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

E Depoortere (depoortere@ecdc.europa.eu)¹, J Mantero¹, A Lenglet¹, P Kreidl¹, D Coulombier¹

1. European Centre for Disease Prevention and Control, Stockholm, Sweden

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. 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. Interpretation 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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Rapid communications

SHIGELLA SONNEI INFECTIONS IN NORWAY ASSOCIATED WITH SUGAR PEAS, MAY – JUNE 2009

B T Heier (BeritTajford.Heier@fhi.no)¹, K Nygard¹, G Kapperud¹, B A Lindstedt¹, G S Johannessen², H Blekkan³

1. Nasjonalt Folkehelseinstitutt (Norwegian Institute of Public Health), Oslo, Norway

2. Veterinærinstituttet (National Veterinary Institute), Oslo, Norway

3. Mattilsynet (Norwegian Food Safety Authority), Oslo, Norway

In May 2009, the Norwegian Institute of Public Health (NIPH) identified a possible outbreak of *Shigella sonnei* infection involving four cases. Additionally, five suspected cases in two separate households were reported. Inspectors from the Norwegian Food Safety Authority (NFSA) visited the two households and found an unopened package of sugar peas imported from Kenya in one of the households. One sample from the sugar peas was positive for *Shigella sonnei* by two PCR methods. Based on this result and information from patient interviews, the NFSA prohibited all sales of sugar peas imported from Kenya.

Introduction

In Norway, shigellosis is a mandatorily notifiable disease, and all isolates are submitted to the NIPH for verification and typing. Around 150 cases of shigellosis are confirmed per year, the majority caused by *Shigella sonnei*. Only around 10 to 20 of the shigellosis cases reported each year are acquired in Norway, usually as secondary cases caused by faecal-oral transmission in households.

On 27 May 2009, the National Reference Laboratory at the NIPH alerted about a suspected outbreak involving four cases of *Shigella sonnei* infection. The infected persons were living in two different counties in Norway, and they had no foreign travel history during the week before onset of illness. On the same day, a municipal medical doctor reported to the NIPH five suspected cases of shigellosis in two separate households.

Methods

Epidemiological investigation

An outbreak investigation was initiated on 27 May by interviewing the four confirmed cases using a trawling questionnaire. On the same day the NFSA inspectors visited the two households where suspected cases were reported and found an unopened package of sugar peas imported from Kenya in one household, and the packing of the same brand of sugar peas in the other. The sugar peas were bought in the same shop. Based on this suspicion, it was decided to focus the interviews on consumption of fresh vegetables and lettuce.

Microbiological investigation

All suspected human *Shigella* isolates received at NIPH are routinely verified, speciated and typed with multilocus variable-number tandem-repeat analysis (MLVA) using a protocol developed by BA Lindstedt et al. (manuscript in preparation). Isolates of

Shigella sonnei showing a distinct MLVA-profile were defined as the outbreak strain. Food samples were analysed at the National Veterinary Institute first by using NMKL no. 174 (*Shigella* spp. PCR method for detection in food), followed by immuno-magnetic separation (IMS) and plating on selective agar. Positive PCR results were confirmed by using a modified version of an octaplex PCR developed for identification of human diarrheagenic *Escherichia coli* and *Shigella* spp. [1]. Any isolates obtained from food samples would be MLVA-typed at NIPH to compare with the patient isolates.

Results

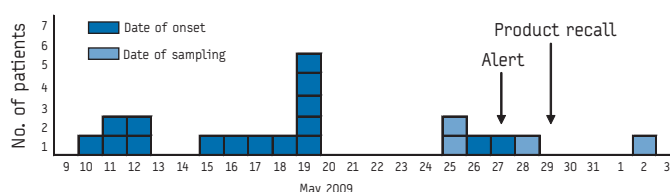
By 16 June, the reference laboratory has registered a total of 20 cases with the outbreak strain of *Shigella sonnei*, who had not travelled abroad prior to illness onset. The cases live in different municipalities, but mainly in the central and western parts of Norway. The date of onset for the first case was 10 May (Figure). All cases were adults except for one teenager, and 16 of them were women. All 20 cases reported to have eaten sugar peas, and there were no other obvious common exposures identified. The majority of the patients had bought the sugar peas in one of the large supermarket chains and only a few in another chain. The NFSA traced the suspected food product and found that all the implicated sugar peas were produced in Kenya. One sample from the unopened package of sugar peas collected in a patient household was positive for *Shigella sonnei* by both PCR methods, but could not be culture-confirmed.

International alerts

On 27 May the NIPH sent an urgent inquiry through the European Food and Waterborne Diseases Network at the European Centre for Disease Prevention and Control (ECDC) asking whether an increase

FIGURE

Cases of *Shigella sonnei* in an outbreak in Norway in May 2009, by date of illness onset or date of sampling (n=20)



in the number of *Shigella sonnei* cases had been registered in other countries. On the same day, the NFSA sent an information notice through the European Rapid Alert System for Food and Feed (RASFF). Based on information from the interviews, the main importer voluntarily recalled the product on 29 May. Further results from tracing of the food product and preliminary results from the microbiological investigation led the NFSA to prohibit all sales of sugar peas imported from Kenya later the same day.

Discussion

As a response to our urgent inquiry Denmark reported an increase in the number of domestic *Shigella sonnei* infections in April and May 2009. They initiated an outbreak investigation to find out if the Danish cases were related to the outbreak in Norway. The investigation in Denmark also pointed at sugar peas as the source of the outbreak, and microbiological investigations (including MLVA typing) to compare the outbreak strains are ongoing.

