Eurosurveillance
Europe's leading journal on infectious disease epidemiology, prevention and control

Vol. 15 | Weekly issue 49 | 9 December 2010

Editorials

Surveillance and outbreak reports

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Responding to new severe diseases – the case for routine hospital surveillance and clinical networks in Europe

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Citation style for this article:
Thomson G, Nicoll A. Responding to new severe diseases – the case for routine hospital surveillance and clinical networks in Europe . Euro Surveill. 2010;15(49):pii=19745. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19745

Article published on 9 December 2010

Any review of the emergence of the more important infectious disease threats in the past few decades will note how many of them were first detected, or recognised as being serious, through unusual patterns of severely ill people appearing in hospitals (Table 1).

That was also the case for the 2009 influenza A(H1N1) pandemic: While the first detected cases were mild infections in children in the south-west of the United States, it was severe disease in Mexico City that led to the appreciation of the potential seriousness of the threat [8,10]. In this issue of *Eurosurveillance* a series of articles describes the initial surveillance in the European Union (EU) [11], how new comprehensive surveillance was developed in Iceland [12], the response in Italy [13], the form that detected mortality took in Germany [14] and clinical surveillance for severe cases in Denmark [15]. The Danish paper notably describes successful efforts to mount surveillance in intensive care units. It is striking that at a time when there was infection and disease in the community, it was the hospitals, and their paediatric services and intensive care units in particular, that were most under pressure [16-18]. It is a truism that the severe cases are to be found in hospital. However, that is where some of the most important information on this pandemic was found, i.e. data and analyses that were needed to guide the countermeasures. A number of the analyses that filled in the gaps for ECDC's *Known Unknowns* (the important features that vary between pandemics and need to be known for control activities) eventually had to come from hospital sources [19]. It is therefore logical to make an effort to gather the early clinical, virological and epidemiological information during a pandemic from hospitals and clinicians in general and intensive care units in particular.

Table 1

Examples of important emerging infections detected through hospital observations since 1981

New condition or threat (year)	First appreciation of emergence and severity	References
Human Immunodeficiency virus (HIV) (1981)	Severe and unusual opportunistic infections in men who have sex with men in Los Angeles and then New York, United States	[1]
Escherichia coli O157 causing haemorrhagic colitis and renal failure (1982)	Haemolytic uraemic syndrome causing acute renal failure in children presenting to paediatricians and other physicians in the United States	[2]
Avian influenza A(H5N1) in humans (1997)	Severe respiratory infections in hospitalised patients in Hong Kong	[3]
Emergence of new variant Creutzfeldt-Jakob disease (CJD) and eventual indication that bovine spongiform encephalopathy (BSE) was transmissible to humans (1996)	New variant CJD recognised by neurologists in the United Kingdom	[4]
Deliberate release of anthrax (2001)	Severe or unusual infections seen in hospitals and emergency rooms in the United States	[5]
Severe acute respiratory syndrome (SARS) (2003)	Severe infections spread nosocomially in hospitals in Hong Kong and then in other countries	[6]
Multidrug-resistant *Acinetobacter* causing severe infections (2004-5)	Observations in injured military personnel in the United States with severe infections of the extremities	[7]
Pandemic influenza A(H1N1) (2009)	Severe respiratory infections seen in hospitals in Mexico City	[8]
Highly drug-resistant *Klebsiella* with a new mechanism of resistance (2009)	Identification and detailed microbiological investigation following diagnosis by hospital physicians of a resistant urinary tract and other infections	[9]

At the same time, hospital surveillance for severe acute respiratory infections (SARI) was one of the two most obvious weak links in the European strategy of surveillance in a pandemic [20] – the other weak link was delivering timely population-wide serological data and analyses [21]. These are not so much issues on a European level as weaknesses in the national systems. There are very few formal systems for hospital-based clinical surveillance in the EU. Neither ECDC nor the World Health Organization (WHO) can ask the Member States for additional analyses and data that they do not routinely collect. Collecting detailed clinical data in real time while clinicians are busy dealing with an outbreak remains a challenge. Even if the rapid collection of data is completed, e.g. via web-based tools, there also needs to be a rapid analysis fed back into the outbreak response.

These reasons alone make a strong case for establishing routine hospital-based clinical surveillance at least in sentinel settings and for linking clinical-microbiological services in international networks that collaborate with public health services and the authorities. However, there are other reasons why clinical networks should be there and function in emergencies (Table 2): The main aim should always be to improve patient care, to ensure that the care given is as safe as possible and that appropriate infection control measures are taken. The clinical lessons learned should ideally be captured in real time and linked with the microbiological and epidemiology results. Rapid analyses should be fed back into the response, providing for instance revised case definitions and improved clinical care [22].

These are not new observations. In 2003, the WHO rapidly set up a clinical network to respond to the epidemic of severe acute respiratory syndrome SARS [25]. It consisted of clinicians from as many as 10 countries discussing case management issues in real time, sharing experiences that were invaluable for the front line clinicians and ultimately improved patient care. Efforts were always made to have an epidemiologist and a virologist on the calls to ensure a more coherent and cross-disciplinary approach [25].

Of course there is a plethora of existing clinical networks and societies in Europe, including ones that deal with intensive care, clinical virology, respiratory disease and infections. However they are not usually structured to respond to emergencies, their links to the public health authorities tend to be unclear and they do not receive enduring official funds. It is also asking a lot of the voluntary officers that run these networks in their spare time to do more in a crisis when individual members are already stressed by an increased workload. However the example of the one international emergency clinical network set up during the 2009 influenza pandemic by the Health Protection Agency (HPA) in the United Kingdom (UK) is encouraging [25]. Similar networks were active or formed de novo in France (REVA-GRIPPE-SRLF), Spain and the Ukraine, and there are undoubtedly others [26].

Following the admission of the first severe cases of pandemic influenza A(H1N1) into intensive care units in the UK, the HPA facilitated and coordinated discussions between intensive care clinicians from a wide range of fields, including specialists in intensive care, paediatrics, thoracic medicine, virology, epidemiology, and infectious diseases [22], including also the UK Department of Health and the WHO (Europe Regional Office and HQ Geneva). Disease experts and clinicians from outside of Europe were included from the beginning to ensure that the experiences made in Mexico and the rest of North America with 2009 pandemic influenza A(H1N1) and in the Far East with avian

Table 2

Potential purposes of clinical networks linked with public health in Europe

Activity	Benefit
Empower clinicians at a local level, allowing for detection, early warning and alerting of new threats	Essential for the implementation of the International Health Regulations 2005 [23]
Share clinical experience and provide support to other teams for challenging clinical decisions	Particularly important when dealing with a novel disease and limited information in the literature
Respond rapidly with evidence-based clinical advice where possible	Evidence readily available to help with decision making
Collect clinical data in real time linked to laboratory and epidemiological data	Data analysed and fed back into the system promptly will help the clinical response
Coordinate and contribute to the writing of guidance, in cooperation with relevant stakeholders, notably professional societies	In a novel disease scenario it is important to capture evidence of best practice
Agree on a platform to disseminate the guidance	Readily accessible guidance
Provide early warning from the first affected localities for other European countries	Countries have the opportunity to prepare for a new threat and to fulfil the obligations of EU Decision 2119 to disseminate information that benefits other European Countries European [24]
Provide training for clinicians in basic principles of outbreak response, personal protective equipment, epidemiology, laboratory test limitations and interpretation of result	Continue to strengthen the clinical frontline, so that when the next novel disease emerges it will be easier for them to manage
Assist the Global Outbreak Alert and Response Network (GOARN) and European authorities such as the Humanitarian Aid department (ECHO)	Opportunity to support other countries and foster international relations; experience gained abroad could be fed back into national plans

influenza A(H5N1) did not have to be relearnt. They followed a format similar to the traditional clinical 'Grand Round' with treating clinicians seeking peer review of their proposed clinical management programmes. The Practice Notes for the care of critically ill adults and children were disseminated via the websites of relevant societies and the HPA [27,28]. Dedicated teleconferences examined particular elements of care including infection control in intensive care, paediatric care, and pregnancy. This was a demanding process requiring the time and efforts by clinicians and experts in many countries as well as the HPA itself.

It is striking how well the initial impressions from these networks held up to the evidence that eventually appeared in the peer-reviewed literature, for example the early observations regarding differences to seasonal influenza (children being relatively overrepresented and older people underrepresented), special challenges in managing the profound hypoxaemia, groups at higher risk of severe disease (the very obese, pregnant women, asthma patients, certain ethnic groups), and the benefit of higher than normal doses of oseltamivir [22].

Particularly valuable for the early risk assessments was to combine the hospital experience with that in the community. It was apparent early on that severe as the cases seen in hospital were, they were uncommon compared to the many infections known to have occurred in places with good surveillance affected early (New York and parts of the UK)[21]. This allowed ECDC to be cautiously optimistic in its risk assessments in early 2009 [29].

The first HPA teleconference call took place in early June and the first practice note that the UK clinicians could look to for guidance was published in August on the professional websites [27,28]. However the formal dissemination of much of that information was a problem. Publication of most clinical observations proceeds slowly and those with the information did not always appreciate the obligation to disseminate their core messages through rapid systems like the Early Warning and Response System (for Europe) and the International Health Regulations alerting system (global). In a novel situation there will be a lag time as information is collected prior to wider dissemination.

A number of lessons can be learnt from the experience with the 2009 pandemic. Firstly, there is a need for routine surveillance of severe infections in hospitals. This could be in sentinel hospitals or for some conditions at a population level (in the United States all childhood deaths associated with influenza are notifiable to the Centers for Disease Control and Prevention) [30,31]. Secondly, the surveillance activities should be overseen by interdisciplinary groups of clinicians and microbiologists as well as public health institutes. Thirdly, the specifications for hospital information systems should facilitate this kind of work. And fourthly, when emergencies arise, these surveillance systems should be reinforced with people and resources. These lessons need to be acted upon now as there are indications in Europe of disinvestment in the surveillance systems established during the pandemic at a time when early information on severe cases remains of high importance in Europe [32]. Table 2 highlights the benefits of operational clinical networks. Ideally a framework should be built prior to an outbreak, bringing together the multi-disciplinary groups for training and preparedness. The network would be activated by agreed triggers and contain a core group to facilitate its functions and outputs.

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Initial surveillance of 2009 influenza A(H1N1) pandemic in the European Union and European Economic Area, April – September 2009

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Citation style for this article:
Devaux I, Kreidl P, Penttinen P, Salminen M, Zucs P, Ammon A, on behalf of the ECDC influenza surveillance group, and the national coordinators for influenza surveillance. Initial surveillance of 2009 influenza A(H1N1) pandemic in the European Union and European Economic Area, April – September 2009. Euro Surveill. 2010;15(49):pii=19740. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19740

Article published on 9 December 2010

European Union (EU) and European Economic Area (EEA) countries reported surveillance data on 2009 pandemic influenza A(H1N1) cases to the European Centre for Disease Prevention and Control (ECDC) through the Early Warning and Response System (EWRS) during the early phase of the 2009 pandemic. We describe the main epidemiological findings and their implications in respect to the second wave of the 2009 influenza pandemic. Two reporting systems were in place (aggregate and case-based) from June to September 2009 to monitor the evolution of the pandemic. The notification rate was assessed through aggregate reports. Individual data were analysed retrospectively to describe the population affected. The reporting peak of the first wave of the 2009 pandemic influenza was reached in the first week of August. Transmission was travel-related in the early stage and community transmission within EU/EEA countries was reported from June 2009. Seventy eight per cent of affected individuals were less than 30 years old. The proportions of cases with complications and underlying conditions were 3% and 7%, respectively. The most frequent underlying medical conditions were chronic lung (37%) and cardio-vascular diseases (15%). Complication and hospitalisation were both associated with underlying conditions regardless of age. The information from the first wave of the pandemic produced a basis to determine risk groups and vaccination strategies before the start of the winter wave. Public health recommendations should be guided by early capture of profiles of affected populations through monitoring of infectious diseases.

Introduction

When the 2009 influenza A (H1N1) pandemic started in April 2009 and first cases appeared in Europe, aggregated (number of cases) and case-based (patient-based records) reporting systems were rapidly implemented by the European Centre for Disease Prevention and Control (ECDC), the European Union (EU) and the European Economic Area (EEA) countries to fulfil the reporting requirements of the World Health Organization (WHO) and the EU [1]. The Early Warning and Response System (EWRS) was used to confidentially report aggregated and case-based data [2]. The EWRS was primarily designed as a communication platform and not as surveillance application. However, one of the main advantages of the system at the beginning of the pandemic was that it relies more on a human driven approach to reporting and this allowed timely (daily) reporting of aggregated data by the EWRS focal points in the EU/EEA countries to ECDC. The European data was then rapidly published in the ECDC's daily situation reports [3] to guide and support the response of the countries and the European Commission. Laboratory-confirmed cases of pandemic influenza were reported according to the EU case definition [4] which includes laboratory confirmation by PCR, antigen detection and a four-fold rise in influenza specific antibodies. A preliminary communication in this journal in June 2009, and the 2009 pandemic influenza A(H1N1) individual case reports from 2 June to 10 August 2009 [5,6], showed that community transmission had developed in several of the EU/EEA countries since the beginning of the epidemic. A large proportion (77%) of cases was reported in children and young adults less than 30 years of age. The frequency of reported symptoms was 89% for respiratory and 14% for gastro-intestinal symptoms and for 10% of pandemic influenza cases at least one underlying medical condition was reported. A number of reports from individual countries show similar data [7-15].

The objective of this article is to describe the main characteristics and risk factors of pandemic influenza cases reported by EU/EEA countries during the first pandemic wave from April to September 2009.

Methods

The investigators extracted two datasets from the EWRS to provide numbers and characteristics of the populations infected by the pandemic influenza virus. Aggregated numbers of 2009 pandemic influenza A(H1N1) virus infections were reported by 30 EU/EEA countries by notification date from 27 April to 22 September 2009. Characteristics of cases were described on a weekly basis using case-based data reported from 5 May to 22 September 2009 (Figure 1).

Adoption of a mitigation strategy was defined as the point when a country was no longer recommending laboratory tests for all suspected cases and therefore not all pandemic influenza cases were reported to national public health authorities.

Aggregated data

Weekly notification rates were calculated by dividing the weekly aggregated number of cases reported by EU/EEA countries by their respective population extracted from the Eurostat website in August 2009 [16]. The weekly denominator only included the population of countries for as long as they reported cases to ECDC.

Individual, case-based data

The set of variables reported in the case-based system were compiled using the WHO guidance for surveillance of human infection with the 2009 pandemic influenza A(H1N1) virus [17]. The variables for the characterisation of the cases were: age, sex, travel-association, vital status (alive or dead), dates (notification, onset of symptoms, treatment started and death), clinical presentation, underlying conditions, complications, antiviral treatment and prophylaxis, seasonal influenza vaccination status, and hospitalisation. Trends over time were analysed by calendar weeks (week starting on Monday).

For cases reported from 5 May to 22 September 2009, the proportion of hospitalised cases was calculated using a weekly median (by country with an interquartile range (IQR) and the 95th percentile), the distribution of travel and non travel-associated cases was described by week of onset over 22 weeks and geographic area visited, age-specific notification rates were calculated over the 20 weeks reporting period.
Completeness of reporting was calculated for sex, travel-association, antiviral treatment and prophylaxis, seasonal influenza vaccination and complication. If no data was missing, completeness equalled 100%. It was not possible to calculate completeness of reporting for underlying condition as there was no option for 'none' or 'unknown' underlying condition (see list below).

Age distributions were compared between groups of persons for the variables, sex, travel-association, antiviral treatment or prophylaxis, vaccination status, underlying conditions and complications, by using two-sample Wilcoxon rank-sum (Mann-Whitney) tests.

Underlying conditions were reported according to the following pre-defined categories: cancer, diabetes mellitus, human immunodeficiency virus (HIV) infection and other immune deficiencies, heart disease, seizure disorder, lung disease, pregnancy and malnutrition. Underlying conditions could also be reported

Figure 1

Data for analyses of 2009 pandemic influenza A(H1N1) cases reported through the Early Warning and Response System to the European Centre for Disease Prevention and Control by European Union and European Economic Area countries, 27 April - 22 September 2009

	Aggregated data	Case-based data
Overall analyses	n= 51,768 27 April - 22 September 2009	n = 11,037[a] 5 May - 22 September 2009
Trend over time	By date of notification n= 51,575 27 April - 20 September 2009	By date of onset n= 8.197 17 April - 20 September 2009
Frequency of symptoms and underlying condition[b]		n=5,205 5 May - 22 September 2009
Risk factor analysis (hospitalisation and complication)[c]		n= 3,381 5 May - 22 September 2009

[a] No data submitted by Greece and Liechtenstein.

