calculated excess of cases in France between week 28 (6 to 12 July) and 37 (7 to 13 September) of 2009

Week number	Observed incidence	Expected incidence			Excess of cases		
		Expected	5 th percentile	95 th percentile	Average	Inferior bound	Superior bound
28	15,516	4,545	1,256	13,190	10,971	2,326	14,260
29	10,704	3,899	628	10,050	6,805	654	10,076
30	13,868	4,388	1,256	13,190	9,480	678	12,612
31	30,255	4,083	0	13,190	26,172	17,065	30,255
32	23,151	4,493	0	13,190	18,658	9,961	23,151
33	24,435	4,528	0	8,793	19,907	15,642	24,435
34	24,985	5,217	0	11,934	19,768	13,051	24,985
35	31,660	5,749	1,256	11,934	25,911	19,726	30,404
36	46,134	6,778	1,256	18,215	39,356	27,919	44,878
37	102,712	9,805	1,256	30,149	92,907	72,563	101,456
Total	323,420	53,485	6,908	143,835	269,935	179,585	316,512

for 25 years in the FSN, making it likely that it is currently well applied by GPs. To further improve specificity, we retained only cases in excess of the expected incidence at this time of year in the calculations. Second, the heavy media coverage of the pandemic may have increased the propensity to visit a GP in case of symptoms, leading to an upward bias in the number of excess ILI cases. The change in age pattern of patients consulting their GPs argues against a mere change in consultation frequency; however an age-specific change in propensity to consult may also lead to

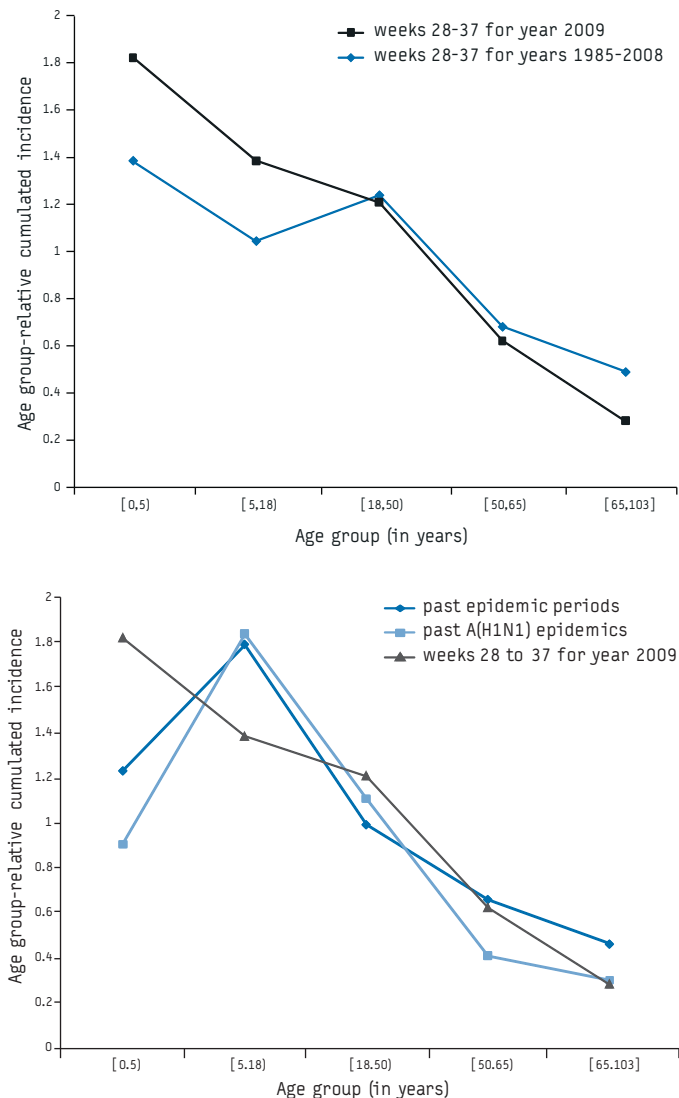
this change. Last, cases of 2009 pandemic influenza A(H1N1) virus infection with mild disease and/or not seeking care are not taken into account in the estimates. We did not change the case definition to include milder cases so that direct comparison with the past years was possible.

As reported in other countries, a relatively higher incidence of 2009 pandemic influenza A(H1N1) virus infection is observed in the young. In most reports, the increased incidence among young subjects could be ascribed to case finding and ascertainment, with more young people being tested, for example as part of outbreaks of influenza in schools [7-9]. Cases seen by the sentinel network GPs may provide a better picture of what is happening in the population at large. Using the same definition as before makes it possible to compare the current situation with the past.

The data confirmed and quantified an epidemic of ILI that started during the recent summer months in France, and had never been observed in the previous 25 years, with an age-specific incidence different from previous epidemic periods. These preliminary data highlight the heavy burden of this ILI epidemic on small children, relatively to older persons [10].

FIGURE 2

Age group-relative cumulated incidence rates* of influenza-like illness cases reported by the French Sentinel Network general practitioners between weeks 28 and 37 of 2009, compared to weeks 28 and 37 of past years since 1985 (2A)* and to past seasonal epidemic periods and past A(H1N1) epidemics (1986-7, 1988-9) (2B)



*Ratio of incidence in an age group to incidence in the whole population: relative incidence >1 indicates that the corresponding age class experienced larger incidence than the population as a whole.

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* Authors correction

The legend of Figure 2A was corrected after the publication of the article, on 6 October 2009.

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DOES VIRAL INTERFERENCE AFFECT SPREAD OF INFLUENZA?

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This short communication hypothesises that rhinovirus epidemics occurring after start of school may interfere with the spread of influenza during the period when warm and humid climate decreases the influenza spread by aerosol. Limited laboratory data supporting this hypothesis are included in the article, but the report is written mainly to stimulate interest and research concerning the possibility that viral interaction may affect influenza epidemiology.

Modelling and prediction of the spread of influenza are important for rational decisions on how to handle epidemics and pandemics. Apart from immunity in the population, both climate and social behaviour seem to be important factors affecting the spread. Holiday time usually interrupts the spread [1]. In dry and cold weather the aerosol transmission of influenza is more efficient since the virus becomes stabilised by hardening of the lipid membrane, remains airborne for longer time and is spread to longer distances [2-3]. In warm and moist weather, droplet and possibly contact spread and inoculation by contaminated hands seem to become more important [4].

However, these factors do not explain all characteristics of the spread of the pandemic influenza A(H1N1) virus during 2009. In Sweden, and some other European countries, the spread increased after the end of the holidays, but after four weeks of increasing activity the spread suddenly declined, despite similar weather conditions and social behaviour (Figure 1) [5]. Limitation by herd immunity induced by the spread that actually took place is possible, but not very likely, as the reported number of infections and of influenza-like disease in total was rather low. Also, the experience from the United States and the United Kingdom, with considerable, though patchy, spread of the virus during late spring and summer, despite a climate unfavourable to influenza, makes it likely that the virus would have managed to reach a substantial peak in Sweden in early October, unless other factors than the weather affected the spread.

All cases of influenza were made reportable in Sweden on 13 May 2009. Samples were taken from all suspected cases until 16 July, when the strategy was changed from containment to mitigation. Figure 1 shows the number of laboratory-confirmed cases reported in Sweden according to the law. Influenza diagnoses

reported from all Swedish laboratories during the past three seasons are included for comparison.

Since the number of samples sent for influenza analysis was increasing until week 36 [5] while the proportion of samples positive for pandemic H1N1 influenza was already decreasing (Table 1), we hypothesised that some other virus infection may have interfered with the spread of the influenza pandemic.

Laboratories in Sweden conducting extended viral diagnosis on samples sent for influenza examination were asked what viruses they found in the influenza-negative samples, and the answer was unanimous: rhinoviruses dominated, with sporadic findings of other respiratory viruses, such as enteroviruses and adenoviruses. We retrieved all data from one of the dominant laboratories, the microbiological laboratory at Karolinska University Hospital. All respiratory samples received are analysed by PCR for influenzavirus A and B, including pandemic influenza A(H1N1) virus, as well as for respiratory syncytial virus (RSV). Tests for a further thirteen viral pathogens are done if extended diagnoses is requested by the doctor submitting the sample [6]. The number of samples analysed between weeks 32 and 39 2009 at Karolinska University Hospital, as well as the results of the analyses, are shown in Tables 1 and 2. Extended PCR was only requested for samples that were negative for RSV and influenza. As shown in Figure 2, there was an increase in the proportion and number of rhinovirus diagnoses roughly in parallel with the decrease of influenza diagnoses.

A simple but likely explanation for the sudden interruption of the spread of influenza could thus be the increase in the spread of above all rhinoviruses. It is well known that a major rhinovirus epidemic always occurs soon after school has started [7]. The virus is spread mainly by contaminated hands [8], and has not been reported to be climate-dependent. Thus the spread of rhinoviruses may have had an advantage over influenza due to the mild and moist climate. Once a rhinovirus infection has become established, infected cells start producing interferon and other cytokines, similar to those produced by influenza [9]. This immune reaction causes the cells to enter an antiviral state. Though double infections occur, they are probably not common enough to maintain high level spread of both rhino and influenza viruses in the population.