The trace-back investigation of the food product appeared to be very complicated, and the NFSA is still investigating together with the industry. Several whole-sellers are supplying sugar peas to Norway, and the product comes from several producers in Kenya. The two supermarket chains usually do not share the distribution system, but on some occasions they are supplied by the same whole-seller.

Only one previous outbreak in Norway has been associated with fresh vegetables. An increase in the number of domestic cases of *Shigella sonnei* infection was detected in several European countries in 1994, including Norway, Sweden and the United Kingdom [2]. In Norway 110 culture-confirmed cases of infection were recorded at the time. In all three countries epidemiological evidence incriminated imported iceberg lettuce of Spanish origin as the vehicle of transmission. The pathogen was not isolated from the suspected food product.

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Rapid communications

IMPORTED FRESH SUGAR PEAS AS SUSPECTED SOURCE OF AN OUTBREAK OF *SHIGELLA SONNEI* IN DENMARK, APRIL – MAY 2009

L Müller (lum@ssi.dk)¹, T Jensen², R F Petersen³, K Mølbak¹, S Ethelberg^{1,3}

1. Department of Epidemiology, Statens Serum Institut (Danish National Institute of Health, SSI), Copenhagen, Denmark

2. Fødevarestyrelsen (Danish Veterinary and Food Administration), Copenhagen, Denmark

3. Department of Bacteriology, Mycology and Parasitology, Statens Serum Institut (Danish National Institute of Health, SSI), Copenhagen, Denmark

We report on an outbreak of *Shigella sonnei* infections involving ten cases notified through the laboratory surveillance system in Denmark in April and May. The likely source was consumption of fresh, raw sugar peas (sugar snaps) imported from Africa. This conclusion was based on interviews with cases and on the occurrence of a similar outbreak one month later in Norway. Fresh imported produce may occasionally be contaminated with pathogenic bacteria even when sold as ready-to-eat.

Introduction

On 27 May 2009 Norway sent an urgent inquiry through the European Food and Waterborne Diseases Network at the European Centre for Disease Prevention and Control (ECDC) reporting an increase in the number of *Shigella sonnei* cases. By 1 June Norway informed that they suspected the source to be sugar peas. As an increase in the number of *Shigella sonnei* cases was also observed in Denmark in April and May 2009, we initiated an outbreak investigation to find out if the Danish cases were related to the Norwegian outbreak.

Methods

All laboratory-confirmed *Shigella sonnei* cases since 1 April (Figure 1) were interviewed by telephone about date of onset,

symptoms, travel history, consumption of sugar peas and a small set of other exposure variables. Previous data on sugar peas consumption in the background population was reviewed. Isolates were subjected to typing by Pulsed Field Gel Electrophoresis (PFGE) using the enzyme XbaI. Sugar peas sold in three major groups of supermarket chains were traced back.

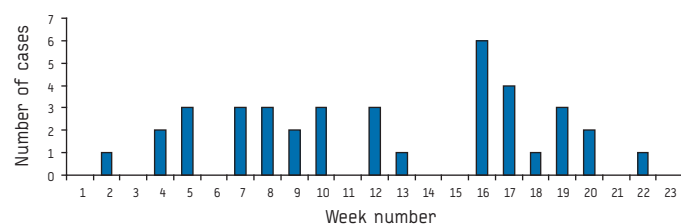
Results

In all, 17 cases of *Shigella sonnei* were reported from 1 April to 1 June 2009. Six cases were travel-related and one was linked to another known outbreak caused by fresh large shrimps from Bangladesh. Of the remaining ten cases, eight reported having eaten sugar peas prior to onset of symptoms. Of these eight cases all were female and their median age was 31 years (range 11-46 years). None had travelled abroad, except for short trips to Sweden before getting ill. The dates of onset of illness ranged from 7 April to 8 May. The two additional cases could be related to the outbreak as likely secondary cases as they were children of one of the cases who had eaten sugar peas. The two children fell ill three weeks after their mother.

A case-control study was not performed; instead, previous food-borne outbreak investigations were reviewed. Consumption of sugar

FIGURE 1

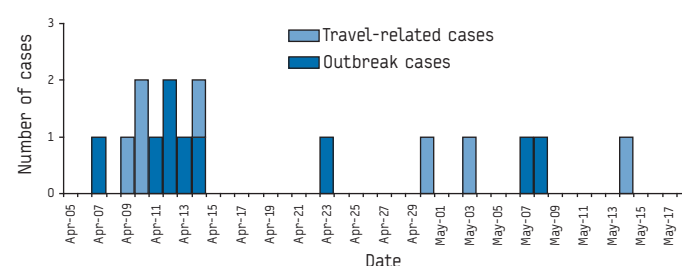
Number of laboratory-confirmed cases of *Shigella sonnei* in Denmark in 2009, by week of the sample arriving in the laboratory (n=38)



Note: The six cases in week 16 generated a signal (which appeared in week 19) in the automated outbreak algorithm which is run every week in Denmark.

FIGURE 2

Number of laboratory-confirmed cases of *Shigella sonnei* in Denmark, in April and May 2009, by date of disease onset (n=16*)



* One case (associated with the outbreak caused by consumption of sugar peas) could not state the date of onset of symptoms and is therefore not included

peas is among the questions included in several of the commonly used trawling questionnaires in Denmark. We looked into three different rounds of trawling questionnaire 'studies' performed among cases of a large outbreak of *Salmonella* Typhimurium U292 [1]. They were done in April, May and August 2008. In these studies 3/10, 2/17 and 0/15 cases reported consumption of sugar peas in a period of seven days prior to illness. This crude comparison indicated to us a significant association between *Shigella sonnei* infections and consumption of sugar peas (using the persons interviewed in April and May as community controls, comparing 8/8 exposed cases to 5/27 exposed controls, gives a Fisher p-value of < 0.0001).