[b] Cases for 26 countries, cases excluded from United Kingdom (inclusion of the first 301 cases only), Belgium and Slovenia (all cases excluded).

[c] Cases for 18 countries, cases excluded from Austria, Bulgaria, France, Latvia, Poland, Portugal, Romania.

in a free-text field. When conditions reported in the free-text fields matched one of the pre-defined categories mentioned above, they were re-classified into this category.

Associations between outcomes of pandemic influenza, hospitalisation or complications, and the variables sex age, fever, respiratory/gastro-intestinal symptoms, antiviral treatment or prophylaxis, seasonal influenza vaccination status, underlying conditions, were analysed by unadjusted and adjusted (for other variables) logistic regression models using STATA software. Interactions between variables were tested by using the likelihood ratio test to assess the significance of each variable in the model.

Datasets for specific analyses

Figure 1 shows how subsets of data are analysed. Analyses related to the epidemiological characteristics of cases reported with pandemic influenza were performed on the full dataset (n= 11,037) for most of the variables. Frequency of symptoms and underlying conditions were analysed on a subset of data (n=5,205) including all cases for countries other than the United Kingdom (UK) (inclusion of the first 301 cases only), Belgium and Slovenia (all cases excluded). Seven countries (Austria, Bulgaria, France, Latvia,

Table 1

Number of cases, notification rate, and hospitalisation rate of 2009 pandemic influenza A(H1N1) cases in European Union (EU) and European Economic Area (EEA) countries, 27 April – 22 September 2009

	Aggregated reporting 27 April to 22 September 2009[a]			Individual, case-based reporting 5 May to 22 September 2009[b]			
	Number of cases	Average weekly notification rate (per 1,000,000)	Week change to mitigation	Number of cases (individual data)	Week of last individual case	Medianweekly hospitalization proportion (%)	Inter-quartile interval of median weekly hospitalisation proportion (95th percentile, %)
Austria	361	2.06	32	357	-	75(3)	18 – 92 (100)
Belgium	126	0.98	29	124	28	5	0 – 58 (100)
Bulgaria	70	0.44	-	68	37	47(3)	5 – 75 (100)
Cyprus	297	31.4	-	205	27	33	20 – 45 (92)
Czech Republic	281	1.29	-	258	36	19	10 – 38 (63)
Denmark	636	5.53	28	97	28	10	5 – 20 (75)
Estonia	68	2.41	-	68	37	0	0 – 27 (100)
Finland	259	2.33	30	175	31	9	0 – 13 (38)
France	1,125	1.10	28	553	29	80[c]	19 – 94 (100)
Germany	19,207	11.01	-	704	27	29	14 – 40 (80)
Greece	2,149	9.13	-	-	-	-	-
Hungary	206	0.98	33	110	31	13	4 – 32 (75)
Iceland	193	29.33	-	87	34	-	-
Ireland	885	10.05	29	174	30	3	0 – 15 (75)
Italy	2,384	1.90	-	134	26	30	20 – 37 (50)
Latvia	30	0.63	-	29	37	47[c]	0 – 71 (94)
Liechtenstein	5	6.73	-	-	-	-	-
Lithuania	51	0.76	-	51	35	15	0 – 36 (86)
Luxembourg	190	18.70	-	267	-	0	0 (19)
Malta	298	34.59	29	105	29	4	0 – 7 (11)
Netherlands	1,473	5.61	33	246	30	0	0 (5)
Norway	1,336	13.43	30	60	31	0	0 – 3 (22)
Poland	164	0.20	35	66	30	100[c]	67 – 100 (100)
Portugal	2,983	13.38	34	344	34	47[c]	40 – 66 (89)
Romania	333	0.73	-	331	37	83[c]	67 – 100 (100)
Slovakia	131	1.15	33	130	37	15	9 – 73 (100)
Slovenia	244	5.74	36	7	26	-	-
Spain	1,538	2.61	28	113	20	-	-
Sweden	1,274	6.61	29	172	28	0	0 – 11 (21)
United Kingdom	1,3471	10.48	30	6,002	26	1	0 – 2 (5)
EU/EEA	51,768	5.33		11,037		21	13 – 29 (40)

[a] Cases were reported by date of notification from 27 April to 22 September 2009.

[b] Cases were reported by date of notification from 5 May to 22 September and by date of onset from 19 April to 20 September 2009.

[c] Countries with high hospitalisation rate.

Poland, Portugal, Romania) where hospitalisation was performed mainly for isolation purposes, leading to an over-representation of mild cases among hospitalised cases, were not included in risk factor analyses (n=1,748).

Results

Aggregated data - weekly notification rates

In total, 51,768 confirmed cases of pandemic influenza were reported as aggregated case reports by all EU/EEA countries. The weekly notification rate was calculated for the 51,575 cases reported from 27 April to 20 September 2009 (Figure 1). It increased from week 18 to week 27 (end of June) where it peaked with eight cases per million population. A second peak in the weekly notification rate was observed in week 32, in early August, with 13.6 cases per million population, and was followed by a decrease from week 33, when countries progressively adopted mitigation strategies (Table 1, Figure 2).

The population used as a denominator for the weekly notification rate decreased after week 29, when countries stopped reporting pandemic influenza cases to ECDC.

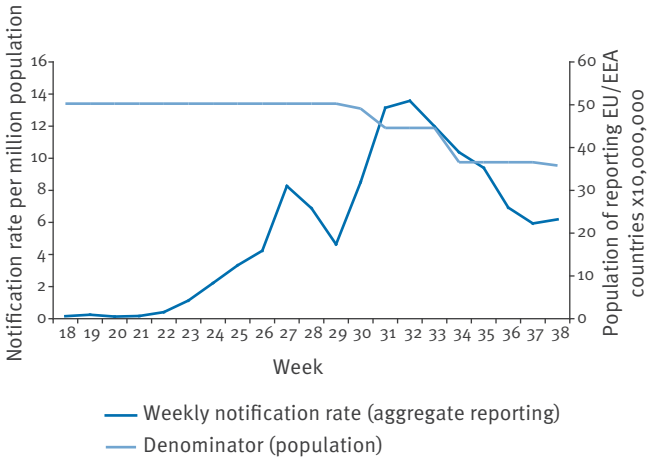
The average weekly notification rate over the period described above was greater than 10 per million population in Cyprus, Germany, Iceland, Luxembourg, Malta, Norway, Portugal and the UK.

Case-based data

A cumulative number of 11,037 cases of pandemic influenza were reported as individual reports by 28 EU/EEA countries (no data submitted by Greece and Liechtenstein) from 5 May to 22 September 2009 (Table 1).The number of cases reported by the UK accounts for more than half (54%) of the individual case reports.

Figure 2

2009 pandemic influenza A(H1N1) notification rate (per million population, n=51,575) and population of reporting European Union and European Economic Area countries by week of report, 27 April (week 18) – 20 September (week 38) 2009



EEA: European Economic Area; EU: European Union

Germany and France reported more than 500 cases; Spain stopped reporting individual cases before the end of June 2009. Data by week of onset were available for 8,197 (74%) cases. The weekly distribution of individual cases reported by date of onset of symptoms peaked in week 25 (mid-end June) with 1,684 cases reported in week 25 and 1,549 in week 26. The decreasing numbers observed after week 26 and until September 2009 can be explained by the fact that the UK, followed by other countries stopped reporting individual cases to ECDC (Figure 3).

Travel-associated cases

Of 10,643 cases with travel-related information i.e. having been outside the country of notification during the incubation period, 7,101 (67%) were reported as domestic cases i.e. having acquired the infection in the country where they were reported. Data on travel history and week of onset of symptoms were available for 7,974 cases (75% of cases with travel-related information) and among those, 3,333 had travelled abroad. The proportion of travel-associated pandemic influenza cases was 100% in week 16 and decreased progressively to 19% in week 25, when the total number of reported cases was highest. In week 25, a large proportion of cases were reported as community-acquired by the UK. The proportion of travel-associated cases increased again after week 25 and remained above 50 % until week 37. Large proportions had travelled to North America (1,314 cases, 39%) or within EU/EEA countries (1,528 cases, 46%). At the start of the pandemic, during weeks 16 to 23, almost all travel-associated cases (≥92%) were linked to travel to North America, and this was gradually replaced by travel within EU/EEA countries after week 24 and, from week 31 to week 38, almost all travel-associated cases were reported within EU/EEA countries (≥83%). The percentage of cases who had travelled to other continents was 6% or less: 159 of 3,333 cases (5%) returned from Asia, 130 (4%) returned from South America and 99 (3%) returned from another country, mainly Australia.

Hospitalised cases

The median of the weekly percentage of hospitalised cases by country was 21% with an IQR of 13 to 29% and a 95th percentile of 40% in 25 EU/EEA countries. Information on hospitalisation was not reported by Iceland, Spain and Slovenia (Table 1). Seven countries were identified with a median proportion of hospitalised cases greater than 40 % (95th percentile): Austria, Bulgaria, France, Latvia, Poland, Portugal and Romania. These countries had similarly high hospitalisation rates during their containment phase of the pandemic which decreased when hospitalisation was no longer recommended for isolation purposes in these countries.

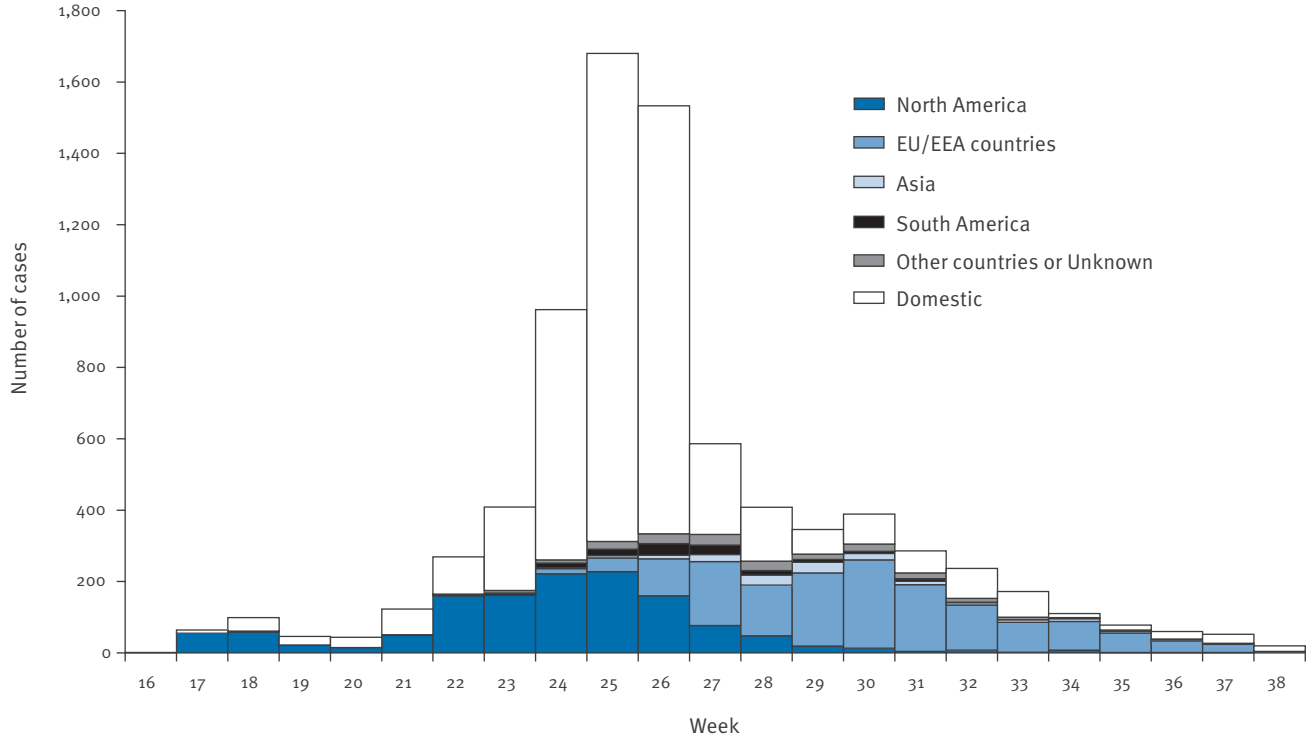
Age, sex and antiviral treatment

In 28 EU/EEA countries, children and young adults less than 30 years of age represented 78% (n=10,846) of cases reported and the highest age-specific

notification rate was observed in the age group 10 to 14 years with 7.7 per 100,000 population (Figure 4). Two peaks were observed in those under 30 years of age: the first peak, in 10 to 14 year-olds, corresponded to a series of school outbreaks reported for example in the UK and Germany [7,8]. The second peak was

Figure 3

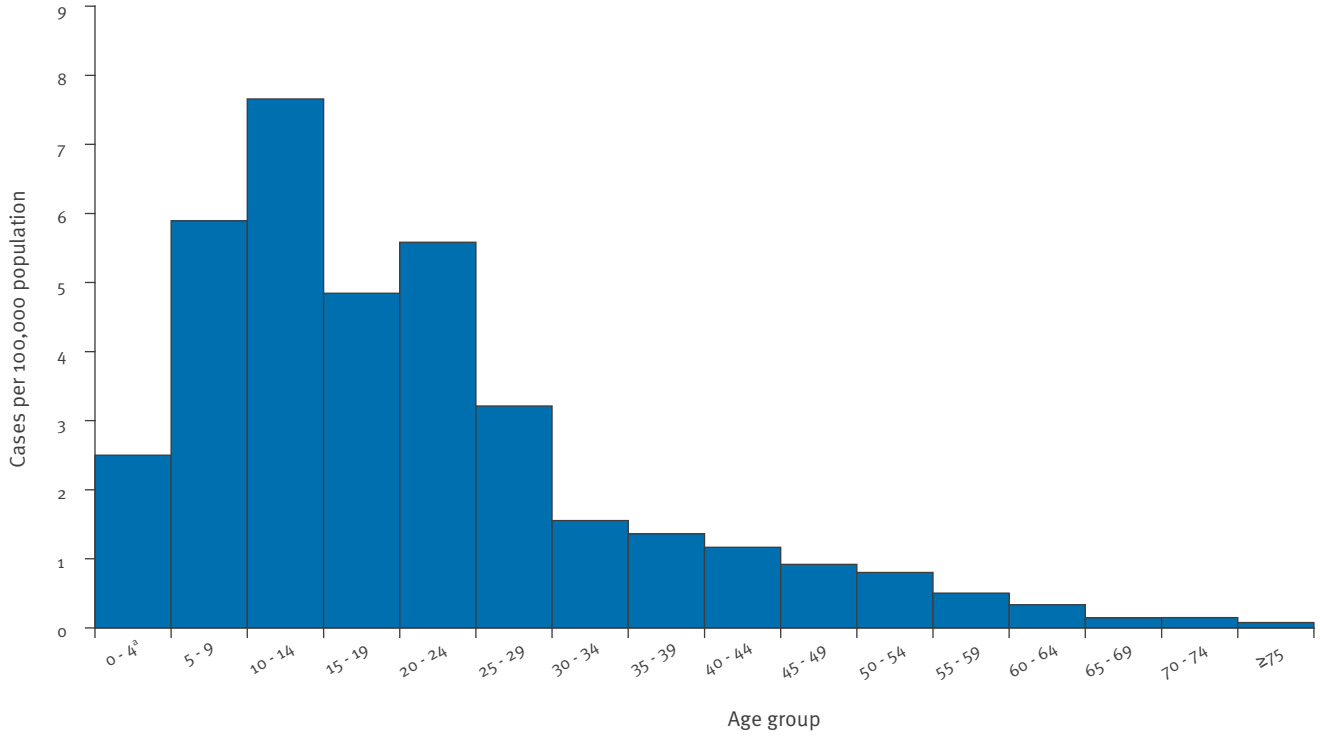
Total (n=7,974), domestic (n=4,641) and travel-associated (3,333) cases of 2009 pandemic influenza A(H1N1) virus infection in European Union and European Economic Area countries by week of onset and continent of travel, 19 April (week 16) – 20 September (week 38) 2009



EEA: European Economic Area ; EU: European Union.