FIGURE 1

Laboratory-confirmed cases of seasonal influenza since 2006-7 and of pandemic versus seasonal influenza in 2009, Sweden

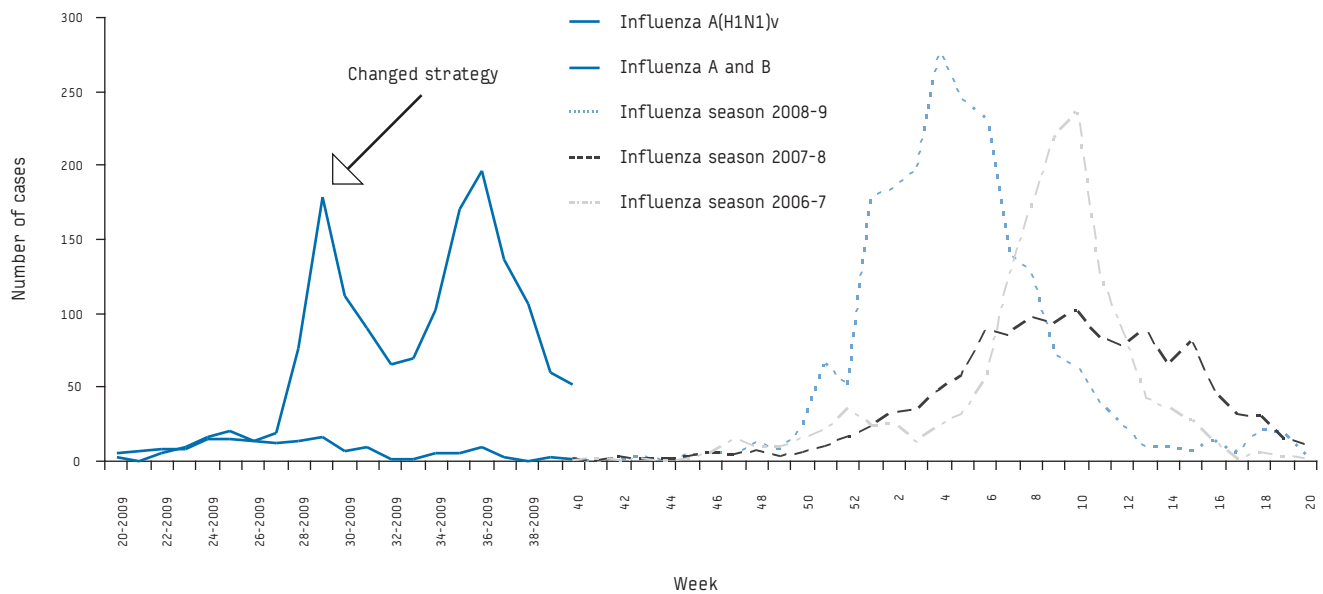


TABLE 1

Number of samples examined with PCR for pandemic influenza A(H1N1) and number and proportion of positives*, Karolinska University Hospital, Stockholm, August-September 2009 (n=2,994)

Week no. (2009)	32	33	34	35	36	37	38	39
Pandemic influenza A(H1N1)-positives, no. (%)	10 (7%)	16 (11%)	38 (14%)	85 (19%)	61 (8%)	33 (5%)	24 (7%)	9 (3%)
Total no. examined	146	150	277	440	754	616	351	260

* Respiratory syncytial virus and seasonal influenza were also included in the examinations, with one positive each during the whole period.

TABLE 2

Number of samples examined for 13 viruses*, Karolinska University Hospital, Stockholm, August-September 2009 (n=401)**

Week	32	33	34	35	36	37	38	39
Rhinovirus, no. (%)	2 (6%)	2 (5%)	7 (19%)	6 (11%)	18 (25%)	16 (27%)	14 (27%)	9 (16%)
Picornaviruses not subtyped, no. (%)	0	2 (5%)	0	1 (2%)	4 (6%)	2 (3%)	1 (2%)	2 (4%)
11 other viruses, no. (%)	1 (3%)	0	4 (11%)	4 (8%)	1 (1%)	1 (2%)	0	1 (2%)
Total no. examined**	35	38	36	53	71	60	51	57

*Rhinovirus, bocavirus, adenovirus, four types of human coronavirus, metapneumovirus, parainfluenzavirus types 1-3, non-subtyped picornaviruses, enteroviruses. Positive results for rhinovirus and non-subtyped picornaviruses, which could be rhinoviruses, are presented separately as numbers and percentages, the other viruses are summarised.

**A subset of samples from Table 1, which had tested negative for pandemic influenza A(H1N1), seasonal influenza and respiratory syncytial virus.

Influenza surveillance with sentinel reporting normally does not start until week 40, and respiratory sampling for viral diagnostics is usually scarce during early autumn. For week 40, most Swedish sentinel doctors usually report zero cases of influenza-like illness (ILI), and we do not know whether the early autumn rhinovirus peak would have been reported as ILI in previous years even if reporting had been in place then. The reason for the large number of rhinovirus infections diagnosed in 2009 was most likely that people who got respiratory tract infections, who would not normally have visited a doctor, did so due to the fear of the pandemic influenza.

In conclusion, we hypothesise that a rhinovirus epidemic that occurred after the end of the summer holidays may have interfered with the spread of pandemic influenza during a period with warm and humid climate that decreases spread of influenza by aerosol. Although the laboratory data supporting this hypothesis are limited, it may stimulate research into the possibility that the interaction between different circulating viruses may affect influenza epidemiology.

We therefore suggest the following:

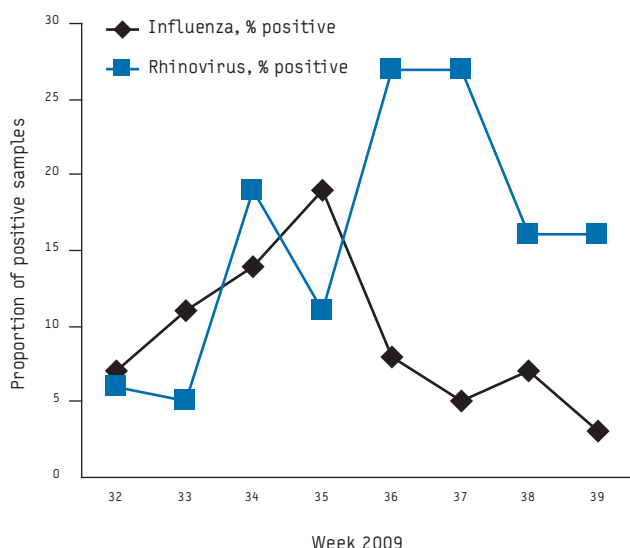
1. The epidemiology of influenza should be related to that of other respiratory viruses for improved understanding of the true epidemiological situation.
2. Surveillance of respiratory infections should be conducted throughout the year to create reliable baselines for ILI and acute respiratory infections, which are useful when a pandemic virus occurs that does not follow the usual pattern of spread.

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FIGURE 2

Proportion of samples examined at Karolinska University Hospital, Stockholm, containing pandemic influenza A(H1N1) and rhinoviruses, August-September 2009



USE OF AN INACTIVATED VACCINE IN MITIGATING PANDEMIC INFLUENZA A(H1N1) SPREAD: A MODELLING STUDY TO ASSESS THE IMPACT OF VACCINATION TIMING AND PRIORITISATION STRATEGIES

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The impact of prioritisation and of timing of vaccination strategies on reducing transmission of pandemic influenza A(H1N1) was evaluated in a community with the structure of the Greek population using a stochastic simulation model. Prioritisation scenarios were based on the recommendations of the United States Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices and vaccination was assumed to initiate either before or during the ongoing epidemic. In the absence of intervention, an illness attack rate (AR) of 34.5% is anticipated. Vaccinating the priority groups before the epidemic (pregnant women, people who live with or care for children <6 months of age, healthcare/emergency services personnel, children 6 months–4 years old and high-risk children 5–18 years old) will have a negligible impact on the overall AR. Vaccinating the recommended groups before the epidemic (priority groups as well as all persons 6 months–24 years old and high-risk individuals 25–64 years old) is anticipated to result in overall and age-specific ARs within the range of seasonal influenza (5%–15%). Initiating vaccination early during the epidemic (AR≤1% of the population) is predicted to result in overall ARs up to 15.2%–19.9% depending on daily vaccination coverage rates. When vaccination is initiated at a later stage (AR: 5%), only coverage of 80% of the whole population at intensive daily vaccination rates would be able to reduce ARs to approximately 15%.

Introduction

On 11 June 2009, the World Health Organization (WHO) raised the pandemic alert level to phase 6 and declared A(H1N1) influenza the first global pandemic of the 21st century. Delays in the development, production and licensure of a vaccine for the current pandemic as well as restrictions in the global manufacturing capacity dictate careful planning of strategies concerning prioritisation and distribution policies. Another important issue to be considered is the timing of vaccination during an ongoing pandemic. Previous modelling studies investigating the impact of various strategies for mitigating a potential pandemic have shown that the benefit of vaccination depends closely on the time it is initiated [1,2].

In the current study we employ a simulation model to investigate the impact of vaccination strategies and of vaccination timing on the overall illness attack rate (AR) of pandemic influenza A(H1N1) in a small community.

Methods

The simulation model

We have used a discrete-time stochastic individual-based simulation model employed previously to simulate A(H1N1) spread [3]. Model parameters were chosen such as to yield age-specific attack rates, in the absence of intervention, similar to that observed in the A(H1N1) outbreak in the community of La Gloria in Mexico [3]. A structured model community of approximately 2,000 people was generated to match the age-distribution, household size and number and size of schools of the Greek population. The model community of 2,000 people was divided into four neighbourhoods of approximately equal size that share one kindergarten, one primary school and one high school. Influenza was introduced at day 0 by randomly assigning a number of initial infective individuals, and person-to-person transmission probabilities were used to simulate influenza spread over time. As the population was assumed to be structured (households, schools, neighbourhoods and community), different transmission probabilities applied to different mixing groups. They were highest for contacts within households and lower for contacts within schools, followed by neighbourhoods and, finally, the entire community [3]. In the absence of intervention, a proportion of symptomatic individuals (80%, 75% and 50% of preschool children, school-age children and adults, respectively) were assumed to stay at home and withdraw from the remaining mixing groups (schools, neighbourhoods, community).