Preliminary PFGE typing results of isolates from five of the 10 cases associated with sugar pea consumption suggest highly similar patterns. The PFGE patterns of the isolates from Danish patients resemble those obtained from the Norwegian patients but it is still too early to say if they are identical. Further typing results (which will include multilocus variable-number tandem-repeat analysis - MLVA typing) and comparisons between isolates from Denmark and Norway are pending.

The cases were generally able to recall in detail the type of product they had consumed and in which shop they had bought it. Six of the 10 cases associated with the outbreak reported buying sugar peas in supermarkets sharing in part the same distribution systems. Trace-back investigation of the sugar peas showed that they had been bought from a single whole-seller in the Netherlands and that they were of three different varieties which can be distinguished by their shapes, namely *sugar snaps*, *sugar peas (snow peas)* and *mange touts*. They originated predominantly from Kenya (from four different farms), but other batches sold in the same period came from Ethiopia and from Guatemala. The Dutch whole-seller was different from the one that supplied sugar peas to Norway. The two remaining cases may have bought their sugar peas in another group of supermarket chains which in part shares distribution systems with the supermarkets that sold the incriminated sugar peas in Norway. Further investigation into the origin of the sugar peas sold in this chain during April is still ongoing. There were no remains of the batch of sugar peas under suspicion and therefore microbiological analysis was not performed. Laboratory results from samples taken from later batches in two of the supermarket chains did not reveal contamination by either *Shigella* spp. or *Escherichia coli* (as indicator for faecal contamination).

Discussion

The investigation points at sugar peas as the source of this outbreak. The Danish and the Norwegian outbreaks do not appear to have been caused by the same type of peas, the batch of sugar snaps that was likely contaminated in Denmark was different from the one imported into Norway and also the Danish outbreak occurred one month earlier than the Norwegian outbreak. It is possible, though, that both outbreaks may have been a result of the same contamination event in Kenya; further investigations may cast light on this.

Outbreaks with a high ratio of females among cases may often point to fresh produce as the source. Only one previous outbreak in Denmark has been associated with sugar peas, an outbreak of *Shigella flexneri* in 2002 in which the epidemiological evidence pointed towards fresh imported sugar snaps of African origin (unpublished). Other fresh tropical vegetables which were eaten raw, have also caused outbreaks of shigellosis in Denmark, most

notable were two *Shigella sonnei* outbreaks in 2007 [2,3] and one in 1998 [4] both caused by baby corn imported from Thailand.

This outbreak underlines that some fresh vegetables imported into Europe from tropic destinations may pose a food safety hazard. In Denmark fresh imported sugar snaps are sold as a ready-to-eat product. Consumers should be aware that these types of products may pose a risk of microbiological contamination. The sugar snaps will remain crispy after being blanched or boiled shortly and it may be advisable for consumers to heat-treat fresh vegetables of this type before consumption.

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Rapid communications

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

Surveillance Group for New Influenza A(H1N1) Virus Investigation in Italy^{1,2,3,4}

1. Department of Infectious, Parasitic and Immune-mediated Diseases, National Institute of Health (Istituto Superiore di Sanità - ISS), Rome, Italy
2. Department of Veterinary Public Health and Food Safety, National Institute of Health (Istituto Superiore di Sanità - ISS), Rome, Italy
3. Regional laboratories with confirmed cases
4. Ministry of Health, Rome, Italy