Figure 4

Age-specific notification rate of 2009 pandemic influenza A(H1N1) cases reported by 28 European Union and European Economic Area countries, individual case reports, 5 May – 22 September 2009, (n=10,846)



[a] 212 cases are reported below 1-year-old with an age-specific rate of 4 per 100,000 population.

attributed to a higher number of travel-associated cases in 20 to 24 year-olds. A decreasing trend over time in the notification rate was observed in individuals aged over 29 years (Figure 4). Five age groups were

Table 2

Characteristics of 2009 pandemic influenza A(H1N1) cases reported in 28 European Union and European Economic Area countries (n=11,037, except for underlying conditions, n=5,205), 5 May – 22 September 2009

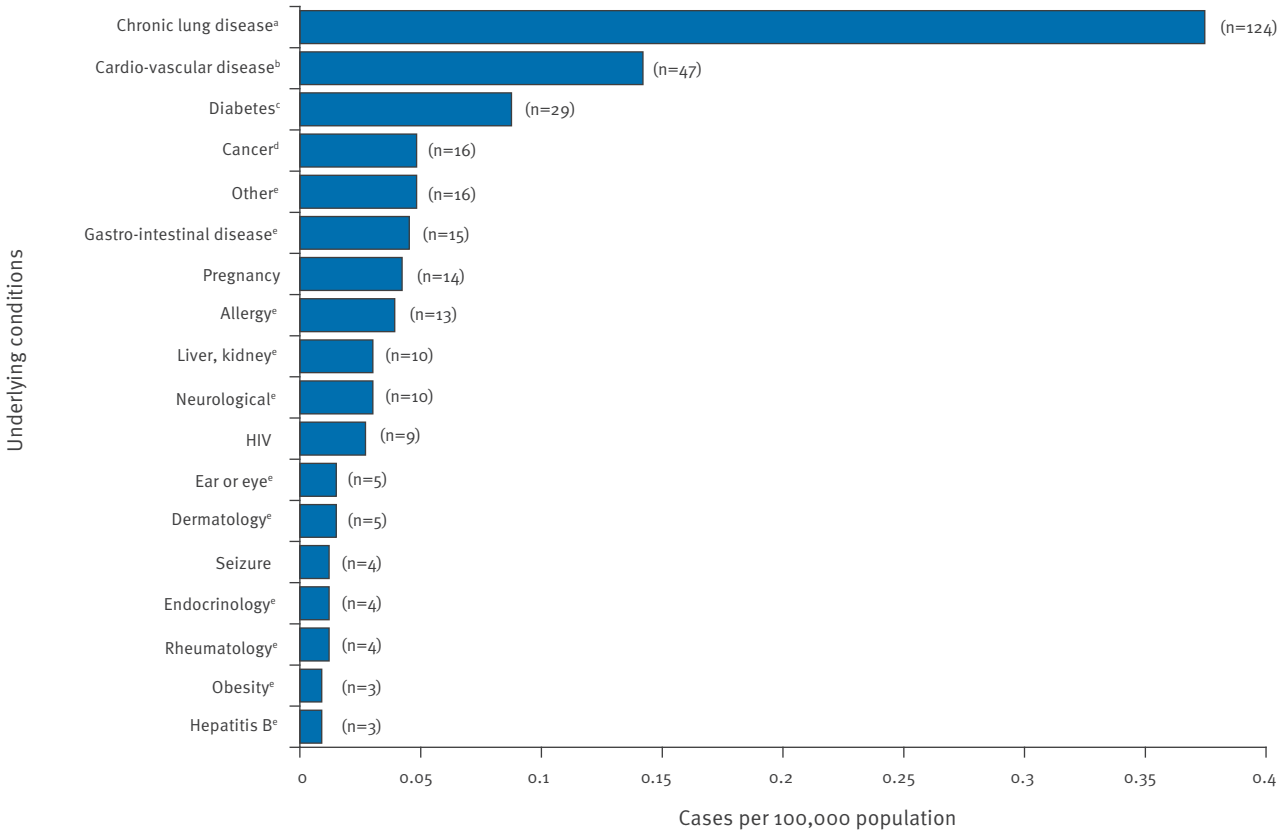
Variables	Category	Number of cases (%)	Completeness %	Age					
				Median age	% 0-9	% 10-19	% 20-29	% 30-59	% ≥60
Sex	M	5,224 (53)	89	19	19	32	28	20	2
	F	4,648		20	18	31	27	23	2
Travel-associated	Y	3,542 (33)	96	24	8	22	39	28	2
	N	7,101		14	26	37	20	16	1
Treatment	Antiviral	2,440 (26)	85	22	12	28	33	25	2
	Other	2,759 (29)		15	25	34	22	17	1
	N	4,193 (45)		16	24	33	23	18	1
Prophylaxis		110 (4)	28	21	17	26	26	28	3
Vaccination against seasonal influenza		263 (3)	81	28	9	17	25	36	12
Complication		94 (3)	26	26	10	19	28	37	6
Underlying condition[a]		343 (7)	-	28	8	23	21	38	10

F: female; M: male; N: no; Y: yes

[a] It was not possible to calculate the proportion of completeness for underlying condition as the category 'none' did not exist for this variable.

Figure 5

Underlying conditions of 2009 pandemic influenza A(H1N1) cases reported in 26 European Union and European Economic Area countries, 5 May – 22 September 2009 (n=331)



HIV: Human immunodeficience virus.

[a] Include 33 cases reported with asthma as a text field.

[b] Include cases reported with other conditions: hypertension, lung disease, kidney disorder, obesity.

[c] Include cases reported with other conditions: hypertension, asthma, obesity.

[d] Include cases reported with other conditions: seizure and/or diabetes and/or other condition.

[e] Reported as text field.

further analysed: 0 to 9 years (20% of all cases), 10 to19 years (32%), 20 to 29 years (26%), 30 to 59 years (20%), and over 60 years (2%).

Table 2 describes the pandemic influenza cases, completeness of reporting, median age and distribution by age group for the variables defined above. Completeness of reporting was over 80% for all variables except antiviral prophylaxis (28%) and complication (26 %).

The male-to-female ratio was 1.1 (n=9,872 cases with available information). The median age of pandemic influenza cases was significantly higher among those who had travelled abroad (24 years) than among domestic cases (14 years), (z=-31.4, p<0.001). Forty-five per cent (n=9,392) of cases did not receive any antiviral treatment, 26% (2,415) received oseltamivir, 0.3% (25) zanamivir and 29% (2,759) another treatment which was specified in 104 (4%) persons only, 66 of those had received antibiotics. As expected, the proportion of patients who received oseltamivir was significantly higher among hospitalised cases (74%) compared with non-hospitalised cases (18%). Prophylaxis was administered to 4% (110 of 3139 cases) and previous vaccination for seasonal influenza was reported for 3% (264 of 8,913 cases). Seventy-two of 262 cases (28%) with available information on vaccination and underlying condition had at least one underlying condition. Complication(s) were reported in 3% (94 of 2,878 cases with available information). Sixty persons (2%) were reported with pneumonia, 25 (0.8%) with other respiratory infections, and six with non-specified complications.

Symptoms and underlying conditions

Frequencies of symptoms were calculated based on 4,452 cases, after exclusion of 753 (14%) cases reported without any symptom. Fever was reported in 87%, respiratory symptoms were reported in 85%, gastro-intestinal symptoms in 18%, and for 27% of cases other symptoms, mainly fatigue or asthenia, chill, loss of appetite were noted. The proportion of gastro-enteritis was 26 % among children aged less than 10 years.

Three hundred and forty-three of 5,205 (7%) pandemic influenza cases were reported with at least one underlying condition. Underlying conditions were specified in 331 (96%) of them. They were described as free text for 137 (41%) cases. The most common underlying conditions were unspecified chronic lung diseases, including asthma (124 cases, 37%). Other underlying conditions reported and associated or not with other conditions, were cardiovascular-diseases, diabetes, gastro-intestinal diseases, allergy, liver or kidney related conditions, neurological disorders, cancer, HIV. Pregnancy was reported in 14 women (4%) (Figure 5).

Epidemiological characteristics and outcomes

For analyses of associations between hospitalisation and potential risk factors the age group 10 to 19 years was chosen as reference group as it had the highest age-specific notification rate. Univariate analysis shows that factors associated with hospitalisation are underlying condition (Odds ratio (OR) 1.95, 95% confidence interval (CI) 1.00-2.73), seasonal influenza vaccination (OR 1.59, 95% CI 1.04-2.41), and age group 20 to 29 years (OR 1.32, 95% CI 1.00-1.74). In the multivariate model only underlying condition remained associated with hospitalisation (OR 1.61, 95% CI 1.07-2.43). Analysis of associations between complications and potential risk factors for complications were performed on data reported by 25 countries (n=2,878, no data reported on complication by Belgium, Slovenia and Spain). Univariate analysis shows that factors associated with complication were: age groups 30 to 59 years (OR 2.1, 95% CI 1.22-3.88) and over 60 years (OR 4.13, 95% CI 1.58-10.8) and underlying condition (OR 3.65, 95% CI 2.24-5.95). In the multivariate model only underlying condition remained associated with complication (OR 3.18, 95% 1.91-5.27).

Discussion

The pandemic influenza cases reported in this article characterise the first wave of the 2009 pandemic in EU/EEA countries. They include a large proportion of travel-related cases that are not necessarily representative of the population affected by the pandemic during the following winter wave. Also representativeness of data varied between countries. The weekly notification rate calculated for aggregated data is a proxy for the notification rate of pandemic influenza over the summer months of 2009. Two peaks were observed: one in week 26 and one in week 31. The first is probably due to a reporting artefact in week 26, when a large number of cases from previous weeks were reported by the UK. The second peak marks the maximum number of cases reported during the first pandemic wave in EU/EEA countries. The sentinel surveillance of influenza-like illness (ILI) and acute respiratory infections (ARI) also showed two peaks at a time similar to that of the reporting data: one in week 25 and one in week 31 [18].

High notification rates in specific countries like Cyprus and Malta can probably be explained by an increase of their population during the summer holiday season that could not be taken into account in the denominator.

The reported percentage of hospitalised patients in (21%) seems extremely high. At the beginning of the pandemic, hospitalisation was used for isolation purposes in some countries and this may have inflated the percentage rather than a high number of severe cases. In the Netherlands, a country that did not recommend hospitalisation for isolation purposes, a hospitalisation rate of only 2.2% (35 of 1,622 patients with confirmed pandemic influenza) was reported until 14 August 2009, when a change in notification criteria to only hospitalised patients was implemented [19].

Case-based data was available for merely 21% of the reported aggregated cases. However, this was expected because the purpose of the case-based system was to

capture the first few hundred cases of pandemic influenza reported in all Member States, while case-based reporting was still feasible. This purpose was achieved in most countries that have reported more than 100 cases in the aggregated reports.

Table 3

Univariate and multivariate analysis for factors influencing hospitalisation and complications of 2009 pandemic influenza A(H1N1) cases in 18 European Union and European Economic Area countries, 5 May – 22 September 2009

		Hospitalisation					Complication				
	Category	Total number of cases	% hospitalised	OR	OR lower limit	OR upper limit	Total number of cases	% complication	OR	OR lower limit	OR upper limit
Univariate analysis											
Gender	Male	1,609	13%	1	–	–	1,563	3%	1	–	–
	Female	1,380	14%	1.12	0.91	1.38	1,297	4%	1.16	0.77	1.75
Age	0–9	353	14%	1.21	0.81	1.8	318	3%	1.26	0.56	2.84
	10–19	963	11%	1	–	–	766	2%	1	–	–
	20–29	1,027	15%	1.32	1	1.74	961	3%	1.2	0.65	2.21
	30–59	915	14%	1.23	0.93	1.65	732	5%	2.1	1.22	3.88
	≥=60	72	11%	0.83	0.39	1.76	69	9%	4.13	1.58	10.8
Treatment	Yes	1,447	14%	1.25	0.96	1.63	1,770	4%	1.21	0.75	1.96
	No	783	11%	1	–	–	754	3%	1	–	–
Prophylaxis	Yes	83	18%	1.43	0.8	2.54	59	2%	0.47	0.06	3.43
	No	1,658	13%	1	–	–	2,255	4%	1	–	–
Vaccination	Yes	156	19%	1.59	1.04	2.41	171	6%			
	No	1,909	13%	1	–	–	1,840	3%	1	–	–
Underlying	Yes	222	22%	1.95	1	2.73	250	9%	3.65	2.24	5.95
conditions	No	2,778	13%	1	–	–	2,628	3%	1	–	–
Multivariate analysis											
Age	0–9	–	–	0.92	0.58	1.47	–	–	1.06	0.49	2.3
	10–19	–	–	0.77	0.55	1.06	–	–	0.86	0.46	1.58
	20–29	–	–	1	–	–	–	–	1	–	–
	30–59	–	–	0.85	0.61	1.18	–	–	1.67	0.99	2.81
	≥60	–	–	0.51	0.21	1.26	–	–	2.32	0.89	6.05
Vaccination	Yes	–	–	1.48	0.95	2.33	–	–	–	–	–
	No	–	–		–	–	–	–	–	–	–
Underlying	Yes	–	–	1.61	1.07	2.43	–	–	3.18	1.91	5.27
conditions	No	–	–	1	–	–	–	–	1	–	–

OR: Odds ratio.

Table 4

Percentage of underlying and co-morbid conditions reported in studies performed among patients hospitalised with 2009 pandemic influenza A(H1N1)

Study	Number of patients	Chronic lung disease, including asthma	Cardio-vascular disease	Diabetes	Obesity	Pregnancy
US [11]	272	36%	13%	15%	-	7%
US, California [12]	1,088	37%	15%	11%	48%	10%
Canada[a] [13]	168	32%[b]	15%	21%	33%	8%
Australia & New Zealand[a] [14]	722	33%	11%[c]	16%	29%	9%
Mexico[a] [15]	58	7%	10%[d]	17%	36%	n.a.
EU/EEA	331	37 %	15%	9%		4%

EEA: European Economic Area; EU: European Union; US: United States.

[a] Patients hospitalised in critical care units.

[b] Asthma and/or chronic obstructive pulmonary disease.

[c] Only chronic heart failure.

[d] Arrhythmia and valvular heart diseases.

The completeness of data for prophylaxis (28%) and complication (26%) was low. This can be interpreted in two different ways: either the missing information corresponds to 'no prophylaxis' or 'no complication', or to unknown information. As we chose to remove missing values from the denominator, proportions of persons who have received prophylaxis or with complication(s) may be over-estimated in our analysis.
Clinical presentations of patients reported in our system are similar to those listed in a review (WHO consultation) of clinical aspects of 2009 pandemic influenza [20]. In September 2009, the number of cases reported without any symptom was considered as quite high (14%) as information about the proportion of asymptomatic cases was still scares at that time. Asymptomatic cases when reported in the context of tracing contacts during the containment phase could have been underestimated if contact tracing was not systematically performed.

However, it is not known if these cases were really asymptomatic or if symptoms were not reported. In the latter case, 14% would be an over-estimation of the proportion of asymptomatic cases. Serological surveys are the only way to estimate the proportion of asymptomatic 2009 pandemic influenza cases. In the meanwhile, results from such studies suggest that a considerable number of those infected with pandemic influenza A(H1N1) virus may have been asymptomatic [21,22].

The overall proportion of underlying conditions (7%) reported in our dataset is similar to the information reported by WHO for Ontario, Canada in June 2009 [23]. We compared proportions of underlying conditions with results from other studies among hospitalised patients with pandemic influenza in the United States [24,25], Canada [26], New Zealand [27] and Mexico [28] (Table 4). Although not necessarily all cases reported with underlying conditions in our dataset were hospitalised, the proportion of chronic lung diseases (including asthma) and cardio-vascular diseases among hospitalised patients were similar to those reported elsewhere [24-27]. However, the proportions of cases reported with metabolic conditions (diabetes and obesity) and pregnancy are lower in EU/EEA countries than those reported in hospitalised patients in the countries mentioned above. In our dataset, patients with underlying conditions were more likely to be hospitalised and underlying conditions were associated with complications regardless of age.

The fact that 45% of our cases did not receive any treatment may either indicate that they did not have a severe condition or it may reflect the treatment policies in the countries who may have only recommended treatment for severely ill.

Most cases were found in younger or middle-aged age groups. Above the age of 60, there was a steep decline in the number of pandemic influenza A(H1N1) cases. This could be related to previous exposure of individuals over 60 years to influenza A(H1N1) viral strains circulating after the 1918 pandemic until the 1950s [29]. Recent sero-surveys conducted in the UK [30] and in Finland [31] support this hypothesis.

Only three deaths were reported in the individual case data, this contrasts with the 159 deaths reported in EU/EEA countries in the ECDC situation report of 22 September 2009 [3]. Information about deaths is essential to assess severity of the disease appropriately. Additional monitoring systems are needed to collect this type of information in a timely manner.