Vaccine efficacy

We have modelled key vaccine efficacy parameters defined previously, i.e. efficacy for infection-confirmed symptomatic illness (VE_{sp}), efficacy for susceptibility (VE_s) and, given infection, efficacy for illness (VE_p) and efficacy for infectiousness (VE_i) [4]. Based on estimates from previous trials on the efficacy of homologous inactivated vaccines [5–14], we have assumed a VE_{sp} of 80% for individuals 2–64 years old and of 60% for children 6–24 months and adults > = 65 years old. Estimates for VE_s and VE_p

for individuals 2-64 years old were obtained from Basta *et al.* [15] (40% and 67%, respectively) with a modification in the case of children 0-24 months old and elderly to yield a lower VE_{SP} ($VE_S=20\%$ and $VE_P=50\%$).

Vaccination strategies

Four vaccination scenarios, based on the United States Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC's ACIP) recommendations [16], were evaluated (Table 1). In all scenarios, 80% vaccination coverage was assumed (total coverage). High-risk groups included individuals with chronic respiratory diseases (including asthma), chronic cardiovascular diseases, chronic metabolic disorders (including diabetes mellitus), chronic renal and hepatic diseases and immunosuppression.

Timing of vaccination

All scenarios were evaluated under the assumption that vaccination takes place early enough so that the vaccinated persons have developed immunity before the introduction of pandemic influenza A(H1N1) in the community. Selected scenarios were further explored assuming that 2%, 6% and 10% of the

2,000-persons community are vaccinated daily (daily coverage) and the first vaccinated individuals develop an immune response when the AR reaches 1%, 5%, 10% or 15% of the population.

Results

Effectiveness of vaccination strategies

In the absence of intervention, an AR of 34.5% is anticipated [3]. Vaccinating the priority groups would reduce the AR to 28.0% (Table 2). Under the scenario of vaccinating the recommended groups, the estimated AR is anticipated to be reduced below 10% (AR: 9.6%). When vaccination is extended to all individuals aged between 25 and 64 years, the AR is estimated to be reduced to 2.7%. Offering vaccination additionally to individuals ≥ 65 years of age is not anticipated to further lower the AR (AR: 2.5%).

The age-specific attack rates under these vaccination strategies are depicted in the Figure. Vaccinating the recommended groups results in low attack rates in all age groups (9.4%, 10.2%, and 8.1% for 0-24, 25-64 and 65+ years, respectively). When vaccination is extended to include also all individuals aged between 25 and 64 years, low attack rates are predicted for all age groups (5.0%, 1.5% and 2.7% for 0-24, 25-64 and 65+ years, respectively). Offering

TABLE 1

Evaluated vaccination strategies proposed by the Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices [16] in a community of 2,000 people representative of the Greek population

1. Priority groups		2. Recommended groups		3. Recommended groups + 25-64 years		4. Whole population	
Target groups	% of the whole population	Target groups	% of the whole population	Target groups	% of the whole population	Target groups	% of the whole population
Pregnant women	1.0%	Pregnant women	1.0%	Pregnant women	1.0%	Pregnant women	1.0%
Household contacts of children younger than 6 months of age	1.7%	Household contacts of children younger than 6 months of age	1.7%	Household contacts of children younger than 6 months of age	1.7%	Household contacts of children younger than 6 months of age	1.7%
Health care and emergency services personnel	0.9%	Health care and emergency services personnel	0.9%	Health care and emergency services personnel	0.9%	Health care and emergency services personnel	0.9%
Children 6 months-4 years	4.3%	Persons 6 months-24 years	28.9%	Persons 6 months-24 years	28.9%	Persons 6 months-24 years	28.9%
High-risk children 5-18 years	0.9%	High-risk individuals 25-64 years	4.9%	Individuals 25-64 years	53.8%	Individuals ≥ 25 years	70.5%
Total*	6.6%	Total*	28.5%	Total*	66.7%	Total*	80.3%

*Estimated in 200 simulations assuming vaccination coverage of 80% within each target group

TABLE 2

Simulated illness attack rates and effectiveness of different vaccination strategies based on the Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices [16] in a community of 2,000 people representative of the Greek population

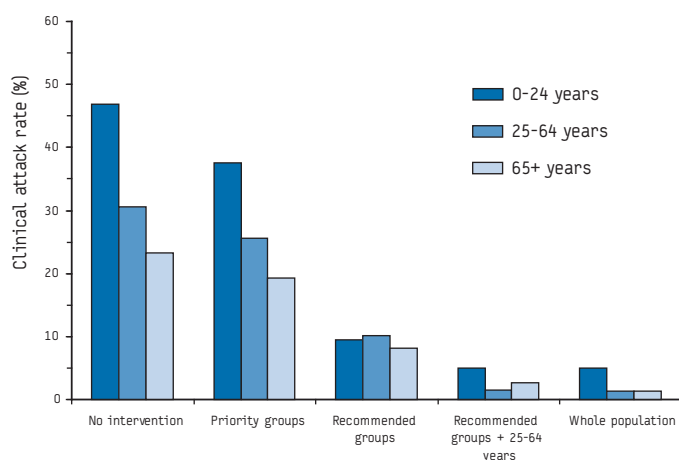
Target population	Attack rate (AR)	(% decrease)*	Number of vaccinations /1,000 persons	Number of cases prevented/person vaccinated
Priority groups	28.0%	(18.8%)	66	0.96
Recommended groups	9.6%	(72.2%)	285	0.86
Recommended groups + 25-64 years old	2.7%	(92.2%)	667	0.47
Whole population	2.5%	(92.8%)	803	0.40

Note: The model assumes 80% vaccination coverage of the target populations and that vaccinated persons become immune before the start of the epidemic

*Compared to an AR of 34.5% in the absence of intervention

vaccination to individuals ≥ 65 years of age is not anticipated to offer a notable additional benefit for this age group (Figure).

FIGURE
Age-specific clinical attack rates according to the implemented vaccination strategy, pandemic influenza A(H1N1) 2009



Note: The model assumes 80% coverage of the target groups and that vaccination takes place early enough so that the vaccinated persons have developed immunity before the introduction of influenza A(H1N1) in the community.

Impact of timing and daily rate of vaccination

Under the scenario where vaccination of the recommended groups starts early so that the first vaccinated persons develop an immune response when the cumulative AR is 1%, the AR at the end of the epidemic is predicted to be 15.2%-19.9% for 2%-10% daily vaccination rates (Table 3). Initiating vaccination at a later stage of the epidemic (cumulative AR of 5%) would lead to moderate decreases in the total number of symptomatic cases that is not expected to decrease below 21% of the population, even with intensive daily vaccination rates (100 persons vaccinated daily/1,000 population). When the first vaccinated persons develop immunity near or at the peak of the epidemic (AR: 10% or 15%, respectively), the effectiveness of the intervention in reducing the number of symptomatic infections is estimated to be low (AR: 24.8%-28.5% and 27.8%-29.8%, respectively, for 2%-10% daily vaccination rates). Under the scenario of staged vaccination of the whole population, overall attack rates below 10% are anticipated only in the case where vaccination is initiated early in the epidemic (AR 1%) with intensive daily vaccination coverage (6%-10% of the population vaccinated/day) (Table 3).

Discussion

In the present study, mathematical modelling was used to evaluate the impact of vaccination strategies recommended by CDC's ACIP for pandemic influenza A(H1N1) as well as the impact of the timing of vaccination in a community typical of the European setting [3]. Vaccinating only the priority groups will have a negligible impact on the overall clinical attack rate. Vaccinating the groups recommended by CDC (i.e. priority groups and all children and young adults up to 24 years old) is predicted to be successful

TABLE 3
Impact of vaccination according to the timing of vaccination and to daily coverage during an ongoing epidemic (assuming up to 80% vaccination coverage of the target populations): A. Vaccination of recommended groups; B. Vaccination of the whole population.

		A. Vaccination of recommended groups			B. Staged vaccination of the whole population (first recommended groups, then individuals 25-64 years, then ≥ 65 years)		
		Attack rate (AR)	(% decrease)*	Number of cases prevented/ person vaccinated	Attack rate (AR)	(% decrease)*	Number of cases prevented/ person vaccinated
Before the epidemic (vaccinated individuals already immune when the epidemic starts)		9.6%	(72.2%)	0.86	2.5%	(92.8%)	0.40
During the epidemic							
The first vaccinated persons develop an immune response when the AR is:	Proportion of population vaccinated/day (%)						
1%	2%	19.9%	(42.3%)	0.57	17.0%	(50.7%)	0.26
	6%	15.7%	(54.5%)	0.70	8.8%	(74.5%)	0.34
	10%	15.2%	(55.9%)	0.72	7.3%	(78.8%)	0.36
5%	2%	26.2%	(24.1%)	0.38	25.5%	(26.1%)	0.16
	6%	22.8%	(33.9%)	0.47	16.9%	(51.0%)	0.25
	10%	21.7%	(37.1%)	0.50	15.3%	(55.7%)	0.26
10%	2%	28.5%	(17.4%)	0.31	28.2%	(18.3%)	0.12
	6%	26.2%	(24.1%)	0.36	23.2%	(32.8%)	0.17
	10%	24.8%	(28.1%)	0.42	20.6%	(40.3%)	0.20
15%	2%	29.8%	(13.6%)	0.27	29.2%	(15.4%)	0.11
	6%	28.3%	(18.0%)	0.30	26.2%	(24.1%)	0.14
	10%	27.8%	(19.4%)	0.32	24.6%	(28.7%)	0.15

*Compared to an AR of 34.5% in the absence of intervention

in mitigating the pandemic as it results in clinical attack rates below 10%, i.e. within the range of regular seasonal influenza (5%-15%). An additional advantage of this strategy is that it has significant indirect effects in the age groups that are not included in the target populations (i.e. individuals aged 25-64 and ≥ 65 years). Extending vaccination to include also individuals 25-64 years old is anticipated to result in very low attack rates of approximately 3%. However, once the demand for vaccine for these prioritised groups as well as for individuals 25-64 years old is met, offering vaccination to people over the age of 65 will not offer a notable additional benefit for this age group.