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 1

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

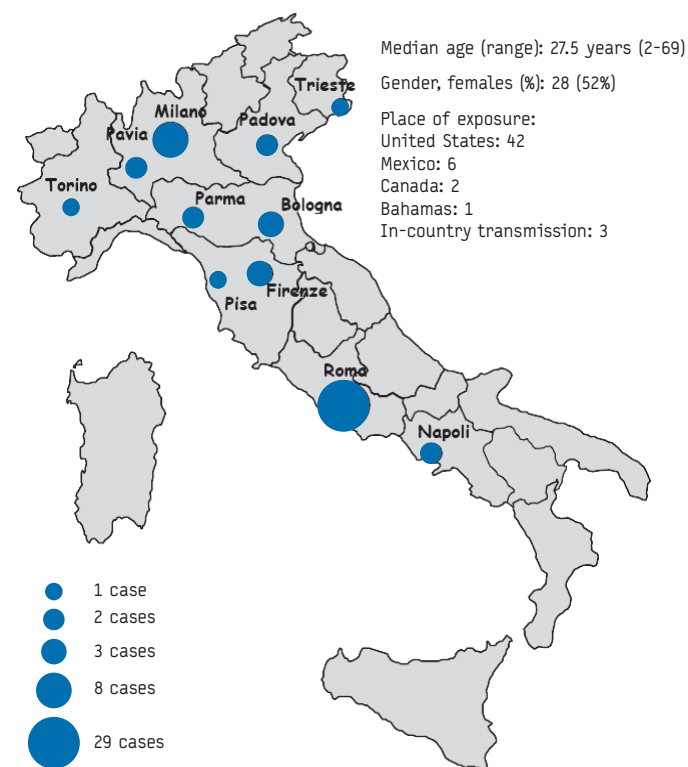


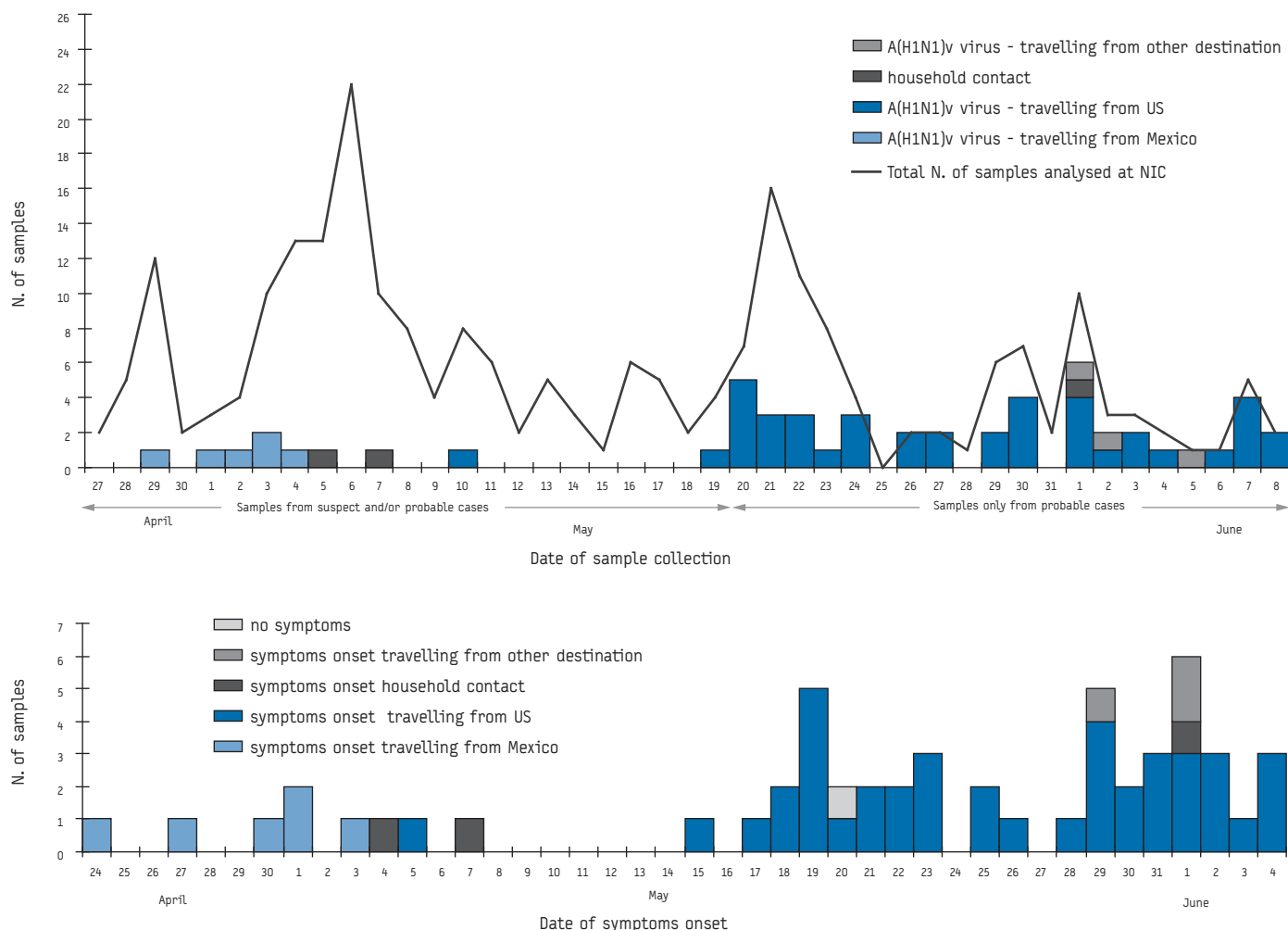
Figure 2a shows the distribution of all samples analysed and the laboratory-confirmed cases by day of sample collection, whereas Figure 2b shows the distribution of cases by day of symptoms onset and travel history. The median age of the patients was 27.5 years (Figure 1), ranging from 2 to 69 years, 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 MGB-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 basis of the sequence analysis of the final amplification M fragment