Conclusion

The primary focus of this article was to present the case-based data collected during the first phase of the pandemic in EU/EEA countries and their implications for rapid public health action. The case-based reporting system was stopped in September 2010, due to the associated heavy work load and the high numbers of affected people. Case-based data were not collected in the population-based system during the second phase of the pandemic and thus our data cannot be used for comparison between the two waves. Overall, our results are in line with other observations that the early phase of the pandemic mainly affected children and young adults in European countries [7-15]. Individuals infected with 2009 pandemic influenza A(H1N1) and with underlying condition(s) were more likely to be hospitalised or to develop (severe) complications regardless of their age, particularly those with underlying respiratory diseases. The epidemiological information collected during the first wave of the pandemic provided some initial indication to determine risk groups and vaccination strategies. In the early phase of the pandemic, results from serological studies would have been helpful to determine if and to what extent individuals over 60 years have pre-existing immunity against pandemic 2009 pandemic influenza A(H1N1) from H1N1 strains circulating after the 1918 pandemic up until the 1950s. Our reporting system provided baseline data and helped to guide initial public health recommendations, however, as the profile of the affected population may have changed over time it is important to continue monitoring. The initial surveillance system was followed by a case-based reporting system of severe acute respiratory infections among influenza cases. Both systems provided timely information of public health relevance about profiles of populations affected by 2009 pandemic influenza.

Acknowledgements

We would like to thank Johan Giesecke, Gilles Desve, Vincente Lopez and Bartoz Pedzinski for their support and contributions.

The ECDC working group on influenza surveillance
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Surveillance of influenza in Iceland during the 2009 pandemic

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Citation style for this article:
Sigmundsdottir G, Gudnason T, Ólafsson Ö, Baldvinsdóttir GE, Atladottir A, Löve A, Danon L, Briem H. Surveillance of influenza in Iceland during the 2009 pandemic. Euro Surveill. 2010;15(49):pii=19742. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19742

Article published on 9 December 2010

In a pandemic setting, surveillance is essential to monitor the spread of the disease and assess its impact. Appropriate mitigation and healthcare preparedness strategies depend on fast and accurate epidemic surveillance data. During the 2009 influenza A(H1N1) pandemic, rapid improvements in influenza surveillance were made in Iceland. Here, we describe the improvements made in influenza surveillance during the pandemic , which could also be of great value in outbreaks caused by other pathogens. Following the raised level of pandemic influenza alert in April 2009, influenza surveillance was intensified. A comprehensive automatic surveillance system for influenza-like illness was developed, surveillance of influenza-related deaths was established and laboratory surveillance for influenza was strengthened. School absenteeism reports were also collected and compared with results from the automatic surveillance system. The first case of 2009 pandemic influenza A(H1N1) was diagnosed in Iceland in May 2009, but sustained community transmission was not confirmed until mid-August. The pandemic virus circulated during the summer and early autumn before an abrupt increase in the number of cases was observed in October. There were large outbreaks in elementary schools for children aged 6–15 years throughout the country that peaked in late October. School absenteeism reports from all elementary schools in Iceland gave a similar epidemiological curve as that from data from the healthcare system. Estimates of the proportion of the population infected with the pandemic virus ranged from 10% to 22%. This study shows how the sudden need for improved surveillance in the pandemic led to rapid improvements in data collection in Iceland. This reporting system will be improved upon and expanded to include other notifiable diseases, to ensure accurate and timely collection of epidemiological data.

Introduction

The first reports of 2009 pandemic influenza A(H1N1) in humans in the United States and Mexico appeared in April 2009 [1]. Initial descriptions of the outbreak in Mexico were alarming, with severe cases of pneumonia and high mortality in previously healthy young adults being reported [1]. On 27 April 2009, the World Health Organization (WHO) raised the level of pandemic influenza alert from phase three to four and two days later from phase four to five [2,3]. Countries were encouraged to activate their pandemic preparedness plans and remain on high alert for unusual outbreaks of influenza-like illness and severe pneumonia. In a pandemic, both clinical and epidemiological data are essential in attempts to assess the severity of the illness. The allocation of healthcare resources and choice of appropriate intervention strategies also rely on accurate and timely surveillance data. Such data are essential in identifying groups at risk of severe illness and who should be prioritised in vaccination strategies. Surveillance is also needed to evaluate the impact of different interventions. Heightened surveillance was therefore a high priority during the pandemic in order to detect the first cases and monitor the spread of the disease.

Conventional surveillance methods for influenza are mostly based on laboratory surveillance and sentinel surveillance of influenza-like illness (ILI), but interest in mortality surveillance has increased during the last decade [4,5]. Unconventional surveillance methods, such as school absenteeism, syndromic surveillance and mobile phone surveillance, have also been used but these methods require further validation [6-8]. All elementary schools for children aged 6–15 years in Iceland enter information on school absenteeism into a common database, but these data have not been analysed for epidemiological purposes so far [9].

There were differences in healthcare services, surveillance and interventions between European countries during the 2009 pandemic. Reports from individual countries on the pandemic are therefore crucial to compare experiences, share knowledge and maximise the lessons learned after the pandemic. In this article we report the changes made in the surveillance of influenza in Iceland and describe the data collected during the pandemic.

Surveillance systems in Iceland

Surveillance of influenza-like illness

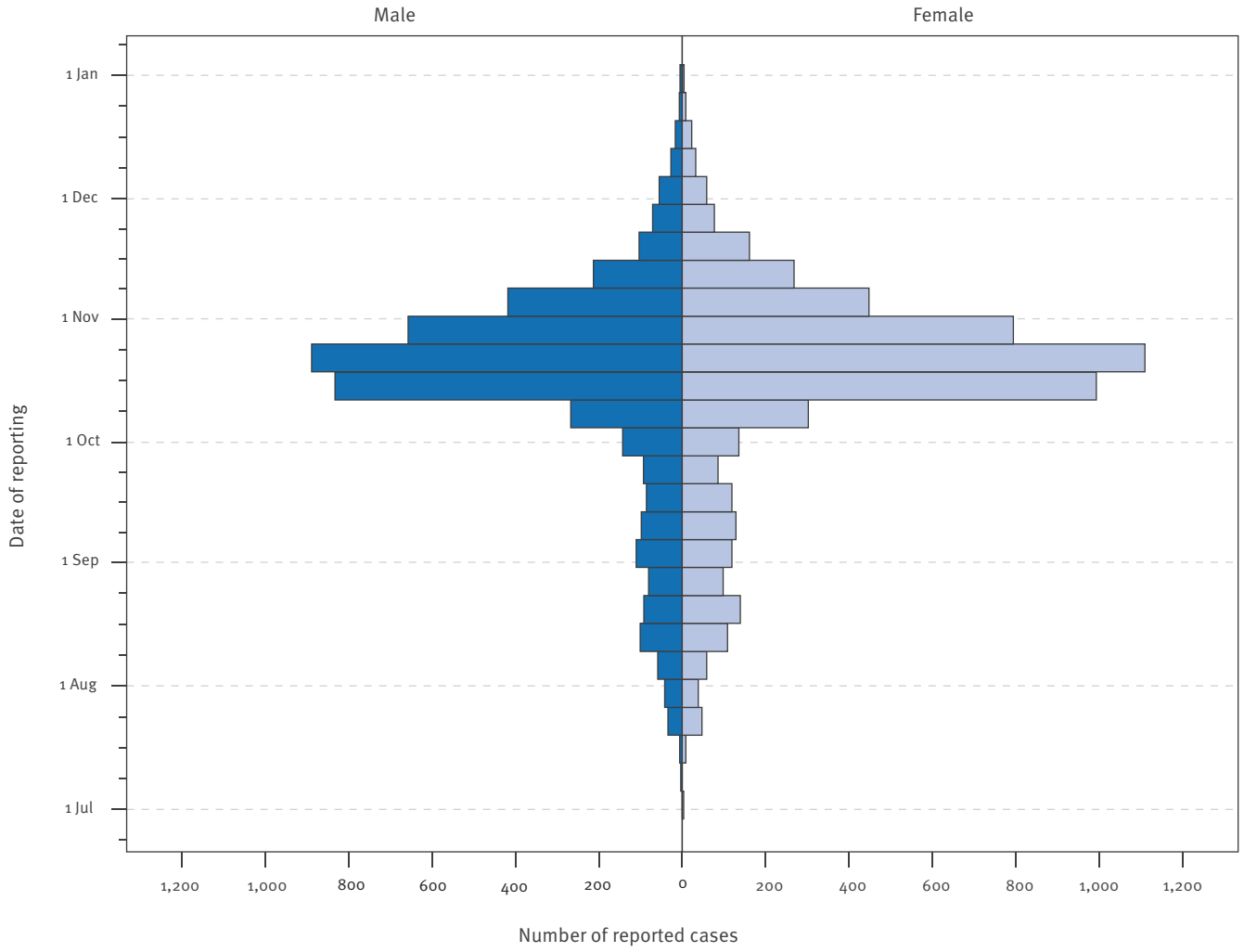
In April 2009 surveillance of ILI in Iceland was based on monthly paper-based reporting of aggregated data from primary healthcare centres to the Centre for Health Security and Communicable Disease Control (CHS-CDC). After WHO initially raised the pandemic alert level, Icelandic legislation was changed allowing personal, identifiable information to be collected for each case. Simultaneously, an online automatic system for immediate reporting of ILI and cases with laboratory-confirmed influenza to the CHS-CDC was developed, using the same software used for electronic patient records in primary health care and hospitals in Iceland [10].

The current International Classification of Diseases (ICD-10) for standard diagnostic classification and International Classification of Primary Care (ICPC-2) for standard classification of a patient's reason for encounter were used to identify ILI and confirmed influenza cases for automatic online reporting in the system [11,12]. The following ICD-10 codes were used: J10, J10.0 J10.1, J10.8, J11, J11.0, J11.1, J11.8 and U05.9; the ICPC-2 code used was R80. Whenever physicians suspected ILI or diagnosed confirmed influenza they were asked to use the appropriate ICD-10 code in their reporting. After the physician confirmed his record for the patient visit in the electronic patient journal cases with ICD-10 codes for ILI and confirmed influenza were automatically selected and automatically reported within 24 hours via a closed electronic network to the CHC-CDC comprising all healthcare centres and hospitals in Iceland. The data collected for each case included: name, personal identification number, date of birth, place of residence, date of visit to the healthcare centre or hospital, patient's age, sex, which healthcare service the case attended, medical licence number and name of attending physician, the ICD-10 code and the ICPC code. Patients registered with ICD-10 codes for the most common acute respiratory infections (ARI) were also reported automatically and online in the same way as the influenza and ILI cases. Unlike sentinel systems, the automatic reporting system allowed data to be collected from each and every primary healthcare centre and hospital emergency room, thus capturing the vast majority of all diagnosed cases.

The European case definitions for ILI, confirmed cases of seasonal influenza and confirmed cases of

Figure 1

Weekly number of reported cases of influenza-like illness by sex, Iceland, 1 July to 31 December 2009 (n=9,887)



2009 pandemic influenza A(H1N1) were used and the selected ICD-10 and ICPC-2 codes were recorded by the physicians [13-14]. In mid-June, when the system was in place, it was also possible to gather data retrospectively from 1 April 2009.

Laboratory surveillance

The Department of Virology at the Landspitali University Hospital in Reykjavik is the sole diagnostic laboratory for influenza in the country. The laboratory received respiratory samples from the nasopharynx and/or throat that were collected from patients with ILI by physicians in primary healthcare centres and at hospitals.

Influenza was diagnosed by real-time polymerase chain reaction (PCR) according to a recommended protocol from the United States Center for Disease Control and Prevention (CDC) [15]. Clinical information and the country of infection were collected on confirmed cases both at the laboratory and at the CHS-CDC. The weekly number of tested respiratory samples and personal information on confirmed cases was reported to the CHS-CDC.

Surveillance of school absenteeism

All elementary schools in Iceland routinely enter information on school absenteeism for schoolchildren aged 6–15 years into a central database maintained by the information technology company Mentor ehf in Reykjavik [9]. School absence was recorded as the number of days absent; comparable data were available for 2007, 2008 and 2009.

Mortality surveillance

Mortality data are collected by the National Registry and sent to the CHS-CDC routinely on a weekly basis. The data included the name, personal identification number, date of birth, place of residence and date

Figure 2

Age-specific incidence of reported influenza-like illness cases by sex, Iceland, 1 July to 31 December 2009

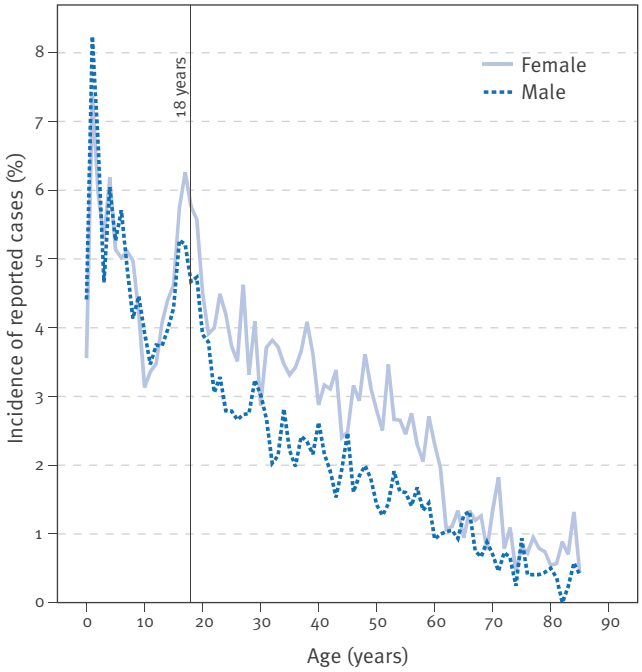
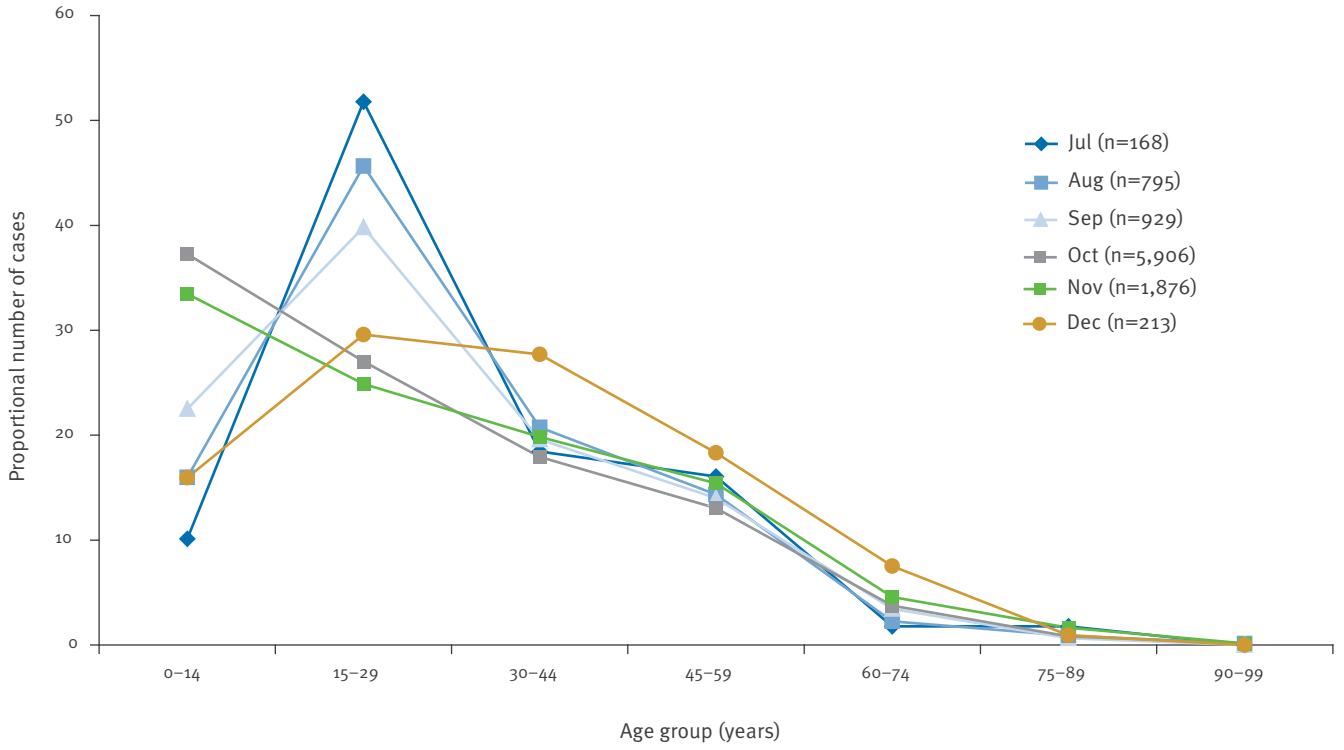


Figure 3

Proportional number of reported influenza-like illness cases by age group, Iceland, July to December 2009



of death for each individual. A temporary system for surveillance of patients with ILI and confirmed pandemic influenza admitted to hospital was developed within all hospitals and these cases and deaths in this group were reported immediately to the CHS-CDC. Unexpected deaths in the community in patients with ILI or confirmed pandemic influenza were also to be reported by the physicians to the CHS-CDC.