The above findings refer to the best-case scenario where vaccines are available before the onset of the epidemic in the population, such as e.g. in the case of countries of the northern hemisphere with still a small number of influenza A(H1N1) cases. When vaccination is implemented during the epidemic, its impact on the attack rate is predicted to be lower. Under intensive daily coverage, clinical attack rates of approximately 15% may be achieved by initiating vaccination either of the recommended groups early in the epidemic (AR 1%) or of the whole population somewhat later (AR 5%).

In the current analysis, we assumed that the pandemic evolves in a single wave whereas 2-3 waves have been observed in the majority of past pandemics [17,18]. As a result, although the model predicts modest to negligible reductions in the overall attack rate when vaccination is not introduced early during the ongoing epidemic, it might be used to abort the second and third waves [17]. Vaccination strategies were evaluated in a community with the structure of the Greek population (age and sex distribution, number and size of households etc). As a result, the quantitative results reported here are valid for Greece alone. However, due to the similarity in the age structure and household size of the Greek and the European population, results may apply qualitatively to other communities in the European region. A further point that requires caution is that the model was set up such as to simulate the age-specific attack rates of the pandemic influenza A(H1N1) outbreak in the community of La Gloria in Mexico. This particular outbreak provided very useful information as it evolved in the absence of intervention. However, the age-specific attack rates observed in the community of La Gloria might be considered as a worst-case assumption and the proportion of symptomatic infections that will be observed in European countries is likely to be smaller. A final point is that we did not deal explicitly with the time lag between vaccination and effectiveness and the partial efficacy between doses, in case multiple doses are required, but rather combined this delay time with that of production and distribution and refer only to the date at which vaccination becomes effective. Similarly, we have not estimated the number of doses needed to implement the various strategies but rather the number of vaccinated persons.

In conclusion, vaccinating the groups recommended by CDC's ACIP in countries with still a small number of pandemic influenza A(H1N1) cases is anticipated to reduce illness attack rates within the range of seasonal influenza (approximately 10%) with significant indirect effects among individuals older than 24 years who are not included in the target groups. For countries experiencing an ongoing epidemic, initiating vaccination of the recommended groups early might result in attack rates near the upper limit estimates of seasonal influenza.

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PANDEMIC H1N1 INFLUENZA: PREDICTING THE COURSE OF A PANDEMIC AND ASSESSING THE EFFICACY OF THE PLANNED VACCINATION PROGRAMME IN THE UNITED STATES

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We use data on confirmed cases of pandemic influenza A(H1N1), disseminated by the United States Centers for Disease Control and Prevention (US CDC), to fit the parameters of a seasonally forced Susceptible, Infective, Recovered (SIR) model. We use the resulting model to predict the course of the H1N1 influenza pandemic in autumn 2009, and we assess the efficacy of the planned CDC H1N1 vaccination campaign. The model predicts that there will be a significant wave in autumn, with 63% of the population being infected, and that this wave will peak so early that the planned CDC vaccination campaign will likely not have a large effect on the total number of people ultimately infected by the pandemic H1N1 influenza virus.

Introduction

For several years the United States (US) Centers for Disease Control and Prevention (CDC) have had an established protocol for laboratory influenza testing and collection, and dissemination of associated statistics [1]. These statistics are published and regularly updated online [2].

With the recognition of a new, potentially pandemic strain of influenza A(H1N1) in April 2009, the laboratories at the US CDC and the World Health Organization (WHO) dramatically increased their testing activity from week 17 onwards (week ending 2 May 2009), as can be seen in Figure 1. In this analysis, we use the extrapolation of a model fitted to the confirmed influenza A(H1N1) v case counts during summer 2009 to predict the behaviour of the pandemic during autumn 2009.

Methods

The CDC/WHO influenza count data used in these studies were obtained from the weekly online surveillance reports [2]. At the time of writing, the data up to week 38 (week ending 26 September 2009) were the most recent. However, we observed that in each weekly update the data significantly change for at least five weeks prior to the week of the update, likely due to a large backlog in testing. In this analysis we thus used data only up to week 33 (week ending 22 August).

The pandemic potential of influenza A(H1N1)v was recognised during week 16 (week ending 25 April) [3]. We assumed that there was no time bias in the CDC/WHO seasonal influenza count data prior to that date. Based on the extrapolation of the exponential

decline behaviour of regular seasonal influenza prior to week 16 into the temporal region of heightened testing activity, we found that the data after week 20 (ending 23 May) contain no significant time bias. We thus used the data from week 21 to 33 (from 24 May to 22 August 2009).

The behaviour of the H1N1 influenza pandemic over time was modelled using a seasonally forced deterministic Susceptible, Infective, Recovered (SIR) model [4]:

$$dS/dt = -\beta(t) SI/N \quad (1)$$

$$dI/dt = \beta(t) SI/N - \gamma I, \quad (2)$$

where $N=350,000,000$.

We assumed that $\gamma=1/3$ days⁻¹ [5], and that the contact rate, $\beta(t)$, was periodically forced via

$$\beta(t) = \beta_0 + \beta_1 \cos(2\pi t) \quad (3)$$

The reproduction number was given by $R_0 = \beta(t)/\gamma$.

To simulate the time evolution of the influenza H1N1 pandemic, we assumed an initial number of infective individuals and susceptibles, $I_0=1/N$ and $S_0=N$, respectively, at an initial time t_0 . Given particular values of β_0 , β_1 , and t_0 , we numerically solved equations (1) and (2) to estimate the fraction of the population infected with pandemic H1N1 influenza each week.

We compared the shape of the results of the deterministic model to the shape of the actual pandemic influenza data, and found the parameters $\{\beta_0, \beta_1, t_0\}$ that provided the best Pearson chi-square statistics.

The grid search for the parameters that minimised the chi-square value was performed with parameter ranges:

β_0 between 0.92 to 2.52 in increments of 0.02,

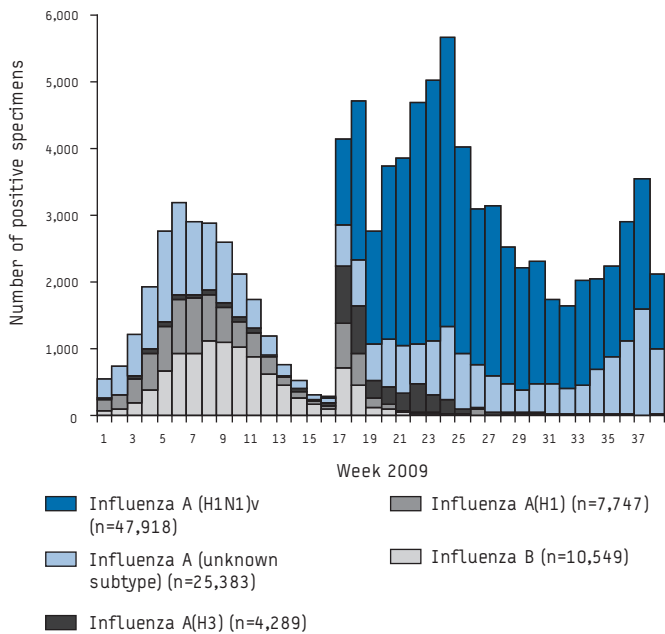
β_1 between 0.05 to 0.80 in increments of 0.01, and

t_0 between weeks -8 to 10 (relative to the beginning of 2009), in increments of one week.

The planned CDC vaccination programme against pandemic H1N1 influenza will begin with six to seven million doses being delivered by the end of the first full week in October (week 40), with 10 to 20 million doses being delivered weekly thereafter [6]. We included the effects of this vaccination campaign into

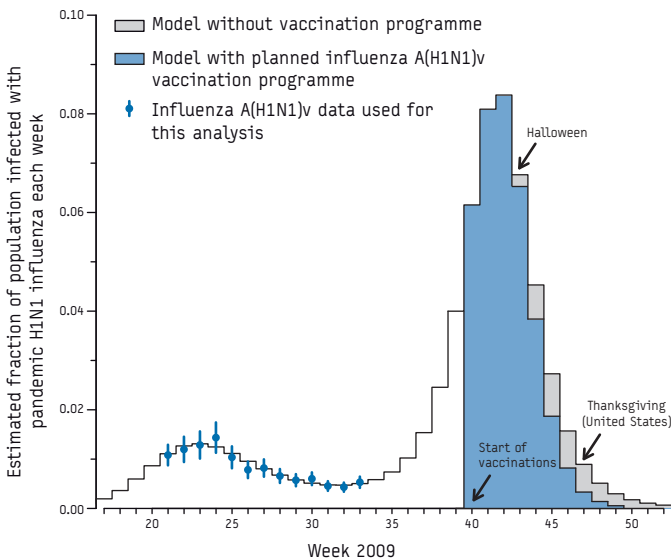
our seasonally forced SIR model by decreasing the number of susceptibles in the population by the corresponding amounts. For healthy adults, full immunity to H1N1 influenza is achieved about two weeks after vaccination with one dose of the vaccine [7,8], and

FIGURE 1
Influenza-positive tests reported to the US CDC by US WHO/NREVSS-collaborating laboratories, national summary, United States, 2009 until 26 September



US CDC: United States Centers for Disease Control and Prevention; NREVSS: National Respiratory and Enteric Virus Surveillance System; WHO: World Health Organization.