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



(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

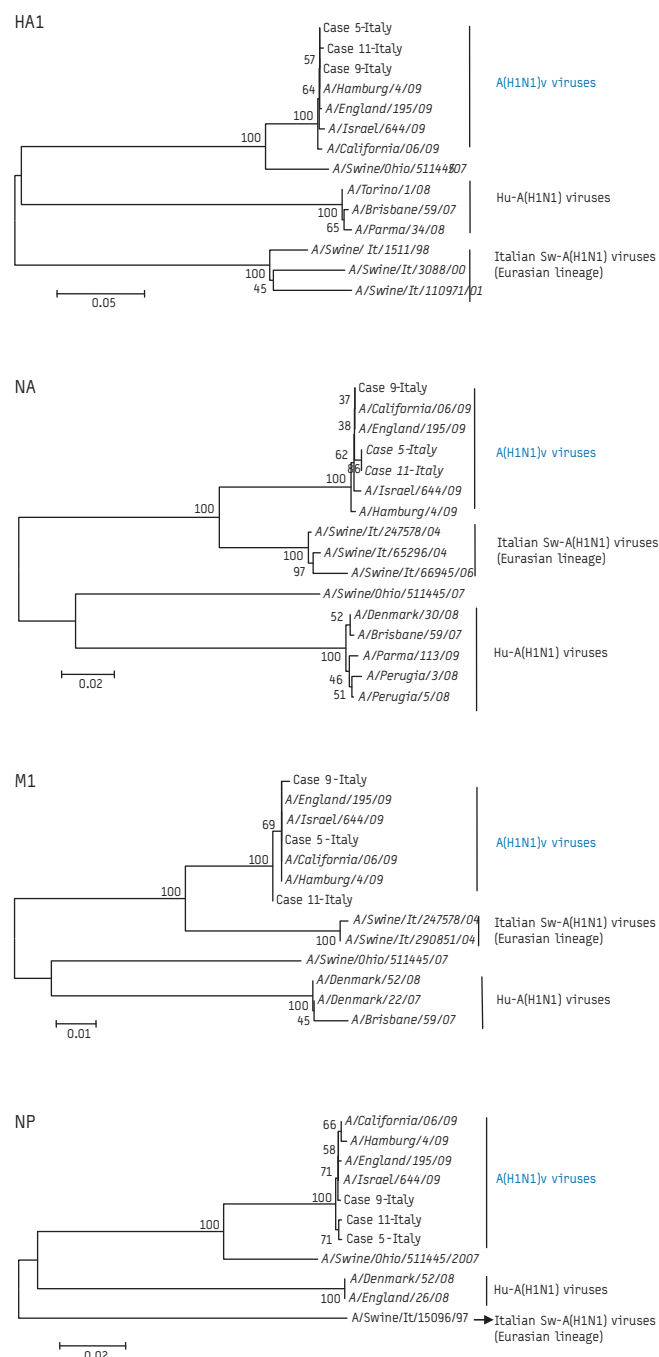
The sequence analyses of the NA and M genes, respectively, revealed that the above mentioned three A(H1N1)v virus isolates were resistant to adamantanes and sensitive to both neuraminidase inhibitors (oseltamivir and zanamivir).

Discussion

During a period of over one month between 27 April and 10 June, 54 laboratory-confirmed cases of influenza A(H1N1) v virus infection were identified in Italy. With the exception of

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

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.

List of contributors

National Institute of Health (Istituto Superiore di Sanità - ISS): S Puzelli¹, M A De Marco¹, A Ruggieri¹, M Facchini¹, M Laura Pasqua¹, A Di Martino¹, A Palmieri¹, C Fabiani¹, L Calzoletti¹, D Spagnolo¹, T Grisetti¹, S Boros¹, M Equestre¹, G Vaccari², L Di Trani², A Cassone¹, G Rezza¹, I Donatelli¹.

Regional Laboratories: City (number of confirmed cases; name of the Director): Pisa (1; L Ceccherini Nelli), Rome-IRCSS (20; M Capobianchi), Rome-Catholic University (9; G Fadda), Florence (3; A Azzi), Milan (8; A Zanetti), Pavia (2; F Baldanti), Trieste (1; C Campello), Naples (2; C Esposito), Parma (2; M L Tanzi), Bologna (3; V Sambri), Padua (2; G Palù), Turin (1; V Ghisetti).

Ministry of Health, Rome: M G Pompa.

Acknowledgements

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Rapid communications

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

T Shimada (tomoesh@nih.go.jp)¹, Y Gu¹, H Kamiya¹, N Komiya¹, F Odaira¹, T Sunagawa¹, H Takahashi¹, T Toyokawa¹, Y Tsuchihashi¹, Y Yasui¹, Y Tada¹, N Okabe¹

1. Infectious Diseases Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan

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:

- a) within the last seven days returned from a country or region with an epidemic of influenza A(H1N1)v;
- b) was in close contact (within two meters) with a confirmed case within the past seven days;
- c) 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 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.

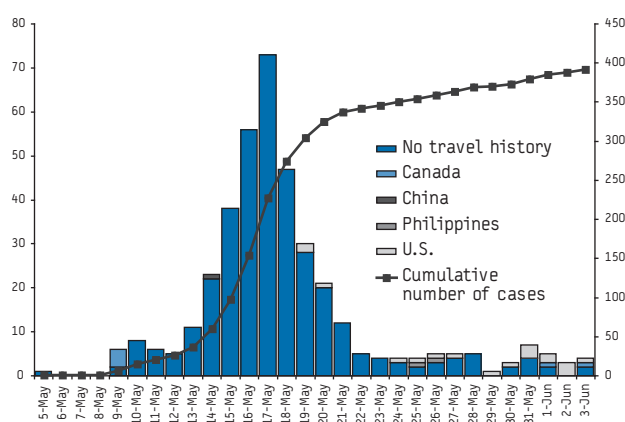
None of the sick high school pupils in Ibaraki had travel history to the countries affected by the new influenza. On 16 May, five teenagers were confirmed with influenza A(H1N1)v virus infection: one from the school in Ibaraki in Osaka prefecture, and four from Kobe City in the neighbouring Hyogo prefecture. 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