Data analysis

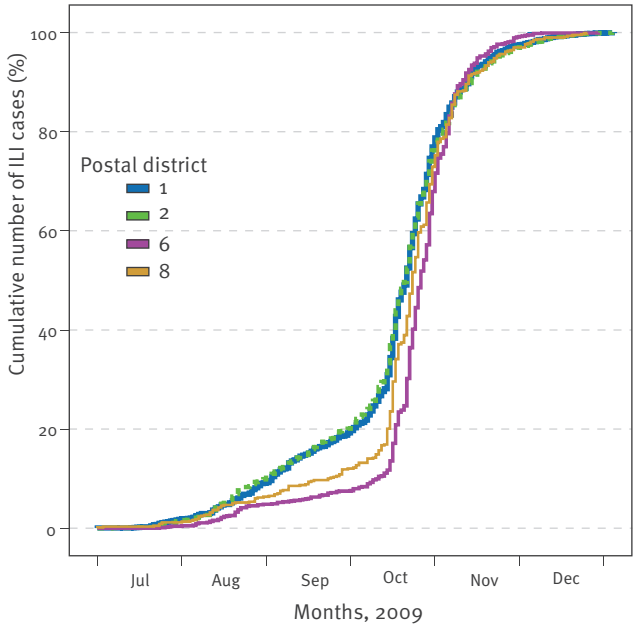
Estimated number of infections in the community

The percentage of positive laboratory samples was used as an estimate of the proportion of ILI cases in the community with pandemic influenza. To estimate the total number of infected individuals in the community, we therefore multiplied the weekly number of reported ILI cases by the weekly percentage of laboratory samples confirmed positive for pandemic influenza and summed over the course of the pandemic.

The denominators used in this study were mid-2009 demographic data from the Icelandic Population Registry, according to age, sex and place of residence, as appropriate.

Figure 4

Cumulative number of reported ILI cases as a proportion of the total number of ILI cases by postal district, Iceland, 1 July to 31 December 2009



ILI: influenza-like illness.

Table

Reported cases of influenza-like illness by region, Iceland, July to December 2009 (n=9,887)

Region	Postal district	Number of reported ILI cases	Median time[a]
Capital area	1	3,643	19 Oct
	2	3,019	19 Oct
West Iceland	3	404	22 Oct
West fjords	4	109	21 Oct
North West	5	340	27 Oct
North East	6	1,016	24 Oct
East Iceland	7	466	22 Oct
South Iceland	8	598	21 Oct
Westman Islands	9	80	27 Oct
Unknown	Missing	212	–
Total	**1–9**	**9,887**	**20 Oct**

ILI: influenza-like illness.

[a] The date (in 2009) when half of the ILI cases were reported in the postal district.

Surveillance data

Influenza-like illness

Throughout May and June 2009, few cases of ILI and confirmed pandemic influenza were reported. An increase in the number of laboratory-confirmed cases of pandemic influenza was observed from mid-July, when there was a simultaneous absence of confirmed seasonal influenza. Cases of ILI reported from 1 July 2009 onwards were therefore considered to represent the illness caused by pandemic influenza.

From 1 July to 31 December 2009 a total of 9,887 cases of ILI were reported, of whom 5,372 (54%) were female and 4,515 (46%) were male. The number of cases increased slowly from mid-July to the end of August and fell slightly in mid-September (Figure 1). A sharp increase was observed in October: the number of cases peaked later that month, followed by a rapid decrease. Only sporadic ILI cases were reported in late December.

The incidence of ILI was highest in children and young adults and decreased with age, as shown in Figure 2. ILI incidence was similar in both sexes in people aged under 18 years. However, in people over 60 years, the incidence was higher in women ($p=0.003$), but the largest difference by sex was observed in people aged 18–59 years, with incidence again higher in females ($p<0.001$) (Figure 2).

Figure 3 shows how the age of the reported ILI cases changed with time. In July to September 2009, most cases were reported in the 15–30 years age group, but a sudden change was observed in October, when the majority of cases were aged from 0 to 15 years (Figure 3).

Reported ILI cases were categorised by the postcode of their place of residence. The cumulative number of reported cases over time is given for the four most populated postal districts in the south-west, north and south of the country (Figure 4). There was some indication of spatial dispersal in late September 2009; the number of reported cases increased earlier in the south-west postal districts 1 and 2, followed by an abrupt increase in mid-October in all districts at the same time. The overall number of cases peaked shortly after mid-October (Figure 1, Table).

Data from the surveillance of ARI from the same automatic online system showed similar trends over time as

the ILI cases, with a peak in early to mid-October 2009 (week 41) (unpublished data).

Laboratory-confirmed cases of pandemic influenza

From May to mid-August 2009, physicians were encouraged by the chief epidemiologist to take samples from patients with ILI. The first case of pandemic influenza in the country was laboratory confirmed on 19 May 2009. Three confirmed cases were identified in June, but in late July and August (week 30 to 33) an increase in the number of cases was observed. The first cases in May and June acquired the infection abroad or their infection was domestically acquired with known connection to another confirmed case. The proportion of domestic cases with no known connection to other confirmed cases increased rapidly in July and August. In mid-August (week 33), sustained transmission of infection was confirmed in Iceland and decreased sampling was recommended by the Chief Epidemiologist. From that point on, diagnosis of influenza was based on the physician's clinical examination, and samples were to be obtained only from patients with severe illness or increased risk of serious illness.

Figure 5

Number of respiratory samples and proportion positive for 2009 pandemic influenza A(H1N1), Iceland, 29 June to 27 December 2009

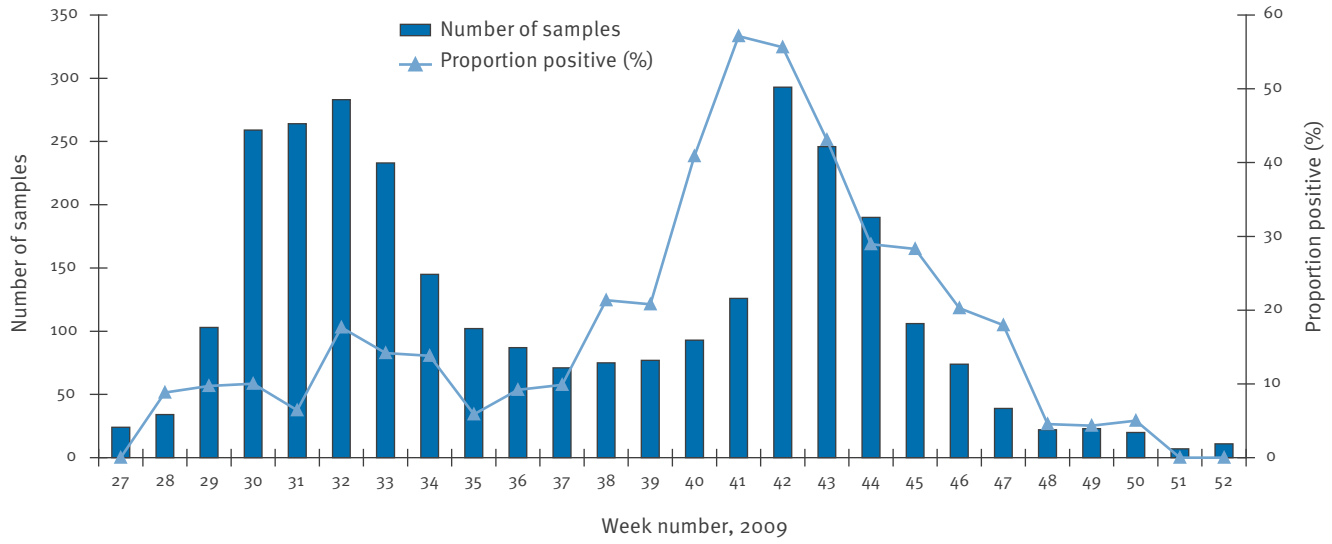
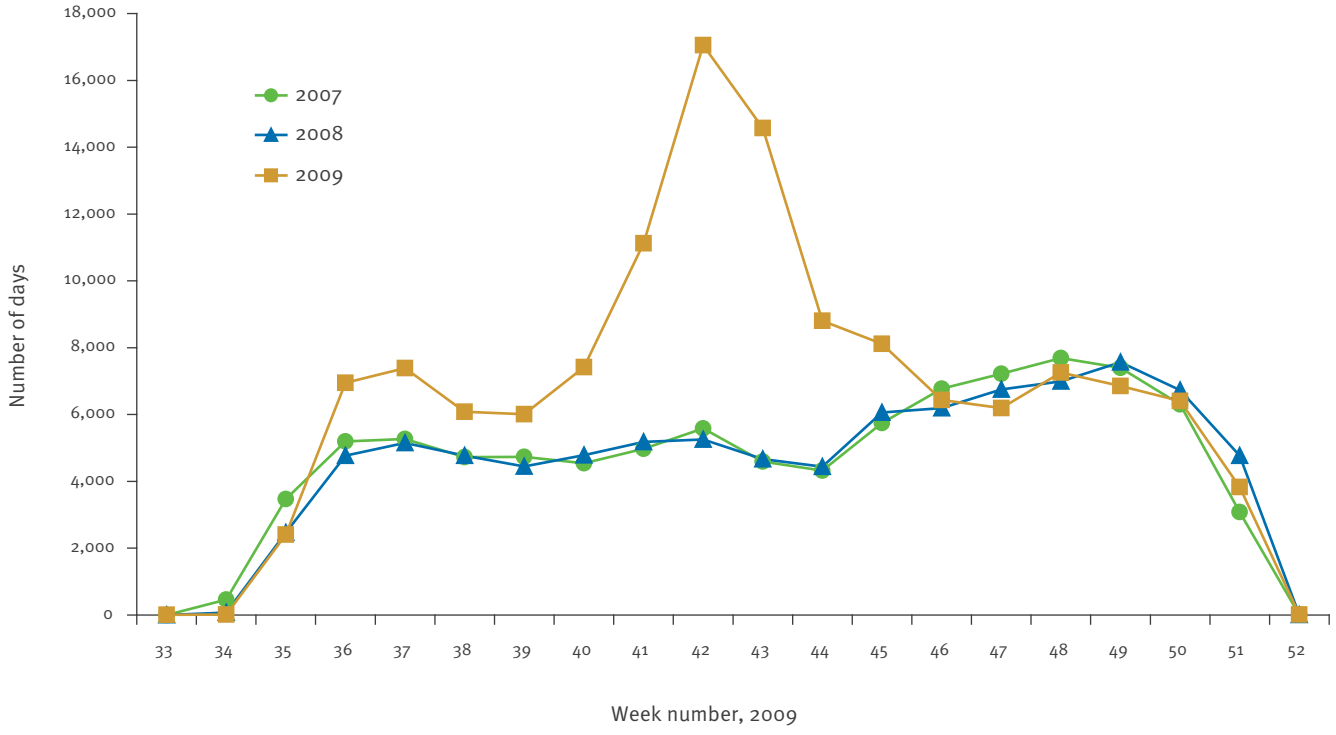


Figure 6

School absenteeism in elementary schools counted in number of days missed, Iceland, weeks 33–52 in 2007–2009



Following this recommendation, there was a decrease in late August 2009 (week 34 and 35) in the number of respiratory samples collected, with a concomitant decrease in the number of laboratory-confirmed cases (Figure 5). From the end of June to the end of December (weeks 27–53), 3,011 samples were collected, of which 702 (23%) tested positive for the pandemic virus. The number of samples and the percentage of samples positive increased in late September (week 40) and peaked in mid-October (week 42), when 293 samples were collected, 56% of which tested positive. These patterns were consistent with the changes observed in the number of reported ILI cases.

Pandemic influenza was laboratory confirmed in people living in all regions of the country. The age distribution of cases with laboratory-confirmed infections was the same as that observed for reported ILI cases (unpublished data).

School absenteeism

In September 2009 (week 40), shortly after the school year started, an increase in school absenteeism was observed, compared with the levels at that time in the previous two years (Figure 6). A sharp increase was observed in October 2009, compared with the same period in the previous two years, with a high peak in mid-October (week 42) (Figure 6). In late October and November (week 43 to 46), there was a rapid fall in school absenteeism and from mid-November to the end of December it was similar to that seen in the two previous years.

Mortality levels

No increase in overall mortality was observed from September to December 2009, according to data from the National Registry. Two persons with laboratory-confirmed pandemic influenza died during this time: an 18-year-old woman and an 81-year-old man who both had underlying conditions.

Estimated number of pandemic influenza infections in the community

A total of 3,336 cases were expected to be positive if all ILI cases were tested. This is a lower bound estimate since, in the latter part of the epidemic; tests were performed primarily on severe cases that could be caused by complications, rather than influenza. According to previous studies, approximately 10% of symptomatic influenza cases occur in the community for each ILI case detected by the surveillance system [16,17]. The expected number of symptomatic cases would therefore be 33,368 or 10.4% of the total population (n=319.246). A large number of asymptomatic infections are also expected to have occurred. A more detailed model has been used to estimate the number of 2009 pandemic influenza infections in the United Kingdom more closely [18], but such modelling is beyond the scope of our study.

Discussion

This article summarises the surveillance and epidemiology of the pandemic influenza in Iceland in 2009, showing how rapid improvements in influenza surveillance were feasible by connecting the existing structure in the healthcare system for patient records to electronic surveillance system for reporting ILI cases. This system does not require any additional input from physicians, enabling comprehensive data from the entire country to be collected with near real-time information on the geographical spread, age and sex of ILI cases.

The initial increase in the number of ILI cases was first observed in the western regions of the country, with eastern regions following approximately one week later; the peak of ILI activity showed a similar delay (Figure 2 and Table). A west-to-east spread has been described in four of eight influenza seasons from 1999 to 2007 in Europe [19]. The most likely explanation for the direction of spread of the epidemic in Iceland is that the densely populated area of the capital Reykjavik in the south-west corner of Iceland provides ample opportunities for the spread of the pandemic virus; most foreign travel, whether for business or leisure, begins or ends in Reykjavik.

The difference in the number of reported ILI cases by sex in our data could be due to females being more prone to the disease than men, but this hypothesis is not supported by previous studies, with the exception of increased risk of severe illness in pregnant women [20]. An alternative explanation could be that females contact physicians more often than males. The initiative to contact the physician for children and older people who are ill often comes from parents or other close relatives without regard the patient's sex, which could explain equal ILI reporting rate by sex for children and minor sex differences in the rates of reporting of older people. Adults from 18 to 60 years, however, decide themselves when to contact the physician and the differences between males and females observed in that age group in our data probably reflect more frequent visits to the physicians by females in general. Analysis of all encounters by age and sex in primary healthcare centres in Iceland during 2005, which shows a pattern similar to that observed in our data, gives support to this explanation [21].

People aged 15–30 years were probably at increased risk of acquiring the pandemic virus during July to September 2009 due to risky behaviour with frequent travel abroad and spending weekends at crowded outdoor festivals in Iceland. The age distribution in Iceland is in accordance with a recently published serological study from England that showed pre-existing antibodies in older age groups that protected against infection [22].

There are uncertainties in our estimate of the true number of pandemic influenza cases in the community.

The number of samples sent for virological analysis varied over time and it is possible that some samples were false negative. The exact proportion of patients with ILI in community who contacted healthcare was unknown and may have varied between regions and by sex and age group. Multiplying each reported ILI case by 10 should give a rough estimate of the number of cases in the community. Although the care-seeking behaviour for influenza in Iceland has not been studied, an estimate of 1 in 10 seeking care is supported by a recent serological study [22]. It may be possible to estimate the proportion of infected individuals seeking healthcare more accurately using a detailed disease transmission model, but such analysis is beyond the scope of this paper and we leave this for future study.

A small study, based on a questionnaire, carried out in the Akureyri municipality in northern Iceland in mid-November 2009 on the true incidence of ILI in the community showed a 22% cumulative attack rate (unpublished data), supporting the outcome of the simple model described in this study with regard to age, sex and timing of the epidemic curve by onset of illness. We therefore estimated that the percentage of symptomatic people infected in the community ranged from 10% to 22%. Estimates from other countries for the 2009 pandemic also concluded that the percentage of people infected with the pandemic virus was less than 30% of the population [18,22].

There are limitations to our ILI surveillance system. It was developed just in time for the pandemic, had not been adequately tested and baseline data for ILI had not been established. It is possible that physicians were affected by the introduction of a new reporting system and the ongoing pandemic in their clinical assessment. However, the ARI surveillance data do not support this hypothesis. They showed that physicians used ICD-10 codes for ARI when influenza was not suspected. The number of ARI cases peaked in week 41, which probably reflects the increase in illness caused by respiratory viruses other than influenza and/or the pandemic virus in cases with mild symptoms. In our study, ARI was used for quality assurance but further development is intended to enable timely and accurate ARI surveillance.