FIGURE 2
Model of the H1N1 influenza pandemic in the United States and prediction for autumn 2009



we took this into account in the model by beginning the reduction in susceptibles in week 42 instead of in week 40. We optimistically assumed the higher-end estimate of the planned vaccine roll-out, and we also optimistically assumed that 100% of vaccinated people would achieve full immunity within two weeks.

Results

When the seasonally forced SIR model was compared to the influenza H1N1 data, the parameters $\{\beta_0, \beta_1, t_0\}$ that yielded the minimum chi-square value were {1.56, 0.54, 24 Feb 2009}, with 95% confidence intervals (CI) of {1.43,1.77, 0.39,0.54, 8 Feb 2009,7 Mar 2009}.

The best-fit model is shown in Figure 2, with the influenza H1N1 data overlaid. The model predicts that the peak wave of infection will occur near the end of October in week 42 (95% CI: week 39,43), with 8% of the population being infected during that week (95% CI: 6%,13%). By the end of 2009, the model predicts that a total of 63% of the population will have been infected (95% CI: 57%,70%).

When the model was modified to include the effect of the planned vaccination scheme, it predicted a relative reduction of about 6% in the total number of people infected with influenza A(H1N1)v virus by the end of the year 2009 (95% CI: 1%,17%). The predictions of the modified model are shown in Figure 2.

Discussion

Based on a model with simple harmonic seasonal forcing, the peak of the H1N1 influenza pandemic was predicted to occur between weeks 39 to 43 with 95% confidence. However, it should be noted that the actual periodic function underlying seasonal forcing of influenza has not been well studied, and the uncertainties in the model predictions arising from seasonal forcing assumptions are difficult to quantify.

The 95% confidence interval for t_0 predicted by this analysis was [8 Feb 2009, 7 Mar 2009], which is in good agreement with the genetic analysis presented in Fraser *et al.* that found t_0 between 3 November 2008 and 2 March 2009 with 95% confidence [9]. Further, the value of R_0 predicted by the model between mid-March and the end of April 2009 was between 1.3 and 1.7. This is in agreement with the results presented in Fraser *et al.*, who estimate R_0 to be in the range 1.4 to 1.6, based on an analysis of Mexican H1N1 influenza data collected during that time period [9].

We predict that almost two thirds of the US population will be infected with pandemic H1N1 influenza by the end of 2009. However, the serological analysis presented in King *et al.* showed that up to 60% of seasonal influenza infections are asymptomatic [10]. If the same is true of the current pandemic influenza, about a quarter of the population will fall ill.

The most optimistic assumptions about the CDC vaccination campaign yielded a relative reduction of only 6% in the total number of infected individuals. If we assume a 40% symptomatic infection rate, and a mortality rate of between 0.05% and 0.5%, this corresponds to an estimated prevention of between 2,500 and 25,000 deaths. The actual reduction would certainly be lower because 10-30% of adults vaccinated will not achieve immunity [7,8]. Also a large fraction of the population targeted by influenza A(H1N1) vaccinations are children. Vaccination immunity in

children develops at least four weeks after vaccination and would occur too late in the pandemic to make a significant difference to the number of infected in that age group.

The cost benefit analysis involved in devising a pandemic influenza vaccination campaign is extremely complicated, especially due to the ever evolving nature of the pandemic. What we learn from the successes and mistakes of vaccination programmes developed during the current H1N1 influenza pandemic will greatly aid us in decision making during future influenza pandemics.

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RESISTANCE OF TURKEYS TO EXPERIMENTAL INFECTION WITH AN EARLY 2009 ITALIAN HUMAN INFLUENZA A(H1N1)V VIRUS ISOLATE

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We performed an experimental infection of 21- and 70-day-old meat turkeys with an early human isolate of the 2009 pandemic H1N1 influenza virus exhibiting an α -2,3 receptor binding profile. Virus was not recovered by molecular or conventional methods from blood, tracheal and cloacal swabs, lungs, intestine or muscle tissue. Seroconversion was detected in a limited number of birds with the homologous antigen only. Our findings suggest that in its present form, the pandemic H1N1 influenza virus is not likely to be transmitted to meat turkeys and does therefore not represent an animal health or food safety issue for this species.

Introduction

Following the emergence of the human pandemic influenza A(H1N1)v virus in spring 2009, questions about the circulation of this virus in an animal reservoir were raised by international organisations. In particular, three aspects appeared to be of relevance, namely implications on animal health, aspects of food safety, and epidemiological aspects related to animals being infected with a human virus and perpetuating a parallel channel of infection in the animal reservoir.

Turkeys (*Meleagris gallopavo*) are highly susceptible to type A influenza virus infection and have been infected in the past with viruses of swine origin [1-4]. In August 2009, infection of two turkey flocks in Chile with the human influenza A(H1N1)v virus was reported [5]. The genetic profile of the virus appeared to be closely related (similarity ranging between 99.7% and 100%) to the strain that was circulating in the human population in Chile at the time [6]. The aim of this experiment was to establish the susceptibility of turkeys of different ages to infection with the human virus and to assess whether it would be detectable in the blood or in tissues of meat birds following administration of a high viral dose.

Materials and methods

Animals

Commercially available turkeys were used in this study. The birds originated from a flock that was serologically negative for all avian influenza subtypes, including influenza A(H1N1)v, by agar gel immunodiffusion test (AGID) and enzyme-linked immunosorbent assay (ELISA) and negative for influenza A virus by real-time reverse transcription-PCR (RRT-PCR) on cloacal and tracheal swabs [7]. All animals were identified by means of wing tags and received feed and water *ad libitum*. Birds were housed in negative pressure, high

efficiency particulate air (HEPA) filtered isolation cabinets for the duration of the experimental trial.

Challenge virus and protocol

Challenge of turkeys was carried out with the influenza A virus isolate A/Italy/2810/2009(H1N1). The virus was isolated from a human case detected in Verona, Italy, in specific pathogen-free (SPF) embryonated hens' eggs via the amniotic cavity and was characterised according to chapter on swine influenza in the World Organisation for Animal Health (OIE) Manual of Diagnostics Tests and Vaccines for Terrestrial Animals [8]. The number of virus passages in SPF embryonated hens' eggs was limited to the minimum (two) in order to limit laboratory manipulation and adaptation.

The haemagglutinin (HA) and neuraminidase (N) genes of the virus obtained from nasal swabs of the patient and the HA of the virus obtained from the allantoic fluid after the second passage in eggs, were genetically analysed and sequences were deposited in the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAID), accession numbers EPI181386, EPI181387 and EPI211620. The A/Italy/2810/2009(H1N1) virus isolate has 99.6% homology with influenza A/California/4/09. The HA gene of the strain grown in eggs, which was used for the infection, contains arginine (Arg) instead of glutamine (Gln) at position 226. This substitution is associated with a receptor binding affinity to α -2,3 sialic acid receptors which are typical of avian viruses and thus bind preferably to avian cells [9].

For viral titration, 100 μ l of 10-fold diluted A/Italy/2810/2009 virus was inoculated into five SPF embryonated hens' eggs and the median embryo infectious dose (EID₅₀) was calculated according to the Reed and Muench formula [10].

Molecular tests

Extraction of RNA

Viral RNA was extracted from 200 μ l of blood using the commercial kit 'NucleoPsin RNA II' (Macherey-Nagel) and from 200 μ l of phosphate-buffered saline (PBS) suspension of cloacal and tracheal swabs and homogenised organs using the 'High Pure RNA Isolation Kit' (Roche®) commercial kit.

Real time RT-PCR (RRT-PCR)

Published primers and probes [7] targeting the Matrix (M) gene of type A influenza virus were used. The reverse primer M-124 was modified in order to have a perfect match with the M gene sequence of the influenza A(H1N1)v virus isolates. The forward, M-25, and reverse primers were used at the optimised concentration of 300 nM each, the specific fluorescent-labelled probe, M+64, was used at the final concentration of 100 nM. RNA was amplified in a final volume of 25 µl using a QuantiTect Multiplex® RT-PCR kit (Qiagen, Hilden, Germany). The PCR reaction was performed using the RotorGene 6000 (Corbett, Australia) apparatus with the following protocol: 20 minutes at 50 °C and 15 minutes at 95 °C followed by 40 cycles at 94 °C for 45 sec and 60 °C for 45 sec. All samples were also analysed using the RRT-PCR protocols for the M and HA genes recommended by WHO [11].

Serology

Type- and subtype-specific antibodies were detected by means of a commercial ELISA (ID-VET®) and AGID tests and by haemagglutination inhibition (HI) test according to the European Union (EU) diagnostic manual [12] using 1% chicken red blood cells. For the HI test, the detection of antibodies to the H1 subtype of avian influenza A virus was performed using four haemagglutinating units of the homologous antigens of the human H1N1v strain (A/Italy/2810/2009), an H1N1 strain of swine origin (A/swine/Italy/711/06) or an avian H1N1 strain (A/duck/Italy/1447/05).

Naïve animals were considered positive with a serologic titre of $\geq 4 \log_2$, as indicated by the EU guidelines.

Experimental design

Experiment 1: Evaluation of the presence of virus in blood, meat and viscera

A group of 10 70-day-old turkeys were oro-nasally infected with 100µl of the challenge virus containing 107 EID₅₀. On days 1, 2,

3, 4 and 5 post infection (p.i.), blood was collected from each bird from the wing vein, mixed with anticoagulant (Alsever's solution 1:1), and the establishment of viraemia was evaluated by RRT-PCR. If blood samples yielded positive results, up to two birds presenting viraemia were killed humanely on the day of testing. When blood samples yielded negative results and no animals showed clinical signs, two turkeys were killed humanely on a random basis. In case of any death, lungs, intestine, superficial and deep pectoral muscles and thigh muscles were collected on the day of death.