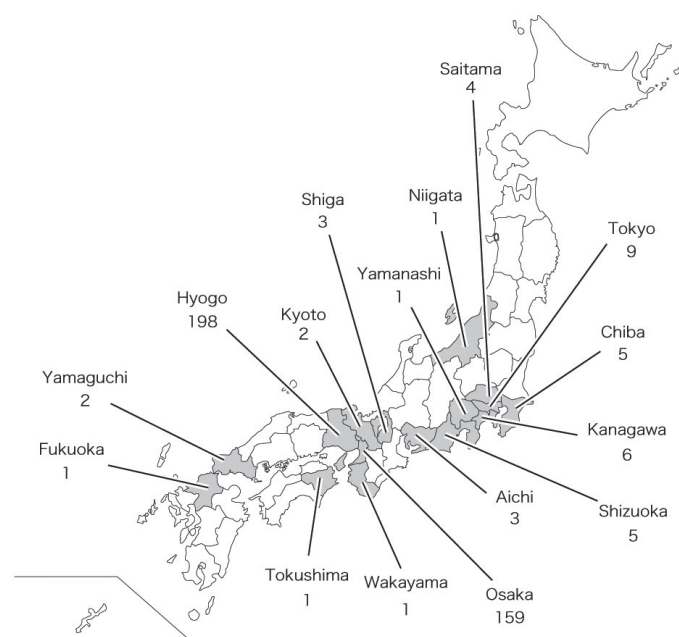
Confirmed cases of influenza A(H1N1)v virus infection in Japan, by date of onset and cumulative number as of 4 June 2009 (n=392*)



* 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)

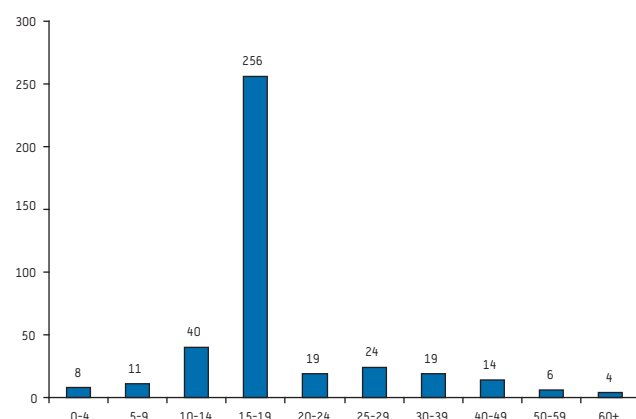
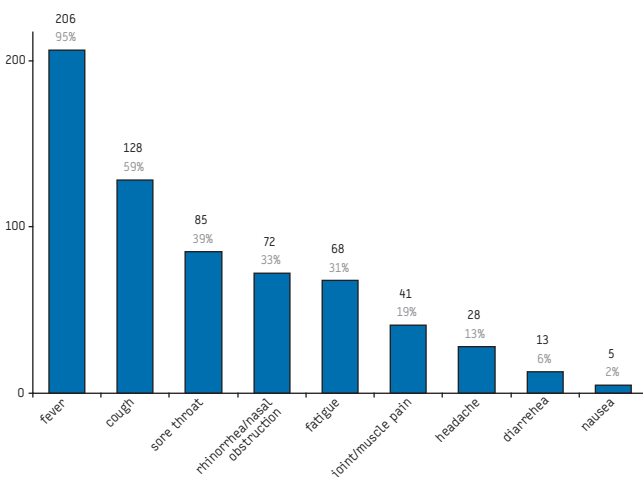


FIGURE 4

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

V Sypsa¹, A Hatzakis (ahatzak@med.uoa.gr)¹

1. Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, Athens, Greece

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

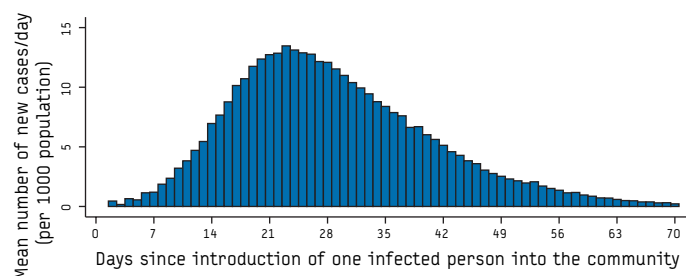
The effect of the intervention strategies is shown in Figure 3 and Table 6.