Our analysis of the data from elementary schools accounts for school absenteeism in number of days absent. The analysis of school absenteeism needs to be developed further with age-specific data on the number of children absent in each school. It is a novel method to estimate the number of children with ILI in the community for every ILI case registered in the healthcare system. It also enables assessment of the socio-economic impact of parents caring for sick children at home and ultimately enables real-time monitoring of local or widespread outbreaks in schools.

The pandemic virus circulated in the community in Iceland during summer and autumn. Elementary schools started in late August, with moderate spread of ILI in schoolchildren during September. But it remains unclear why a large outbreak occurred in October in children attending these schools, rather than in early September, immediately after the schools started.

Our study shows how the sudden need for improved surveillance during the pandemic led to rapid improvements in data collection. However, it is, of course, preferable to have a system in place when pandemics hit. Retrospective data were not collected during the pandemic for two main reasons: firstly, the amount of data would have overloaded both the database and the electronic reporting system and secondly, there was no time to check the validity of the older data and compare with the real-time data during the pandemic. Retrospective data will be collected and a baseline for ILI will be established in future work.

Using the same software for patient records and for surveillance provides a unique opportunity for real-time surveillance and risk assessment. No human input is needed to report the cases, which secures the sustainability of the system and improves the data delivery, compared with the old paper-based reporting system, with regard to the completeness and the timeliness of the data. The data are delivered when the physician has confirmed his record for the patient visit in the electronic patient journal, which can be a problem if physicians postpone their confirmation for weeks, months or even longer. The physicians were, however, constantly reminded during the pandemic to confirm the patient record, but this may need improvements.

The surveillance system established during the pandemic has replaced the older paper-based reporting system for ILI and will be expanded and improved to replace the current system of surveillance of all other notifiable diseases, thus eliminating all paper-based reporting, Changes to the system can be done rapidly, enabling real time surveillance of new and emerging diseases and syndromes that may appear in hospitals and primary healthcare centres in Iceland.

Acknowledgements

The authors thank Ingi Steinar Ingason, Auður Jóhannesdóttir, Júlíana Jóna Héðinsdóttir, Kristinn Jónsson and our co-workers at EMR for their support and solutions during the pandemic and development of the automatic reporting system for ILI.

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National surveillance of pandemic influenza A(H1N1) infection-related admissions to intensive care units during the 2009–10 winter peak in Denmark: two complementary approaches

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Citation style for this article:
Gubbels S, Perner A, Valentiner-Branth P, Mølbak K. National surveillance of pandemic influenza A(H1N1) infection-related admissions to intensive care units during the 2009–10 winter peak in Denmark: two complementary approaches. Euro Surveill. 2010;15(49):pii=19743. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19743

Article published on 9 December 2010

Surveillance of 2009 pandemic influenza A(H1N1) in Denmark was enhanced during the 2009–10 winter season with a system monitoring the burden of the pandemic on intensive care units (ICUs), in order to inform policymakers and detect shortages in ICUs in a timely manner. Between week 46 of 2009 and week 11 of 2010, all 36 relevant Danish ICUs reported in two ways: aggregate data were reported online and case-based data on paper. Cases to be reported were defined as patients admitted to an ICU with laboratory-confirmed 2009 pandemic influenza A(H1N1) infection or clinically suspected illness after close contact with a laboratory-confirmed case. Aggregate numbers of cases were reported weekly: during weeks 48-51 (the peak), reporting was daily. The case-based reports contained demographic and clinical information. The aggregate surveillance registered 93 new cases, the case-based surveillance 61, of whom 53 were laboratory confirmed. The proportion of beds used for influenza patients did not exceed 4.5% of the national capacity. Hospitals with cases used a median of 11% of bed capacity (range: 3–40%). Of the patients for whom information was available, 15 of 48 patients developed renal insufficiency, 19 of 50 developed septic shock and 17 of 53 died. The number of patients with pandemic influenza could be managed within the national bed capacity, although the impact on some ICUs was substantial. The combination of both reporting methods (collecting aggregate and case-based data) proved to be useful for monitoring the burden of the pandemic on ICUs.

Introduction

The first case of 2009 pandemic influenza A(H1N1) in Denmark was diagnosed on 1 May 2009. The incidence, assessed as the percentage of influenza-like illness (ILI) seen by general practitioners in the national sentinel system, rose in July 2009 and remained stable at around 0.75% for many months, until it started rising again in the week of 8 November 2009 (week 45) and peaked at 5.03% in the week of 22 November 2009 (week 47) [1]. Surveillance of ILI seen by the Danish medical on-call service showed a similar pattern [2]. Considering that the age distribution of patients with pandemic influenza as well as the distribution of risk factors differed from those seen in seasonal influenza [3-5], the impact on the healthcare system was also likely to be different from that during a seasonal influenza epidemic. Moreover, as the pandemic vaccine was available in week 45, a vaccination campaign after that would possibly not have been able to prevent many of the severe cases. It was therefore important to monitor severe disease due to the pandemic influenza.

Surveillance systems were enhanced to include hospitalisations and admissions to intensive care units (ICUs), as recommended in the Danish influenza pandemic plan [6]. The surveillance system to monitor the burden on ICUs was created in weeks 45 and 46 of 2009 in cooperation with the ICU of the Copenhagen University Hospital, Rigshospitalet, Denmark. The Danish Society for Anaesthesia and Intensive Care endorsed the system and the National Board of Health recommended that all ICUs in Denmark participated in the reporting. The system was set up to assess the ICU bed capacity used for pandemic influenza patients, and to provide demographic and clinical data as well as risk factors for death in order to estimate the impact of the pandemic on ICUs and contribute to an assessment of the severity of the pandemic and the severity of disease.

Methods

Clinical notification of patients with pandemic influenza was not mandatory in Denmark. Danish ICUs were, however, requested to report two types of data

to the Statens Serum Institut: (i) aggregate numbers of pandemic influenza patients by age group and (ii) clinical information for each individual patient. A case that should be reported was defined as a patient admitted to an ICU with laboratory-confirmed pandemic influenza A(H1N1) infection or a patient whose infection was clinically suspected and had had close contact with a patient with laboratory-confirmed pandemic influenza.

All hospitals with acute care facilities (n=53) in the five hospital regions of Denmark, excluding the Faroe Islands, were invited to take part in the surveillance system. The system started in week 46 of 2009 and was planned to continue until week 20 of 2010, or until no new cases had been reported by the ICUs for three consecutive weeks, and other surveillance systems, such as the sentinel system, also showed low and stable incidence levels.

Aggregate data

Starting on 15 November 2009 (week 46), ICUs reported aggregate data once a week on a Monday morning before 12:00. During weeks 48 to 51 inclusive of 2009, they were asked to report on a daily basis. Then the deadline was 09:00 on Mondays to Thursdays; data for Fridays and the weekends were reported on Mondays.

A web-based reporting form was created on the homepage of the Statens Serum Institut. A dedicated contact person in the ICUs reported the number of new cases, as well as the number of cases present in the ICU at 08:00 on the day of reporting. The number of cases was reported by the following age groups: <1 year, 1–4 years, 5–14 years, 15–24 years, 25–64 years, 65–74 years and ≥75 years.

We entered the data from the web-based form to a master dataset in a Microsoft Access database. Each report in the aggregate system was evaluated and validated. Reports were corrected for double reporting when a case was transferred to another hospital, but this could only be done if the hospitals actively informed us. Similarly, reports were amended or removed when we were informed of errors or when they contained obvious inconsistencies that needed further follow-up. Bed capacity, expressed as a percentage, was calculated as the number of cases present in an ICU divided by the total number of beds available at that moment.

A summary of the data received was disseminated to the ICUs and the National Board of Health once a week and each day during weeks 48–51 of 2009 (the winter peak). The National Board of Health presented these reports in the parliamentary standing committee on health.

Case-based data

The form used to gather information on each patient included demographic and clinical data, such as underlying medical conditions, co-presenting illnesses, dates of onset of symptoms and admission to ICU and details on treatment. A physician completed this paper form. ICUs were asked to send the completed forms as soon as possible after a patient was admitted and to send any additional information at a later stage if anything was unknown on admission.

A unique patient identifier (the person's number from the Danish Civil Registry System [7]) was reported on the case-based form. The Civil Registration number enabled us to complement the case-based surveillance with data from several registers. From the Danish Civil Registry System we could verify cases who had died as a result of pandemic influenza. A case who died of pandemic influenza after ICU admission was defined as a patient reported in the case-based surveillance who died within 30 days after initial laboratory confirmation of the infection. The Statens Serum Institut laboratory database was used to verify the laboratory confirmation of the patients reported in the case-based surveillance. During the pandemic, laboratories in Denmark were obliged to send samples from patients with ILI to the reference laboratory in Statens Serum Institut, either for initial testing or for confirmation. Vaccination status was verified using the Danish vaccination registry, which was set up in 2009 and was assumed to cover the majority of pandemic vaccine recipients. The vaccination registry also included the reason for vaccination.

Data were analysed using Fisher's exact test for categorical variables with a binary outcome and the Mann–Whitney test for continuous variables. The level of significance was set at $p<0.05$.

Results

We implemented the pandemic surveillance system, both for aggregate and individual data in week 46 of 2009. The system was discontinued after week 11 of 2010 as no new cases had been reported for three consecutive weeks and both sentinel surveillance and on-call monitoring showed low activity for several weeks [2].

Of the 53 hospitals in Denmark with acute care facilities, five had no ICU and 16 were part of a larger group of hospitals that reported for them. As a result 32 hospitals across Denmark were identified for reporting. They reported for 36 ICUs: 32 general ICUs, two paediatric ICUs and two ICUs for neurosurgery.

Aggregate data

All 36 ICUs took part in the surveillance system, although the level of participation varied: until week 8 of 2010 the number of reporting ICUs varied between 22 and 29 after which the numbers dropped to 15 and 16, in weeks 10 and 11 of 2010, respectively. Late reports usually did not contain any cases. Personal contact with hospitals that had a low response rate confirmed that they had not reported because they had no cases.

After data cleaning, 355 weekly and 758 daily reports were validated and used for analysis. During the surveillance period 93 new cases were reported. Figure 1 shows the number of new cases by week of admission and the timeliness of reporting. Late reports were usually received within a week after the deadline. Only two cases admitted during the Christmas week were reported two weeks later. Data from the national sentinel surveillance system were added, showing the proportion of patients with ILI among the total number of patients who consulted a general practitioner. The peak of new pandemic influenza cases in ICUs was seen in week 48 of 2009, one week later than the peak seen in the sentinel data and two weeks after the on-call monitoring peak [2]. The last new case in an ICU was reported in week 8 of 2010.

The proportion of beds used for pandemic influenza cases did not exceed 4.5% of the total national ICU bed capacity. Hospitals with cases used a median of 11% of ICU beds for pandemic influenza patients (range: 3–40%).

Case-based data

A total of 74 case-based forms were received from 19 hospitals. These forms contained details of 61 individual patients: for 13 patients we received a second, updated form, either from the same hospital or from another hospital to which the patient had been transferred. Of the 61 reported cases, 53 were laboratory confirmed by polymerase chain reaction (PCR). Four cases tested negative in several PCR tests; for another four, the laboratory results could not be traced. Only the 53 laboratory-confirmed cases were used for analysis.

The number of laboratory-confirmed cases from the case-based surveillance is shown in Figure 2 by week of admission, as well as data from the sentinel system. Unlike the epidemic curve of the aggregate data, the peak of the case-based data coincided with the peak of the sentinel data and was one week after the on-call monitoring peak [2].

Demographic data

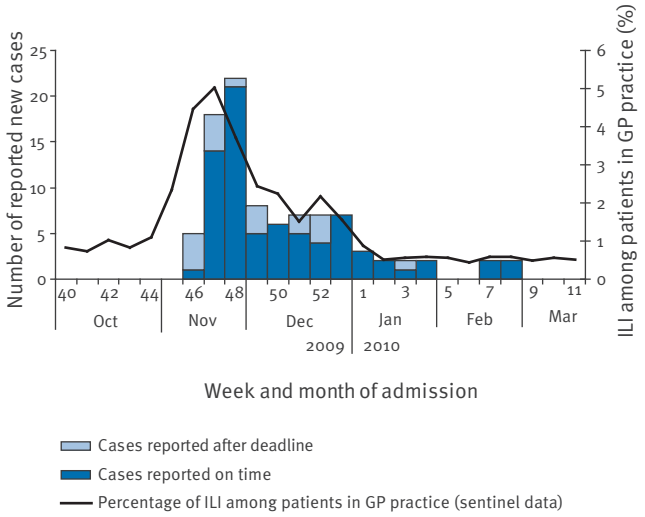
Of the 53 laboratory-confirmed cases, 31 were male and 22 were female. The median age was 47 years (range: 3–80 years). Figure 3 shows the age- and sex-specific incidence. The median age among men was 50 years (range: 3–75 years) and among women 45 years (range: 5–80 years; Mann–Whitney test p=0.96).

Medical history

Details on medical history were complete for most cases, but for a few patients some details were missing. The presence or absence of an underlying medical condition was reported for 52 of the 53 laboratory-confirmed cases: 11 had no pre-existing underlying medical condition, while 41 had at least one. Table 1 shows the underlying conditions for cases under 15 years of age and those aged 15 years and older. The presence of specified underlying illnesses varied between 9 of 47

Figure 1

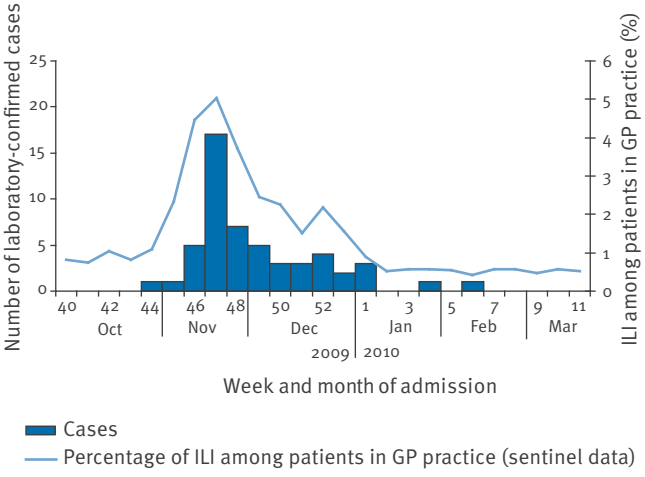
Weekly aggregate data: reported new 2009 pandemic influenza A(H1N1) cases by week of admission (n=93) by timeliness of reporting and data from the national sentinel system, Denmark, week 40 of 2009 to week 11 of 2010



GP: general practioner; ILI: influenza-like illness.

Figure 2

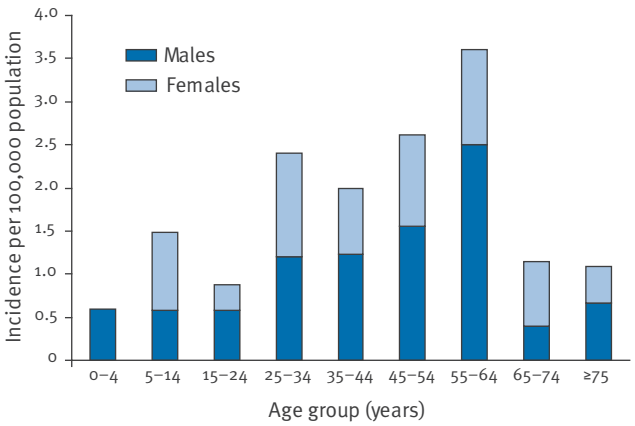
Case-based data: laboratory-confirmed 2009 pandemic influenza A(H1N1) cases by week of admission (n=53) and data from the national sentinel system, Denmark, week 40 of 2009 to week 11 of 2010



GP: general practioner; ILI: influenza-like illness.

Figure 3

Case-based data: incidence of laboratory-confirmed 2009 pandemic influenza A(H1N1) cases by sex and age group, Denmark, week 46 of 2009 to week 11 of 2010



and 12 of 49 except for renal insufficiency, which was observed in fewer (3 of 49) cases. In addition, 14 of 47 of the cases had other underlying illnesses that were not further specified. One case was reported to have been pregnant when admitted to the ICU and one had recently given birth.