Experiment 2: Evaluation of clinical signs, tracheal and cloacal shedding and seroconversion following experimental infection

A group of 12 21-day-old turkeys were used in this experiment. All animals were experimentally infected oro-nasally with 100µl of challenge virus containing 107 EID₅₀. Twice a day clinical signs were recorded. On days 2, 4, 6, 10 15 p.i. tracheal and cloacal swabs were collected from each bird. On day 14 and 21 p.i. blood samples were collected to evaluate seroconversion.

Results

Mild, non-specific clinical signs were observed in the 21-day-old birds a few days following administration of the challenge virus. These signs were considered to be non-specific because the birds did not exhibit the conjunctivitis, sinusitis or nasal discharge typical of low pathogenicity avian influenza infection. In both experimental groups, the virological and molecular results from all collected samples were negative. Seroconversion was detected in 41.6%, 8.3% and 33.3% of birds belonging to the younger age group by ELISA, AGID and HI tests (only with the homologous antigen), respectively. The results are presented in detail in the Table.

Discussion

The data reported here indicate that both 21- and 70-day-old turkeys are resistant to infection with early strains of the human influenza A(H1N1)v virus. Notwithstanding the high infectious dose and the mutation Arg to Gln in 226 of the HA gene, it was not possible to achieve infection or to detect virus in blood, respiratory and enteric organs or in muscles of experimentally infected birds. What is surprising is the evidence of seroconversion in a proportion of the infected poults. Since active infection was not achieved, it is likely that the seroconversion is related to the high viral dose administered. In any case, antibodies were detectable only with the homologous virus, thus indicating that intra-subtypic cross-reactivity was below HI detection limits.

Our findings indicate that unless the human influenza A(H1N1)v virus undergoes substantial changes, the risk that meat turkeys become infected with the virus is negligible. Therefore, there is no reason to be concerned about the animal health or food safety implications of this infection in this species.

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TABLE

Results of serological tests after infection (n=12)

Turkey (ID number)	14 days post infection			21 days post infection		
	HI*	ELISA	AGID	HI*	ELISA	AGID
71	n	p	d	n	p	d
72	1:64	p	d	1:32	p	d
73	n	n	n	n	n	n
74	1:16	p	d	1:16	d	d
75	n	n	n	n	n	n
76	1:4	p	d	1:8	p	d
79	n	n	n	n	n	n
80	n	n	n	n	n	n
81	1:32	p	p	1:64	p	p
82	n	n	n	n	n	n
83	n	n	n	n	n	n
84	1:16	p	n	1:16	p	n

AGID: agar gel immunodiffusion test; ELISA: enzyme-linked immunosorbent assay.

*Haemagglutination inhibition (HI) test performed with homologous antigen; n= negative; p= positive; d= doubtful.

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PANDEMIC INFLUENZA A(H1N1) 2009 VACCINES IN THE EUROPEAN UNION

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Pandemic vaccines from four manufacturers are now available for use within the European Union (EU). Use of these vaccines will protect individuals and reduce the impact on health services to more manageable levels. The majority of the severely ill will be from known risk groups and the best strategy will be to start vaccinating in line with the recommendation from the European Union Health Security Committee prioritising adults and children with chronic conditions, pregnant women and healthcare workers. The composition of authorised vaccines is reviewed in this article. The vaccine strain in all authorised pandemic vaccines worldwide is based on the same initial isolate of influenza A/California/7/2009 (H1N1)v but the vaccines differ in conditions for virus propagation, antigen preparation, antigen content and whether they are adjuvanted or not. The vaccines are likely to be effective since no significant genetic or antigenic drift has occurred and there are already mechanisms for estimating clinical effectiveness. Influenza vaccines have good safety records and no safety concerns have so far been encountered with any of the vaccines developed. However, special mechanisms have been devised for the early detection and rigorous investigation of possible significant side effects in Europe through post-marketing surveillance and analysis. Delivery of the vaccines to the risk groups will pose difficulties where those with chronic illnesses are not readily identifiable to the healthcare services. There is considerable scope for European added value through Member States with excess vaccines making them available to other states.

Introduction

Vaccines from four manufacturers are now becoming available for protection against pandemic influenza A(H1N1) 2009 infection. Three vaccines have been authorised through the central European Medicines Agency (EMA) mechanism for use in any European Union (EU) Member State (MS) and a fourth vaccine was recently authorised by the Hungarian National Regulatory Agency for use in Hungary (Table 1). The central mechanism was streamlined by rehearsal through use of mock-up protocols and experience of the development of human avian influenza vaccines including human clinical trial data. Within Europe, vaccination is known to have started in the Nordic countries and Hungary and will shortly begin in other EU countries. Pandemic vaccines have during the last few weeks been authorised for use in China, Australia and the United States (US), where vaccination campaigns have also begun.

The new vaccines are important countermeasures to mitigate the effects of pandemic waves in Europe however they are arriving

too late and in too low quantities to stop population transmission. Instead, the vaccination strategy will have to be the usual one of influenza vaccination in Europe, namely that of protecting the vulnerable [1,2].

Adherence to pandemic vaccine recommendations issued in the vaccine campaigns will be dependent on the current view of the pandemic in the general public, and more specifically among target groups recommended by the European Union Health Security Committee (HSC) / Early Warning and Response System (EWRS) for the initial rounds of vaccinations: healthcare workers, risk groups with underlying conditions and pregnant women [2]. Availability of sound data on safety and effectiveness will also be of importance.

Vaccine composition

The composition of the authorised European pandemic vaccines differ significantly in conditions for virus propagation, antigen preparation, antigen content and whether they are adjuvanted or not (Table 1).

The vaccine strain in pandemic vaccines worldwide is based on the initial isolate of influenza A/California/7/2009 (H1N1)v or a reassortment based on the same isolated strain and a more fast-growing influenza A(H1N1) strain (PR8) which is called influenza A/California/7/2009 (H1N1)v-like. No significant genetic or antigenic drift has occurred since the virus first was isolated in April 2009, which is why these vaccines are expected to be effective against the pandemic waves expected in Europe this winter season. However, the ability of a pandemic influenza vaccine to evoke an immune response against drifted influenza viruses that are different from those included in the formulation would obviously be of major clinical value [3,4] - if such a drift should occur.

Due to limitations in vaccine supply worldwide in the case of a pandemic and the propensity of influenza viruses to antigenic drift, the World Health Organization encouraged development of vaccines with adjuvants when avian flu vaccines were developed. The term is derived from the Latin 'adjuvans' meaning 'to help'. Adjuvants have been used for many years in many vaccines with good effect. In influenza vaccines they can reduce the dose of antigen needed to produce the same immunological (protective) response and improve their ability to provide longer-lasting protection broad enough to cover many antigenic drifted variants. They work naturally by prolonging the exposure time of antigen to the immune system, enhancing the delivery of antigen to antigen-presenting cells, and

providing immunostimulatory signals that potentiate the immune response [5]. In the three current adjuvanted pandemic vaccines the oil-in-water adjuvants (squalene-based) and the aluminium phosphate adjuvant have allowed reduction of the haemagglutinin content per dose by a factor of between two and eight (7.5 µg to 1.875 µg /dose) compared to seasonal influenza vaccines (15 µg/dose) (see Table 1). Squalene is both a natural intermediate product of endogenous human cholesterol metabolism and a component of human cell membranes. It is constantly detected in human blood. It is also found in fish liver oil and vegetable oil (~0.7% in olive oil). When ingested, about 60-80% of squalenes are absorbed from the intestinal tract. The product for vaccine production is isolated from shark liver. There is already a large body of experience from their use in vaccines for humans. No safety concerns of clinical significance have arisen in more than 70 clinical trials with squalene-containing adjuvants. A seasonal influenza vaccine containing the MF59 adjuvant, Fluad, has been used since 1997 with over 40 million doses distributed. The MF59 safety database includes to this date information on more than 20,000 individuals [6]. The AS03 adjuvant contains two oils, squalene and DL-α-tocopherol (vitamin E), both with immunostimulating capacity. DL-α-tocopherol is a nutrient and the daily requirement for humans is 20-30 mg. The safety database for AS03 includes more than 10,000 individuals [personal communication GSK Biologicals].

Both squalene-based adjuvants, MF 59 and AS03, have been shown to induce more local or systemic reactions within three days of vaccination than non-adjuvanted vaccines but there are no major reactions reported [6,7].

The aluminium phosphate adjuvant has been used extensively in vaccines for the past 5-6 decades, and particularly in Hungary in the seasonal influenza vaccine, and has enabled the manufacturer to reduce the dose almost three-fold (see Table 1) [8].

One of the European pandemic vaccines is non-adjuvanted. This is an inactivated wild-type whole-virion vaccine. To reduce early experiences with seasonal influenza vaccines with increased reactogenicity seen with vaccines based on the whole-virion concept compared to split and subunit vaccines, current manufacturer have made a dose-reduction of the haemagglutinin from 15 µg to 7.5 µg per dose (see Table 1) and shown that they still provide a robust immune response [9-10].