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

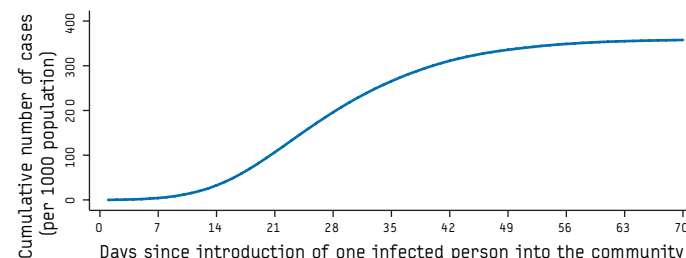


FIGURE 2

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

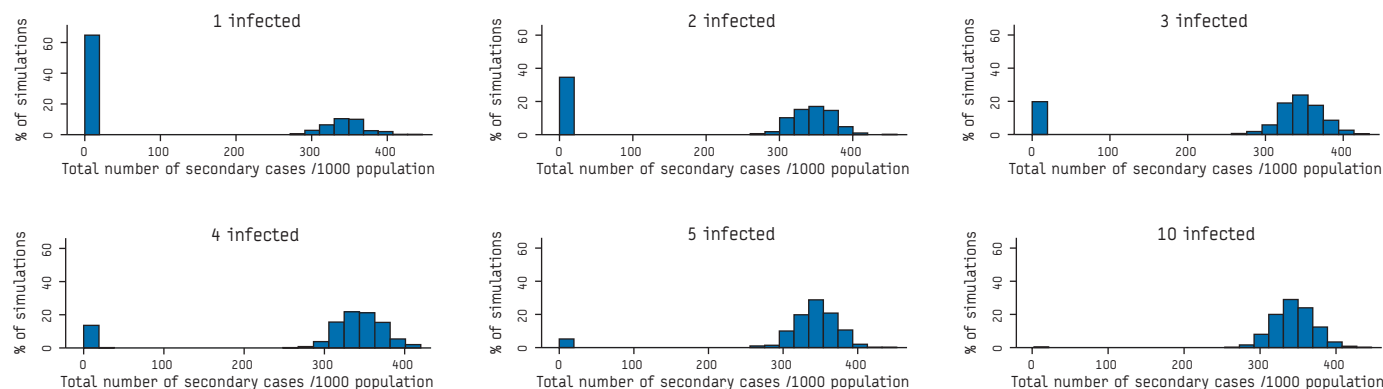
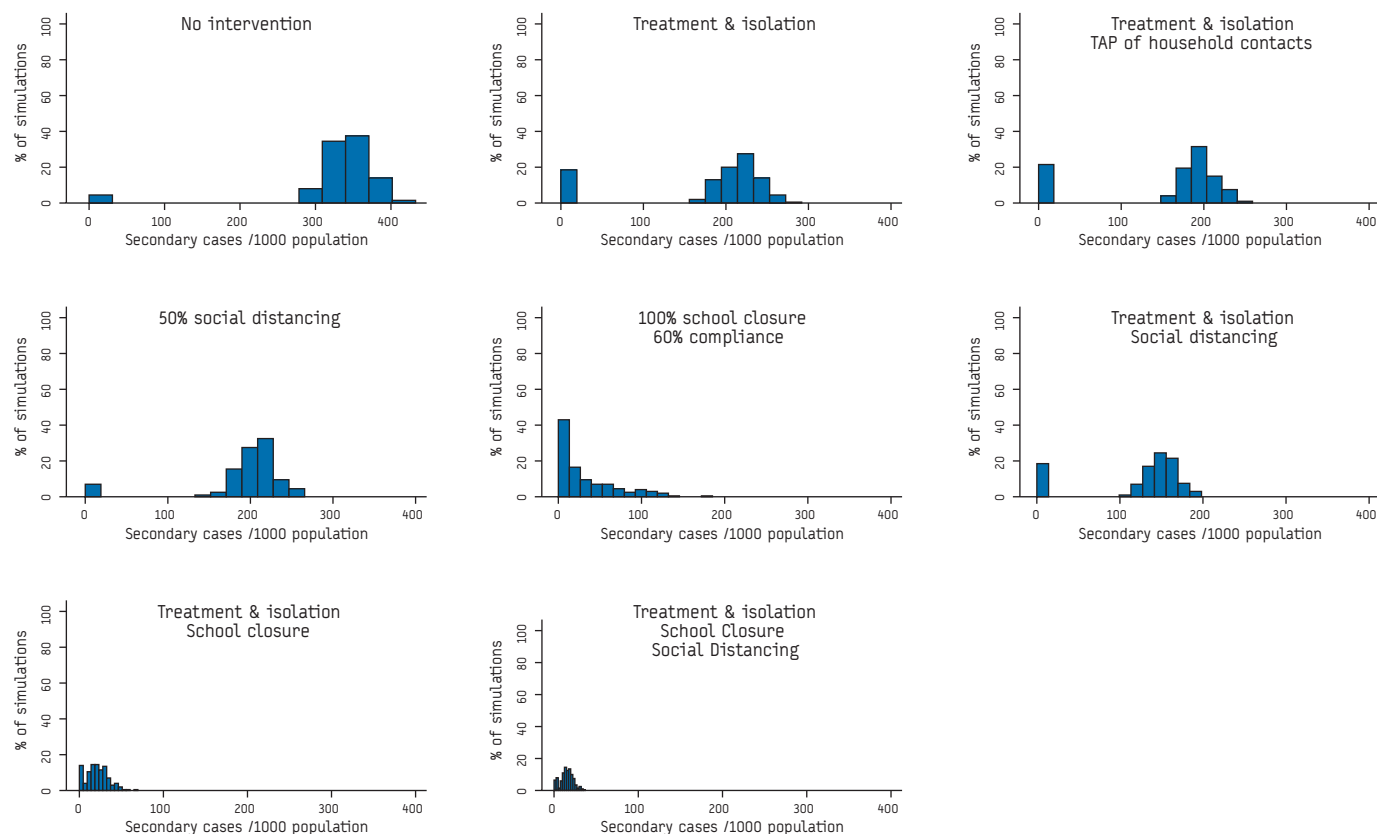


FIGURE 3

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

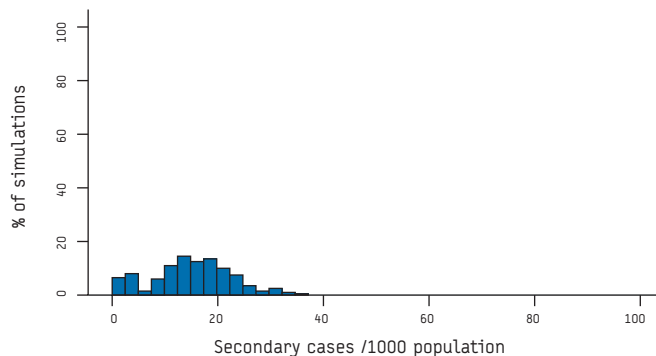
* The average estimates were computed over 200 simulations independently of whether an outbreak occurred or not.

TAP: Targeted antiviral prophylaxis of household contacts.