According to the vaccine registry 10 of the 53 cases had been vaccinated against pandemic influenza A(H1N1): they had been vaccinated because of an underlying chronic illness. One of the 10 had been vaccinated twice, with an interval of a month between the vaccinations. The median time between vaccination and

Table 1

Case-based data: frequency of underlying conditions reported in cases with laboratory-confirmed 2009 pandemic influenza A(H1N1), Denmark, week 46 of 2009 to week 11 of 2010 (n=52)

Underlying condition	Age 0–14 years		Age ≥15 years		Total		
	Number of relevant cases	n	Number of relevant cases	n	Number of relevant cases	n	%
None	1	6	10	46	11	52	21.2
Renal insufficiency (creatinine levels 1.5 times above normal)	0	5	3	44	3	49	6.1
Cancer	2	5	7	43	9	48	18.8
Immunocompromised condition	3	5	6	42	9	47	19.1
Neurological illness	2	5	7	42	9	47	19.1
Diabetes	1	6	9	46	10	52	19.2
Chronic lung disease, including asthma	1	5	10	44	11	49	22.4
Obesity (BMI>30)	NA	NA	10	41	10	41	24.4
Cardiovascular disease	1	5	11	44	12	49	24.5
Other underlying illness	0	5	14	42	14	47	29.8
Pregnancy	NA	NA	1	20	1	22	4.5
<42 days post-partum	NA	NA	1	20	1	22	4.5

BMI: body mass index; NA: not applicable.

Table 2

Case-based data: symptoms, treatment, interventions and outcome in cases with laboratory-confirmed 2009 pandemic influenza A(H1N1), Denmark, week 46 of 2009 to week 11 of 2010 (n=53)

Description		Total		
		Number of relevant cases	n	%
Symptoms				
Pneumonia		41	51	80.4
	Viral	15	41	36.6
	Bacterial	5	41	12.2
	Viral + bacterial	21	41	51.2
Renal insufficiency (creatinine levels 1.5 times above normal)		15	48	31.3
Septic shock		19	50	38.0
Treatment and interventions				
Antiviral treatment		47	51	92.2
	Oseltamivir alone	27	47	57.4
	Zanamivir alone	1	47	2.1
	Oseltamivir + zanamivir	19	47	40.7
No antiviral treatment		4	51	7.8
Mechanical ventilation		42	52	80.8
	Invasive	26	42	61.9
	Non-invasive	4	42	9.5
	Invasive + non-invasive	12	42	28.6
Haemodialysis		10	50	20.0
Extracorporal membrane oxygenation		6	53	11.3
Outcome				
30-day mortality		17	53	32.1

admission to an ICU was seven days (range: 3–35 days); seven cases were admitted to an ICU within 14 days of vaccination. Of the 41 patients reported to have at least one underlying medical condition in the case-based system, 32 were not vaccinated. The pregnant case who had been admitted to an ICU was not vaccinated.

Clinical presentation, treatment, interventions and outcome

Table 2 shows the available data on clinical symptoms related to severe illness as well as treatment, interventions and outcome. The median interval between onset of symptoms and hospitalisation for 47 of the cases was three days (range: –78 to +33). Four of the 47 had already been hospitalised for 1, 5, 10 and 78 days when they developed pandemic influenza. When those four are excluded, the median time between symptom onset and hospital admission was four days. For these patients (n=43), the median interval between hospital admission and ICU admission was one day (range: ‹1–21 days,). The median time between onset of symptoms and the date of ICU admission was five days (range: ‹1–15 days, with one outlier of 54 days, n=43). The number of days in the ICU was calculated for 40 of these patients and ranged from less than one to 65, with a median of 10 days.

A majority of patients (41 of 51) developed pneumonia and 19 of 50 had septic shock. Of 48 patients, 15 developed renal insufficiency, 12 of whom had no history of this condition. Ten patients developed both renal insufficiency and septic shock.

Of 51 patients, 47 were reported to have been treated with antiviral medication, mostly oseltamivir (n=27) or a combination of oseltamivir and zanamivir (n=19). The median interval between onset of symptoms and the start of any antiviral treatment was five days (range: –6 to +53 days, n=42). One person was already on antiviral treatment before symptom onset. The median interval between ICU admission and start of antiviral treatment was less than one day (range: –9 to +8 days, n=47). A total of 13 patients were on antiviral treatment before ICU admission. A total of 42 of 52 patients received mechanical ventilation: most of them received ventilation immediately when they were admitted to the ICU. The median time between admission and ventilation was less than one day (range: ‹1–4 days, n=42). The median period of ventilation was 7.5 days (range: ‹1–45 days, n=22). Of 50 patients, 10 underwent haemodialysis and six of the 53 were treated with extracorporeal membrane oxygenation (ECMO).

The death rate was 32% (17 of the 53 cases). Three patients died more than 30 days after confirmation of their infection with pandemic influenza (34, 41 and 169 days after confirmation). As of 22 October 2010, the other 33 patients were alive. Of the 17 patients who died within 30 days 11 were male and six were female (Fisher's exact test p=0.57). Of the 17 cases whose deaths were related to the pandemic influenza, 13 had a pre-existing underlying medical condition. This was not associated with death (Fisher's exact test p=1.0). ECMO treatment was also not associated with a higher risk of death (three of six patients died after ECMO). Figure 4 shows the number of cases who died by age group. Of the 17 whose deaths were related to pandemic influenza, 12 were aged between 45 and 65 years.

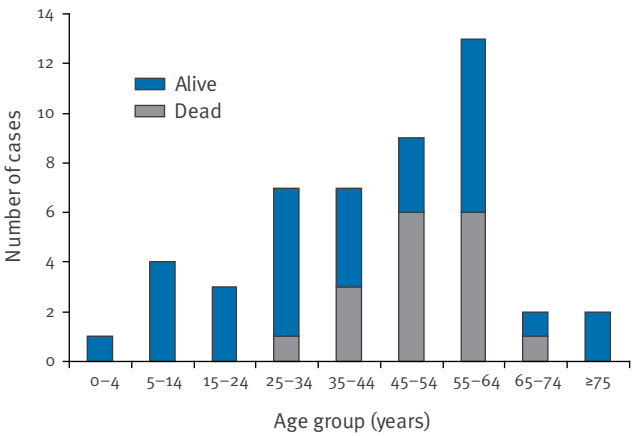
Discussion

The aggregate data obtained through the surveillance system employed between week 46 of 2009 and week 11 of 2010 served as a tool to monitor the capacity in ICUs and to assist in planning for referral of severe cases as the epidemic progressed. Our results showed that the trend in incidence of pandemic influenza A(H1N1) infection was visible from the aggregate data even when only cases reported within the deadlines were considered. The aggregate data showed that the number of new cases reached its maximum a week later than the peak observed from the case-based surveillance and sentinel surveillance. This can be expected as the median period between onset of symptoms and ICU admission was five days.

The aggregate data enabled us to assess the number of patients with pandemic influenza in ICUs, but there are some uncertainties. We consider that the extent of the underestimation, due to inconsistent participation of some hospitals, is limited as we found that hospitals that had not reported usually had no cases. However, there might have been a slight overreporting of patients who had been transferred to another hospital. The choice of case definition, which included patients with an epidemiological link to a laboratory-confirmed patient, might have led to some false-positive cases. Due to the aggregate nature of the data, we cannot quantify this. All things considered, the extent of the uncertainties seems limited and we estimate that the number of reported cases (n=93) closely approaches

Figure 4

Case-based data: laboratory-confirmed 2009 pandemic influenza A(H1N1) cases by outcome 30 days after initial laboratory confirmation and by age group, Denmark, week 46 of 2009 to week 11 of 2010 (n=17)



the actual number of patients with pandemic influenza in Danish ICUs. Therefore, the 53 confirmed cases used in the analysis of the case-based system can be assumed to represent approximately 57% (53 of 93) of the patients with pandemic influenza in Danish ICUs.

Severity of the pandemic

This surveillance system can assess certain aspects of the severity of the winter peak of the pandemic in Denmark: the number of severe cases in the general population, the death rate among severe cases and the specific groups that developed severe illness.

On the basis of the 93 cases reported in the aggregate data, the estimated incidence in Denmark (with a population of 5.5 million) was 1.7 per 100,000 population. This suggests that the overall impact of severe illness was not high at the population level and is in line with the incidence of ICU admissions observed in Australia and New Zealand during the 2009 winter peak [8]. In our study, the death rate was 32% (17 of 53 cases admitted to an ICU). These deaths occurred mainly in the age groups 44–54 years and 55–64 years. A cut-off point of 30 days after initial laboratory confirmation was chosen, to increase specificity, but it is possible that some of the deaths more than 30 days after confirmation were associated with pandemic influenza.

During seasonal influenza epidemics, children under two years of age and adults over 64 years are mostly affected, whereas the 2009 pandemic typically affected young adults [3-5]. The World Health Organization stated that people older than 65 years were the least likely to be infected with pandemic influenza, but if infected they would be at high risk of developing serious complications [9]. In Denmark, children aged 5–14 years contributed heavily to the number of patients admitted to hospitals [10], which was less prominent in the ICU admissions. The median age of 47 years of the cases in our study is within the range described in other studies of ICU patients with pandemic influenza [11-16]. While healthy adults generally do not suffer from severe illness when infected with seasonal influenza, the pandemic showed a different picture worldwide [3-5]. Our case-based data also showed a relatively high number of severe cases among previously healthy individuals.

The pandemic vaccination campaign started in week 45 of 2009 in Denmark. The strategy – to vaccinate all individuals with risk factors independent of age – was in line with the wide range in age distribution seen among patients with pandemic influenza in ICUs. It is important to note that the majority of the reported ICU cases with an underlying disease was not vaccinated. For those ICU patients who were vaccinated the vaccine probably came too late. However, vaccine effectiveness studies are needed to draw conclusions on these issues.

Severity of disease

The median period of five days between onset of symptoms of pandemic influenza and ICU admission was consistent with observations in other studies in Argentina (median of six days) and in Australia, New Zealand and Canada (median of four days) [11-13]. This interval will be influenced by access to healthcare and the perception of severity of symptoms by patients and physicians.

Severe respiratory failure occurred in 42 of 52 cases and for most of them, mechanical ventilation was started the same day they were admitted to the ICU. Also in other ways, the clinical presentation of pandemic influenza patients in Danish ICUs was severe, with 10 of 48 cases developing both renal insufficiency and septic shock, and several cases developing either renal insufficiency or septic shock. Davies *et al.* predicted that Europe had to prepare for an estimated 2.6 persons per million inhabitants needing ECMO treatment as a result of pandemic influenza [12]. Since ECMO treatment was only performed in one hospital in Denmark during the pandemic, we could verify that the six cases reported in our case-based surveillance to have received ECMO were in fact all pandemic influenza cases in Denmark who received ECMO during the surveillance period. This number is of the order of magnitude Davies *et al.* predicted.

Impact of the pandemic on Danish intensive care units

The aggregate data showed that the burden on the ICUs was limited, at a national level. However, for hospitals that had pandemic influenza cases the ICU bed capacity used for these patients was substantial. Similar findings on ICU bed capacity were reported from Australia and New Zealand during the 2009 winter peak [8]. Our case-based data showed that the vast majority of cases needed ventilation and a high number of cases presented with complications, requiring treatment such as haemodialysis and ECMO. This required a high level of care and led to extra pressure on ICU facilities and staff. Due to the absence of baseline data it is, however, not possible to compare this to the situation in ICUs during seasonal influenza epidemics.

The combination of aggregate and case-based data proved to be a useful tool to assess the situation in ICUs during the 2009 pandemic. Since both epidemic curves followed the same trend as the data from sentinel surveillance and on-call monitoring, the sentinel and on-call systems can be used to decide when to put the ICU surveillance in place during the next winter season. The ICU surveillance system could also be used during a seasonal epidemic in order to learn more about the baseline situation for seasonal influenza.

Acknowledgements

We wish to thank all contact persons in the ICUs for their efforts to provide us with the information and the clinical

microbiology laboratories in Denmark for sending the samples to the Statens Serum Institut. We would also like to thank Eskild Petersen (Department of Infectious Diseases, Aarhus University Hospital, Skejby, Aarhus, Denmark), Per Bo Larsen (Unit for Acute Medicine and Health Preparedness, Capital Region, Hillerød, Denmark), Jens Lundgren (University of Copenhagen and Rigshospitalet, Copenhagen, Denmark), Michael Galle, Kenn Schultz Nielsen, Jakob Holck, Katarina Widgren, Steffen Offersen Glismann, Anne Mazick and Tyra Krause (Department of Epidemiology, Statens Serum Institut, Copenhagen, Denmark), Lars Peter Nielsen and Betina Skovgaard Andresen (Virology laboratory, Statens Serum Institut, Copenhagen, Denmark) and the EPIET coordinators.

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Mortality of 2009 pandemic influenza A(H1N1) in Germany

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Citation style for this article:
Wilking H, Buda S, von der Lippe E, Altmann D, Krause G, Eckmanns T, Haas W. Mortality of 2009 pandemic influenza A(H1N1) in Germany. Euro Surveill. 2010;15(49):pii=19741. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19741

Article published on 9 December 2010

The mortality in Germany caused by the 2009 pandemic influenza A(H1N1) seems to have been one of the lowest in Europe. We provide a detailed analysis of all 252 fatal cases of confirmed infection with the pandemic virus notified between 29 April 2009 and 31 March 2010. The overall mortality was 3.1 (95% confidence interval (CI): 2.7 to 3.5) per one million inhabitants. We observed an increase in the case fatality rate of notified cases over time; notified cases aged 60 years or older had the highest case fatality rate (2.16%; 95% CI: 1.61 to 2.83; odds ratio: 5.4; p<0.001; reference group: 35–59 years). The median delay of four days (interquartile range (IQR): 2–7) between symptom onset and antiviral treatment was significantly longer in fatal cases than for non-fatal cases (median: two days (IQR: 1–3; p<0.001). Analysis of the underlying medical conditions of fatal cases, based on the observed frequency of the conditions in the general population, confirms the risk for fatal outcome, which is most notably due to immunosuppression, diabetes and respiratory diseases. Our results suggest that early treatment might have had an impact on overall mortality. Identification of risk groups for targeted intervention to prevent fatalities needs to take into account the distribution of underlying conditions in the population.

Introduction

Based on initial reports from Mexico, the case fatality rate (CFR) of 2009 pandemic influenza A(H1N1) was estimated to be 0.09% (range: 0.07–0.4) and there was considerable uncertainty over what could be expected in other countries [1]. Since March 2009, various countries in Europe and worldwide have experienced one or more pandemic waves, with remarkable differences in the number of reported deaths between countries [2-9]. On 27 April 2009 the first symptomatic cases positive for the pandemic virus were notified in Germany [10]. The first death associated with laboratory-confirmed pandemic influenza was reported on 25 September 2009 from North Rhine-Westphalia, just before the number of autochthonous cases started to rise exponentially in week 42 [11,12]. Despite more than 200,000 cases of laboratory-confirmed pandemic influenza, the overall mortality in Germany based on the notified cases is one of the lowest in Europe. However, an intriguing number of deaths occurred after the incidence of influenza at the population level had already subsided at the end of 2009.

This article presents a detailed analysis of all 252 notified fatal cases in Germany, from the first detection of pandemic cases in April 2009 up to 31 March 2010. We focused on the course of disease, antiviral treatment and the risk factors involved in order to better understand how the situation in Germany differed from that in other countries and to identify groups at risk of severe disease and fatal outcome, in preparation for potential subsequent waves.

Methods

In Germany, in accordance with the protection against infection act, every laboratory-confirmed case of influenza has to be notified by the laboratory to the local health authority and additional clinical information is actively retrieved from the physician [13]. Additionally, on 2 May 2009, a special legal ordinance for pandemic influenza came into force. German physicians had to notify suspected cases of pandemic influenza to the local health authorities. For this the case ascertainment followed the recommendations given by the professional medical societies [12,14]. Suspected cases were tested for presence of the pandemic virus and only laboratory-confirmed cases or clinical cases with an epidemiological link to a laboratory-confirmed case were transmitted for whole Germany from the local health authorities via the federal states to the Robert Koch Institute in Berlin, Germany. These cases are included in this study.

A fatal case is defined as a person whose death was in temporal relation to an infection with pandemic

influenza confirmed by direct identification tests using standard laboratory methods (polymerase chain reaction (PCR) or viral culture) irrespective of other diagnoses. Laboratory confirmation could be ante- or post-mortem. Proof of a causal relationship between death and laboratory-confirmed influenza was not established. All cases (fatal and non-fatal) are transmitted using the official electronic notifying system in Germany (SurvNet) [15]. The system includes information on age, date of onset of illness, hospitalisation and fatal outcome. It allows the update of information including additions and corrections.

Starting on 17 July 2009, the following additional case-based information was included for all notified and transmitted cases, using a standardised free-text format: antiviral treatment (none; oseltamivir; zanamivir), date of start of treatment, reason for hospitalisation (Influenza; other disease, unknown), pneumonia (yes; no) and underlying chronic medical disease conditions (none; diabetes mellitus; impairment of the cardiovascular system including hypertension; impairment of the respiratory system; obesity defined as a body mass index (BMI)›30; pregnancy; immunosuppression; other specified). Data sets of fatal cases in the central database at the Robert Koch Institute were additionally checked for possible inconsistencies and only validated data sets were included in the analysis. A more detailed description of the special issues concerning German data acquisition during the pandemic has been published recently [12].