Three pandemic vaccines contain thiomersal thiosalicylate (ethylmercury, containing 49.6% mercury per weight), a long-used mercury-containing preservative needed to maintain sterility in many vaccines during production and in their final injectable form. The pandemic vaccines contain thiomersal in varying concentration from 5 to 50 µg per dose (see Table 2). Mercury is commonly found as an environmental contaminant in foods, notably in fish and seafood, principally in the form of methylmercury. While exposure to methylmercury varies by country, intake estimates for European consumers are close to internationally established safe intake limits. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established a Provisional Tolerable Weekly Intake (PTWI) of 1.6 µg/kg body weight [11]. Acknowledging that there are different chemical forms of mercury: elemental, inorganic and organic, the conclusion is that in view of the recommendations for food products the total dose of thiomersal provided in one or two doses of pandemic vaccine is regarded to be of little significance and harmless to those vaccinated, which is also the experience from many years of its use in other vaccines [12-16].

Induced immunogenicity

The current European recommendation of two doses for the three centrally authorised vaccines (see Table 1) separated by at least three weeks are based on clinical trials with the avian flu vaccines when two doses were generally needed to achieve a good immunological response [17-19]. Initial reports on immunogenicity

TABLE 1

Overview of vaccines against pandemic influenza A(H1N1) available in the European Union in October 2009

Name, producer	Product description	Culture medium	Haemagglutinin-content	Adjuvant emulsion	Number of doses
Celvapan, Baxter	Inactivated, whole wild-type virus A/California/7/2009 (H1N1)v	Cell-culture	7.5 µg	None	All > 6 months 2 x 0.5 mL
Pandemrix, GSK	Inactivated, split-influenza, reassortant, A/California/7/2009 (H1N1)v-like strain	Egg-culture	3.75 µg (per adult dose)	AS03	>10 years 2 x 0.5 mL
			1.875 µg (per pediatric dose)		6 months – 9 years 2 x 0.25 mL
Focetria, Novartis	Inactivated, surface-influenza antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)v-like strain	Egg-culture	7.5 µg	MF59	All > 6 months 2 x 0.5 mL
Fluval P, Omniinvest	Inactivated, whole reassortant virus A/California/7/2009 (H1N1)v-like strain	Egg-culture	6 µg (per adult dose) 3 µg (per pediatric dose)	aluminium phosphate	Adults and adolescents > 12 years 1 x 0.5 mL Children 3-12 years 1 x 0.25 mL Children 6 months - 3 years* 1 x 0.25 mL (*decision pending)

using non-adjuvanted and adjuvanted pandemic vaccines from several companies have concluded that a single dose of pandemic vaccine provides an unexpectedly good immune response [20,21]. It is good news that the vaccine strain is so immunogenic and most probably provides rapid protective immunity in the majority of vaccinated individuals. Immunogenicity data from clinical trials using the current pandemic vaccines authorised in Europe will soon become available and if possible the Committee for Medicinal Product for Human Use (CHMP) at the EMEA will then consider whether to adjust the recommendations for all or specific age groups. However, it will be important to determine how long-lasting this immune response will be and EMEA has therefore so far taken a safe course of relying on the evidence from the clinical trials with avian flu vaccines that two doses are needed for a robust long-term immune response.

The long-term immune response will be followed closely in vaccinated individuals and if subsequently one dose is deemed enough to provide a sustained protective immunity at least in healthy adults, more vaccine doses will become available for populations currently not targeted for the initial vaccine doses. However, it is quite possible based on previous experience that young children, individuals with congenital or acquired immunodeficiencies and susceptible elderly will need two doses for obtaining a good long-term immune response that will protect them through the whole 2009-10 season.

One European manufacturer of pandemic vaccine (Omninvest, Hungary) recommends one dose to all age groups based on trials with the avian and H1N1 influenza vaccine (Table 1) [8,22].

Vaccine effectiveness

Immunogenicity does not directly reflect high effectiveness but with the use of specific pandemic vaccines against viruses that

are not drifted, vaccine effectiveness is expected to be good. In a pandemic context vaccine effectiveness data should be provided by age group, by number of doses received, and by vaccine brand. This requires very large sample sizes in order to produce reliable effectiveness data in time to contribute to the success of vaccination campaigns. Vaccine effectiveness will be studied on a European level through a project funded by the European Centre for Disease Prevention and Control (ECDC) involving study centres in ten countries (I-MOVE project, coordinated by a research group EpiConcept) [23]. These studies will be based on networks of physicians reporting influenza-like illness (ILI) cases undergoing laboratory testing for influenza. Manufacturers may also undertake separate studies of pandemic vaccine effectiveness as recommended by EMEA. They may use study protocols developed as part of the I-MOVE project and posted on ECDC web portal to improve comparability between studies [24,25].

Vaccine safety

The safety of the vaccines is of prime concern to the authorities and the public. The safety profiles already observed with seasonal and the human avian flu vaccines containing similar compounds including adjuvants will be applicable to the corresponding vaccines containing the influenza A(H1N1) 2009 pandemic strain and they have been well tolerated. The pandemic H1N1 vaccines from all European manufacturers used in the ongoing clinical trials in healthy children, adults and elderly have so far been well tolerated with only minor side effects. The authorised pandemic H1N1 vaccines undergo the same rigorous manufacturing oversight, product quality testing and lot release procedures that apply to seasonal influenza vaccines. EMEA has in its reviewing process evaluated all available published and unpublished safety data [26] for the three centrally authorised pandemic vaccines and so far has found no safety signals that might indicate an increased risk following the use of these vaccines.

At this stage longer-term safety data cannot be available and associations with very rare conditions can only be ruled out by careful post-marketing surveillance. This is always the case with new vaccines and medicines in general at the moment of their introduction. Those monitoring vaccine safety, will keep a special watch for increased incidence of Guillain-Barre syndrome (GBS). GBS is a rare condition and may be associated with several infections; campylobacter, influenza and Epstein-Barr virus [27]. GBS was observed with one crude A(H1N1) vaccine derived from an influenza of swine origin and used in the US in the 1976-7 influenza season. The observed attributable risk for all age groups in the six weeks after vaccination was around nine cases per million vaccines [28]. As the exact causal mechanism of this phenomenon has never been elucidated health officials worldwide will be on alert for reports of GBS this year. However, the overwhelming evidence, including the best study to date in Europe, points to no association of GBS with seasonal influenza vaccines, but instead a documented significant association of GBS with influenza infection itself [29].

Post-marketing surveillance is therefore crucial and will take a number of forms. The routine spontaneous pharmacovigilance system within EU Member States will continue and reports will be sent as usual to the EMEA Eudravigilance database. In addition manufacturers are required to send simplified periodic safety update reports (PSURs) to EMEA. These are usually required on a six-month basis but that has been reduced to monthly reporting. In addition, ECDC in collaboration with a consortium of researchers

TABLE 2
Overview of thiomersal and immunostimulating compounds* included in vaccines against pandemic influenza A(H1N1) available in the European Union in October 2009

	Thiomersal	Adjuvant emulsion
Celvapan, Baxter	No	None
Pandemrix, GSK	5 µg (per adult dose) 2.5 µg (per paediatric dose)	AS03 squalene* 10.69 mg α-tocopherol* 11.86 mg polysorbate 80 4.86 mg per adult dose; half the above amounts per paediatric dose
Focetria, Novartis	50 µg	MF59 squalene* 9.75 mg polysorbate 80 1.175 mg sorbitan trioleate 1.175 mg
Fluval P, Ominvest	50 µg (per adult dose) 25 µg (per paediatric dose)	aluminum phosphate 0.33 mg Al ³⁺ (per adult dose) 0.165 mg Al ³⁺ (per paediatric dose)

(VAESCO) are developing complementary vaccine safety monitoring and hypothesis testing through linkage of large computerised clinical databases and immunisation registries (<http://vaesco.net/internet/en/index.html>) [30].

As with many vaccines, several of the pandemic vaccines are being produced in formulations that contain thiomersal. Multiple analyses showed no increased risk of adverse events associated

TABLE 3

Recommendations and guidance of various bodies concerning priority groups / target groups for specific pandemic vaccines against pandemic influenza A(H1N1) 2009

Key contents from the three organisations	World Health Organization Strategic Advisory Group of Experts (7 July 2009)	United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (28 August 2009) Limited supply	United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (28 August 2009) Plentiful supply option	European Union Health Security Committee (25 August 2009)
General considerations and criteria for selecting the priority and target groups	'SAGE suggests the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions.'	'ACIP recommends that vaccination efforts should focus initially on persons in five target groups (below). In the event that vaccine availability is unable to meet initial demand, priority should be given to a subset of the five target groups (below).' No priority order between the categories below	'ACIP recommends that vaccination efforts should focus initially on persons in five target groups (below).' No priority order between the categories below	'It should be stressed that it is within the mandate and responsibility of Member States to develop a vaccination strategy for influenza A(H1N1) 2009.' No priority order between the categories below
Priority and target groups	Healthcare workers - all countries should immunise their healthcare workers as a first priority to protect the essential health infrastructure	Healthcare workers and emergency medical services personnel - who have direct contact with patients or infectious material	Healthcare and emergency medical services personnel	Healthcare workers
	Pregnant women - since this group appears to be at increased risk for severe disease.	Pregnant women	Pregnant women	Pregnant women
	Individuals aged >6 months with one of several chronic medical conditions - in order to reduce morbidity and mortality	Children and adolescents aged 5–18 years who have medical conditions that put them at higher risk for influenza-related complications	Persons aged 25-64 years who have medical conditions that put them at higher risk for influenza-related complications.	All persons from 6 months of age up with underlying chronic conditions - increasing the risk for severe disease, starting with the ones who have a severe underlying condition (e.g. severe asthma, unstable coronary heart disease, uncompensated heart failure, etc.)
	Healthy young adults (aged >15 years and <49 years) to reduce morbidity and mortality	Persons who live with or provide care for infants aged <6 months	Persons who live with or provide care for infants aged < 6 months (e.g. parents, siblings and daycare providers)	
	Healthy children	Children aged 6 months to 4 years	Persons aged 6 months to 24 years	
	Healthy adults aged >49 years and <65 years to reduce morbidity and mortality			
	Healthy adults aged >65 years to reduce morbidity and mortality			

with thiomersal-containing vaccines. Based on a recent review, Global Advisory Committee on Vaccine safety (GACVS) concluded that “there is no evidence supporting any change in WHO’s recommendations for thiomersal-containing vaccines” [31].