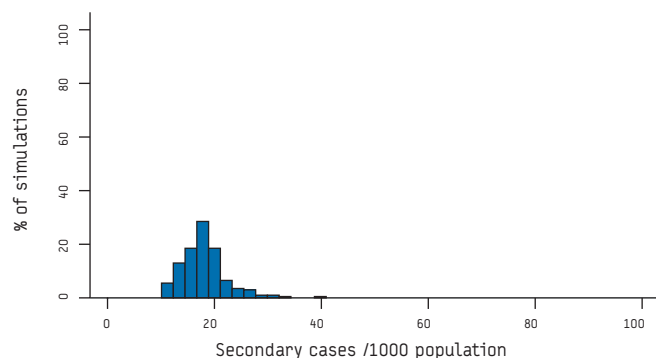
FIGURE 4

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)

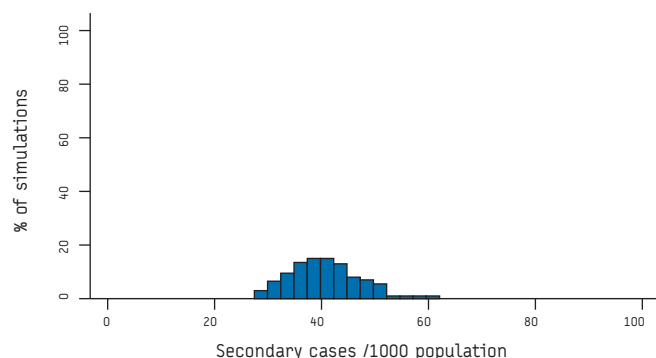
A) Five infected individuals initially seeded into the population



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.

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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

P Föllin (per.follin@vgregion.se)¹, A Lindqvist¹, K Nyström¹, M Lindh²

1. Department of Communicable Disease Prevention and Control, Region Västra Götaland, Sweden

2. Department of Virology, Sahlgrenska University Hospital, Gothenburg, Sweden

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.

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

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	TGACAGTGACACTCTGTCAACCTACTTGAG
IAH3_F	GCAACTGTTACCCCTTATGATGTGC
IAH3_R	CATTGATAAACTCCARRGTGCKGA
IAH3_Probe	ATGCCTCCCTTAGGTCAGTGTGCCTC
IAH1v_F	GGGGTAGCCCCATTGCATT
IAH1v_R	GTGGAGAGTGATTCACACTCTGGA
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.

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.

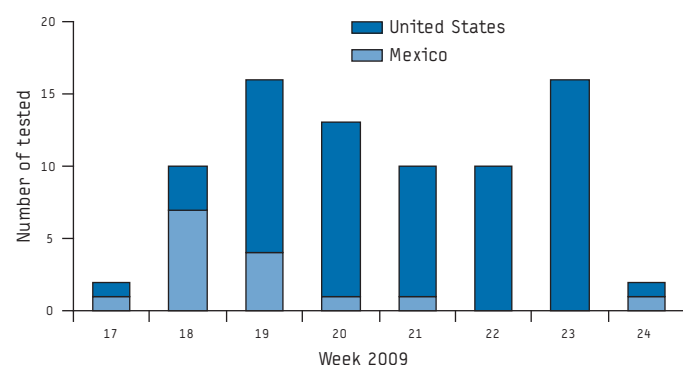
The results of the multiple PCR used in our setting were available within 24 hours after sampling and served at the same time as confirmation for the result of the first, general influenza A PCR. In cases that presented with typical influenza-like symptoms but were negative for influenza A in the first 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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INVITATION TO BECOME PART OF THE EUROPEAN TRAVEL MEDICINE INVENTORY

P Schlagenhauf (review@eurotravnet.eu)¹, F Santos O'Connor², P Parola³

1. The European Travel Medicine Network (EuroTravNet), Zurich, Switzerland

2. European Centre for Disease Prevention and Control, Stockholm, Sweden

3. The European Travel Medicine Network (EuroTravNet), Marseille, France

The European Travel Medicine Network (EuroTravNet) [1] is a European Centre for Disease Prevention and Control (ECDC) [2] network initiated by the International Society of Travel Medicine (ISTM) [3]. It sets out to create a network of clinical experts in tropical and travel medicine and is funded through a public ECDC tender "Travel Medicine in Europe: existing structures, functions and added-value of ECDC. Building a network to support Travel and Tropical Medicine related activities at ECDC" [4]

One of the core tasks of the network is to establish a European inventory of travel medicine providers and resources. The initial step is to create a country by country listing of individuals, practices and institutions involved in the provision of travel medicine. The data collection process has now started and any travel health practitioner in a European Union (EU), European Free Trade Association (EFTA) or EU candidate country can add his or her details by using a quick, easy to access, on line questionnaire, available from: www.surveymonkey.com/s.aspx?sm=t3HkKANexJxKme6ap7GBUg_3d_3d [5]. The brief survey consists of 10 questions which focus mainly on the type of travel health services provided by the respondent, such as pre- or post-travel consultations, yellow fever vaccination, screening and research. Migration medicine is very important in many EU countries and parts of the questionnaire will collate data on European institutions with particular expertise in migrant health.

All health professionals including tropical medicine specialists, nurses, physicians, pharmacists and scientists involved in travel medicine can be included. The advantage is that, in the future, this resource listing will be used to network interest groups and to disseminate information relating to tropical and travel medicine. The inventory is the property of ECDC will not be used for advertising.

At a later stage, the inventory aims to provide an overview of travel medicine services for specific indications in the pre-travel setting and of products such as vaccines and anti-malarials that are used in EU and EuroTravNet Member States. This future aim, is challenging in view of European heterogeneity and varying national guidelines and practices.

To achieve our goals and be able to provide a dynamic overview of the situation of travel medicine in Europe a large response to our

questionnaire is needed. Therefore we call on all practitioners to complete the survey and become a part of the European inventory.

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