Risk benefit analyses and risk communication for making informed choices

Risk benefit analysis is more difficult than usual given an infection that has mild effect on most people but causes severe disease in some individuals, nevertheless it is clear that people in the target groups should be immunised including healthcare workers [32,33]. A European strategy for benefit-risk monitoring of the pandemic influenza A(H1N1) vaccine has been agreed upon by EMEA and ECDC. It is important that those being offered the vaccines are given clear guidance and information on the likelihood of them being affected by the pandemic influenza A(H1N1) 2009 virus and of experiencing severe outcomes to enable them to make informed choices. The most recent risk assessment from ECDC reports the experience from countries in the southern hemisphere temperate zone. These are countries that have experienced the first winter of transmission [33]. While it cannot be assumed that the experience in Europe will be identical they give the best broad idea of what can be expected [34]. In countries such as Australia, Chile and New Zealand clinical attack rates were not high. However, there were pressures experienced by primary care and hospital services, especially intensive care units [35,36]. The demand on secondary and higher levels of care have mostly, though not entirely, come from sick people from the risk groups (Table 3). Hence the emphasis on these groups recommended by the European Union Health Security Committee (HSC) / Early Warning and Response System (EWRS) [2,37]. Individuals with chronic underlying diseases are at greater risk of developing severe disease. Among the hospitalised and fatal cases, 60-70% suffer from some underlying condition [38]. Estimates for case fatality rates are under 0.1% but it is still expected that most pandemic influenza-associated deaths will be in younger adults (those under the age of 60 years) [36]. This estimated case fatality rate is lower than seen in any of the 20th century pandemics. It should be mentioned here that 12-22 deaths per week have been observed in EU and EEA Member States since 1 September 2009.

Among healthy individuals, pregnant women and young children are at greatest risk of severe disease [39]. In the US the estimated rate of admission to hospital has been four to five times higher in pregnant women than in the non-pregnant women general population (0.32 per 100,000 pregnant women, 95% CI 0.13 – 0.52 vs 0.076 per 100,000 population at risk, 95% CI 0.07-0.09). Whether the risk of severe disease increases with gestational age, as it does for seasonal influenza, is not known yet [40]. Providing vaccines to pregnant women will also protect their infants through maternal antibodies as these children cannot be immunised until six months of age. The description of the first fatal case series in children has been published in the US and it is expected that this information will inform parents’ decisions [41]. Similarly to cases in adults, chronic underlying conditions were a risk factor and only a third of the children who died had previously been healthy.

These kinds of data are not yet available from Europe and apart from the above US study concerning pregnant women, more analyses are necessary to answer the questions EU citizens offered vaccination will reasonably ask: If I am affected what is my risk of going into hospital or dying from the infection? What is the risk for my asthmatic son? My handicapped sister? My elderly father? We

also need to be sure that the risk groups are the same for Europe as they are for North America and the southern hemisphere [42].

The overall picture is complicated by the fact that although there are some healthy people who experience severe disease in this pandemic (usually they constitute up to 30% of a series of severe cases) the indications are that most of those infected will experience a mild self-resolving disease. Hence the challenge for those promoting vaccination to healthy people is considerable. They have to convey that if healthy adults and children are infected they will most likely not get very ill, however, at the same time there is a small risk of severe disease or even death. For healthcare workers it is important to ensure that vaccines are readily available and to remind them of their responsibility not to infect their much more vulnerable patients [43].

Vaccination scares

With the implementation of the vaccination campaigns there will be vaccine scares because of coincidence alone, i.e. temporal but not necessarily causal association [44]. For example with the average background incidence of GBS of 1-2 cases per 100,000 population per year it can be expected that in a country of 20 million inhabitants 200-400 cases of GBS per year or four to eight cases per week are registered [45]. If some of these cases occur in temporal proximity to vaccination, concerns may be raised about the association with the vaccine. Special challenges for safety surveillance are related to the fact that some of the groups being immunised initially, such as pregnant women and people with chronic illnesses, are anyway more likely to experience complications including spontaneous abortion or reactivation of the chronic disease. Proper and timely investigation of suspected cases and rapid assessment will be crucial. From recent experience, for example with the HPV vaccines, it can be expected that once proper investigations are undertaken the scares will most often turn out to be the result of coincidence not causation. However that will not be assumed and plausible (and probably some non-plausible), observed associations will be investigated and tested. One attractive prospect of European added value is that observations and a hypothesised relationships from one country can be tested in several other countries enlarging the sample size to test and data may be shared.

Vaccine availability and delivery

The newly authorised pandemic vaccines are now available to European populations. The challenging problem is that much of the manufacturing capacity is already spoken for through advance purchasing contracts held by some but not all European countries. In addition, vaccines will be produced gradually, so initially there will be a limited supply of vaccine doses in Europe and elsewhere. Prioritisation activities have therefore been viewed necessary.

Several governmental and other official organisations worldwide have provided guidance or recommendations on who should be offered vaccine first [46] (Table 3). The priority groups identified in the Table should serve as indication only and countries may wish to adapt, and some have already done so, the prioritisation in line with their epidemiology, health service provision and resources. All organisations have listed healthcare workers, pregnant women and persons with underlying medical conditions as the first three priority groups. These groups were also agreed on by EU Member States through the Health Security Committee (HSC) and Early Warning and Response System (EWRS) [2]. Vaccinating people with chronic

conditions will be difficult in countries where primary care services do not maintain ready lists of such individuals.

The World Health Organization has asked wealthy countries to help poorer ones to purchase limited amounts of these vaccines – cost should not be a barrier to access. A number of the best provisioned European countries and vaccine manufacturers have stated that they would make available vaccine doses to WHO for further distribution. What will be equally challenging is the distribution of vaccines within Europe. Risk will be distributed more evenly than supply. Seasonal influenza vaccines are used very unevenly in Europe. For example, vaccine coverage among people aged 65 years and older varies 40-fold on a per capita basis [47]. If only single doses are needed after review of immune responses to the various vaccines then there will be reasonable expectations that countries ordering late may be able to purchase vaccines from countries that ordered early in large volumes. This possibility was envisaged at the extraordinary EU Health Council under the Swedish Presidency on 12 October [48]. There are contractual and liability barriers that will need to be solved but it should be hoped that the sharing of influenza vaccines will show a good example of European added value.

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INTERFERENCE BETWEEN OUTBREAKS OF RESPIRATORY VIRUSES

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To the editor: Norway, like several other European countries, has experienced a delay in the expected outbreaks with pandemic H1N1 influenza. In a recent paper from Sweden it has been postulated that this delay, at least partly, was caused by interference with other respiratory viruses. This view is supported by the fact that a relatively high rhinovirus activity was registered in late summer and early autumn in Sweden [1].

St. Olav's University Hospital in Trondheim, Norway has for several years conducted extensive laboratory surveillance of respiratory viruses including rhinoviruses. The Figure shows the rhinovirus infections diagnosed in Trondheim in the past three years. An increase in diagnosed rhinovirus infections was observed during late summer and early autumn in 2007 and during autumn 2009.

Compared with the complex and enveloped influenza virus particle, rhinoviruses may have advantages at times of the year when the climatic conditions are suboptimal for respiratory viruses. Thus, if the interference theory is correct, rhinoviruses will usually not have any competition with other respiratory viruses during late summer and early autumn, and the interference effect will be obscured. On the other hand, if a competing virus is introduced,

the interference activity will be apparent in a delayed outbreak development. As an illustration of this, pandemic H1N1 influenza virus was first diagnosed at St. Olav's Hospital in May 2009, and although a little peak in influenza cases was observed near the end of July 2009, only 5-10% of specimens from patients with influenza-like illness have tested positive for pandemic H1N1 influenza virus. The great majority of these patients were infected with rhinoviruses and to a lesser extent with parechovirus.

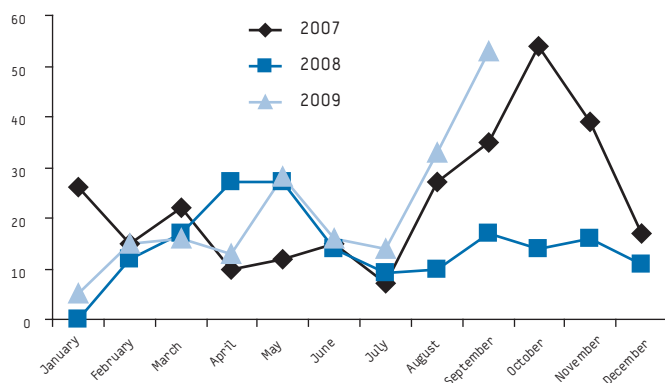
Greer *et al.* observed that co-infections with rhinoviruses and other respiratory viruses were more uncommon than expected, indicating that rhinovirus infection may render the host less likely to be infected with other viruses [2].*

Based on observations in Norway, epidemiological interference between several epidemic viruses including influenza virus has been suggested [3-5]. The present observations may lend some further support to this hypothesis.

*Author's correction: On request of the authors, the number of rhinovirus infections in September 2009 was corrected in the figure on 21 October 2009, and one sentence was added introducing a new reference.

FIGURE

Laboratory-confirmed rhinovirus infections, January 2007-September 2009, Trondheim, Norway (n=646)*



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