Cross-sectional data on the 12-monthly prevalence for chronic disease conditions in Germany was collected via a telephone-based self-reported survey – Gesundheit in Deutschland Aktuell [German Health Update]. For detailed information on the method, see reference 16. The target population was the German-speaking resident population aged 18 years and above. The current survey was conducted from July 2008 to June 2009, covering the start of the pandemic.

The overall mortality for Germany is based on the total population in 2009 reported by the Federal Statistical Office (82,200,000) and we calculated cumulative mortality stratified by age group. For the comparison of mortality between different countries, data provided by the European Centre for Disease Prevention and Control (ECDC) were used [5]. As denominator, estimates for the total populations of European countries were obtained from Eurostat, the United States Census Bureau and Statistics Canada (all 2009 estimates).

All calculations were based on cases with available information as denominator. To calculate the case fatality, we used the number of laboratory-confirmed or epidemiologically confirmed pandemic influenza cases notified in Germany for each week as the denominator. Odds ratios (ORs) were given for the influence of age group on the incidence of fatal outcome in all notified influenza cases. Relative risks (RRs) were calculated as risk of death in persons with underlying chronic conditions divided by the risk of death in persons without these reported risk factors; sex and 10 age strata were used for adjustment, except for pregnancy. We included the exact binomial 95% confidence intervals (CIs) for proportions and the test on the equality of medians if appropriate. For time spans, the median and interquartile range (IQR) as measure of statistical dispersion were given. Stata was used for calculations.

Results

Disease frequency

In Germany 252 fatal cases associated with laboratory-confirmed 2009 pandemic influenza A(H1N1) were reported, starting with the first case on 25 September 2009. The first increase in the number of fatal cases occurred in week 44 of 2009 and within one month the notification of fatal cases rose to a maximum of 37 (in week 47) (Figure 1). A second peak was observed, with 20 fatal cases per week from week 52 of 2009 to week 1 of 2010. Taking all notified and transmitted cases as the denominator (n=226,075), the overall CFR of notified cases (nCFR) was calculated to be 0.11% (95% CI: 0.10 to 0.13). The cumulative mortality by 31 March 2010 was 3.1 (95% CI: 2.7 to 3.5) per million inhabitants. The majority (58%; 95% CI: 52 to 64) of fatal cases was male. In cases aged below 15 years a high proportion (66%: 95% CI: 46 to 82) of fatal cases was female.

During the pandemic wave, the weekly nCFR changed with a period with low values before the calendar week 52 and high thereafter (Figure 1). Taking week 52 as a cut-off date we divided the fatal cases into early (n=189) and late cases (n=63). In a univariate analysis there was a significant association of the late cases with advanced age (≥60 years; p=0.016) and being male (p=0.038). Underlying medical risk factors (p=0.17), interval between the onset of symptoms and death (p=0.56) and the time from onset of symptoms to the start of antiviral treatment (p=0.34) were not associated with late cases. The multivariate model with the above independent variables failed to achieve statistical significance, but this is probably due to small numbers of cases.

Age distribution

The median age of the fatal cases was 47 years (IQR: 29–57), which is significantly higher than for the non-fatal cases (median: 16 years; IQR: 10–28; p<0.001). Generally, all age groups were affected: the age group with the highest mortality was children aged less than 1 year with a cumulative mortality of 4.4 (95% CI: 1.6 to 9.5) per one million children of this age group (Table 1), followed by the age group 35–59 years with 4.2 (95% CI: 3.5 to 5.0) per one million people of this age. However, the 95% CIs and the Kruskal–Wallis rank test (p=0.41) indicate that differences in mortality between the age groups was not pronounced and did not achieve statistical significance.

In contrast, the nCFR was highest in elderly people (≥60 years), at 2.16%, with an OR of 5.4 (95% CI: 3.9 to 7.6) in comparison with the age group 35–59 years. Schoolchildren (5–14 years) showed the lowest nCFR of 0.03% (95% CI: 0.02 to 0.04) with an OR of 0.07 (95% CI: 0.04 to 0.12).

Course of disease

The median interval between the onset of symptoms and death was 13 days (IQR: 6–22). Symptom onset in adult cases was reported to have occurred more than 14 days before the date of death for 91 of 233 (39%) cases and more than 28 days for 44 of 233 (19%) cases. However, this was observed only for adult cases. In children (<15 years), this interval was significantly shorter, with a median of six days (IQR: 3–13), than in the other age groups (p=0.01).

The majority of notified fatal cases (211 of 233, 90.6%) had been admitted to a hospital. In 125 of 164 (76.2%) cases, the influenza infection was indicated as the cause for hospitalisation. The median length of hospitalisation overall was 12 days (IQR: 4–23); in children (<15 years), the median (five days; IQR: 3–12) was significantly shorter than that in the other age groups (p=0.04). Pneumonia was diagnosed in 200 of 220 (90.9%) cases.

Antiviral treatment

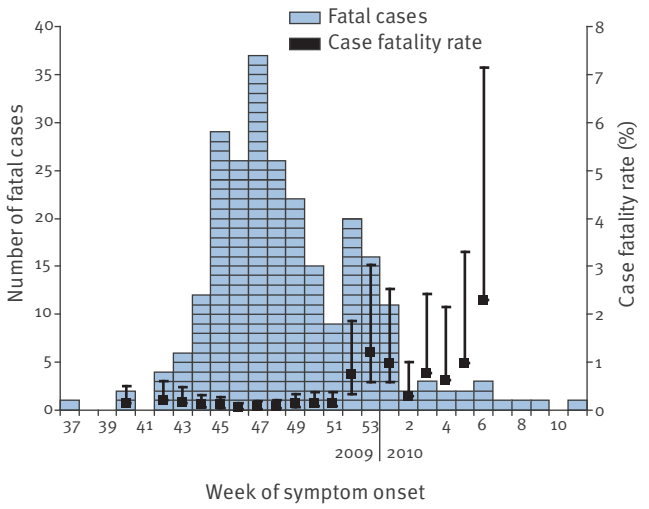
Antiviral therapy was started in more than half of the fatal cases (148 of 230; 64.3%), with oseltamivir in 141 cases and zanamivir in seven cases. In those patients with available data, the median time from onset of symptoms to the start of antiviral treatment was four days (IQR: 2–7) (Figure 2). This interval was significantly longer than that for non-fatal cases (two days; IQR: 1–3; p<0.001). In 11 of 15 (73.3%) fatal cases below 15 years of age and in 93 of 125 (74.4%) of the adult fatal cases, treatment was not carried out within 48 hours of the onset of symptoms as recommended [14]. The median time from the start of antiviral treatment to death was five days (IQR: 2–12).

Risk factors

At least one risk factor for severe influenza illness was present in 200 of the 252 fatal cases (79.4%). More than one underlying medical condition was reported for 61(24.2%) of the patients. For 34 (13.5%) of the fatal cases, no underlying condition regarded as a risk factor was reported. Of these 34 cases, four were aged below 15 years and 13 were female. Half of these cases (16 of 32 with available information) had received antiviral treatment, which was significantly less often than in cases with reported risk factors (p=0.039).

Figure 1

Notified fatal cases of 2009 pandemic influenza A(H1N1) and case fatality rate, by week of symptom onset in 2009 and 2010, Germany (n=252)



Black bars represent 95% confidence intervals.

Table 1

Age distribution of fatal cases of 2009 pandemic influenza A(H1N1), Germany, 29 April 2009 to 31 March 2010 (n=252)

Age group (years)	Number of cases	Percentage male	Cumulative mortality in one million population (95% CI)[a]	Notified case-fatality rate as percentage[b]	Odds ratio (95% CI)[c]	P value
0–1	6	66	4.4 (1.6–9.5)	0.18	0.47 (0.21–1.06)	0.07
2–4	4	50	1.9 (0.5–4.9)	0.05	0.13 (0.05–0.35)	<0.001
5–14	19	21	2.5 (1.5–3.9)	0.03	0.07 (0.04–0.12)	<0.001
15–34	42	57	2.2 (1.6–3.0)	0.07	0.18 (0.13–0.26)	<0.001
35–59	130	62	4.2 (3.5–5.0)	0.40	Reference group	Reference group
≥60	51	63	2.4 (1.8–3.2)	2.16	5.4 (3.86–7.56)	<0.001
Total	**252**	**58**	**3.1 (2.7–3.5)**	**0.15 0.11[d]**	–	–

CI: confidence interval.

[a] Based on the German population of 2008. The output of the Kruskal–Wallis rank test was p= 0.41, which indicates that there were no significant differences in cumulative mortality between the age groups.

[b] Denominator: all notified and transmitted pandemic influenza cases with detailed information on age, unless otherwise indicated.

[c] Odds ratio for the influence of the age group on the incidence of fatal outcome in all pandemic cases. The age group 35–59 years was set as the reference group.

[d] Denominator: all notified and transmitted pandemic influenza cases.

Measures of disease frequency and association with underlying medical conditions among adult (≥18 years) fatal cases are given in Table 2. The relative risk of death of infected individuals with underlying chronic disease conditions in comparison with that for infected individuals without any reported risk factors was 10.0 (95% CI: 6.7 to 15.0). Immunosuppression was most frequently notified, with a proportion of 26.0% (95% CI: 20.0% to 32.7%) fatal cases. This is in keeping with the fact that immunosuppression was notified in 34 of 138 (24.6%) of the fatal cases with only one underlying disease as a risk factor. This is by far the highest proportion in this group of patients, indicating a strong association to severe cases of pandemic influenza. However, no population-based survey data are available to calculate the relative risk.

Diseases of the cardiovascular system were reported, with a proportion of 23.5% (95% CI: 16.7 to 29.3), which is in the same range as the sum of self-reported population-based 12-month prevalences of hypertension: 21.4% (95% CI: 20.9 to 22.0), angina pectoris: 1.7% (95% CI: 1.5 to 1.9) and heart failure: 2.4% (95% CI: 2.2 to 2.6). Obesity was notified with a proportion of 19.9% (95% CI: 14.5 to 26.2) and showed a slight association with fatal outcome RR: 1.2 (95% CI: 0.8 to 1.8). Underlying chronic respiratory disease was notified, with a proportion of 19.9% (95% CI: 14.5 to 26.2). This proportion was twice as high as the combined prevalence of asthma: 5.2% (95% CI: 4.9 to 5.5) and chronic (obstructive) bronchitis: 4.5% (95% CI: 4.3 to 4.8) in the German population. Furthermore, diabetes was frequently reported for the fatal cases (17.2%) and doubled the risk of a fatal outcome (RR: 2.3; 95% CI: 1.5 to 3.6).

Two of the fatal cases were pregnant. One presented no other additional risk factor; the other was reported to be obese. Considering all pregnant women of

Figure 2

Notified fatal cases of 2009 pandemic influenza A(H1N1) by time between symptom onset and start of antiviral treatment, by age group, Germany, 29 April 2009 to 31 March 2010 (n=140)

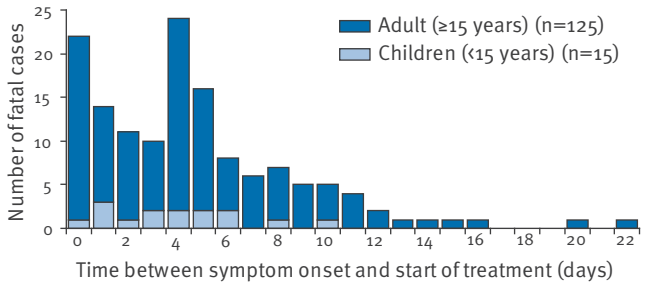


Table 2

Underlying medical conditions of the first fatal cases of 2009 pandemic influenza A(H1N1) in adults ≥18 years, Germany, 29 April 2009 to 31 March 2010 (n=196)

Underlying conditions[a]	Number of notifications in fatal cases (%)	Proportion in fatal cases as percentage (95% CI)	12-month prevalence as percentage (95% CI)[b]	Relative risk (95% CI)[c]
Yes	169 (100)	86.2 (80.6–90.7)	37.4 (36.8–38.1)	10.0 (6.7–15.0)
Immunosuppression[d]	51 (30)	26.0 (20–32.7)	NA[e]	NA
Cardiovascular disease	46 (27.2)	23.5 (16.7–29.3)	NA	NA
Hypertension	NA	NA	21.4 (20.9–22.0)	NA
Angina pectoris	NA	NA	1.7 (1.5–1.9)	NA
Heart failure	NA	NA	2.4 (2.2–2.6)	NA
Obesity[f]	39 (23.1)	19.9 (14.5–26.2)	13.4 (12.9–13.9)	1.2 (0.8–1.8)
Respiratory disease	39 (23.1)	19.9 (14.5–26.2)	NA	NA
Asthma	NA	NA	5.2 (4.9–5.5)	NA
Chronic bronchitis	NA	NA	4.5 (4.3–4.8)	NA
Diabetes	29 (17.2)	14.8 (10.1–20.6)	5.7 (5.4–6.0)	2.3 (1.5–3.6)
Pregnancy	2 (1.2)	1.0 (0.1–3.6)	NA	2.2 (0.5–9.4)[g]
Other	50 (29.6)	25.5	NA	NA
None	27	13.8 (9.3–19.4)	NA	NA
Total	**196**	**100.0**	**NA**	**NA**

CI: confidence interval.

[a] Mutiple answers possible.

[b] German Health Update - Telephone Health Survey 2008/2009 (Germany) [16].

[c] Age- and sex-adjusted relative risk: risk in the exposed divided by the risk in the unexposed.

[d] Including three reported cases with leukaemia.

[e] NA= Not available

[f] Body mass index (BMI)›30 or being treated for obesity or international statistical classification of disease (ICD-10) Code E66 obesity (self-reported).

[g] Estimate for the relative risk of pregnancy: number of births in 2009: 682,514; population based on the female general population in women of child-bearing age (15–45 years): 16,129,518; corrected for the duration of pregnancy: 267 days and the days of the risk period: 338 days. Relative risk = 2 / 682,514 / 365 x 267 / 365 x 338 / 27 / 16,129,518.

childbearing age in the general population at risk of infection, a rough estimate of the relative risk is possible. Taking 27 April 2009 as the start of the risk period, the relative risk was 2.2 (95% CI: 0.5 to 9.4).

Discussion

Disease frequency

The detailed analysis of notification data and risk factors in the general population of Germany presented in this paper gives insight into what might play a role in the differences between countries. Based on reported cases, the overall mortality in Germany of 3.1 (95% CI: 2.7 to 3.5) per one million inhabitants is lower than that in North America – United States: 7.0 (95% CI: 6.7 to 7.3) and Canada: 13.7 (95% CI: 12.4 to 15.1) and shows more similarities to that in other European countries. However, while in some neighbouring countries such as the Netherlands 3.7 (95% CI: 2.8 to 4.7), Belgium 1.8 (95% CI: 1.1 to 2.8) and Austria: 4.8 (95% CI: 3.4 to 6.5), the reported mortality was in the same range, Spain 6.3 (95% CI: 5.6 to 7.1), the United Kingdom 7.6 (95% CI: 6.9 to 8.3) and France 5.1 (95% CI: 4.6 to 5.7) reported a substantial higher overall mortality than that observed in Germany. Special care should be taken when comparing and interpreting CFRs as the number of cases in the denominator is often difficult to estimate [3]. A right shift of the epidemic curve for fatal cases when compared with the non-fatal cases contributing to an increase in CFR might suggests that the risk of severe outcome changed during the pandemic (Figure 1). We consider it more likely, however, that the affected age groups as well as the probability of laboratory confirmation and reporting might have varied during the course of the pandemic wave.

Age distribution of fatal cases

The population-based cumulative mortality in elderly people (≥60 years) was lower than that in adults aged 35 to 59 years. However, this contrasts with the highest nCFR in the age group above 60 years and older. Serology data for pre-existing immunity from the United States, United Kingdom and Finland suggest that this might be the result of lower susceptibility of the oldest age group to an infection with the newly emerged influenza viral genotype, thus causing fewer cases [17-19]. Alternatively, age-dependent contact frequency can become the driving force for an age-related distribution of cases, as studies on contact patterns show that the main contacts occur mostly within the same age strata [20].

Disease course

An intriguing observation has been the difference in the interval between onset of symptoms and death between children younger than 15 years and adults. This might suggest a frequent fulminant course of disease in children, despite the same frequency of hospitalisation and pneumonia in both groups.

Antiviral treatment

In two thirds of the fatal cases, antiviral treatment was started after the 48-hour window following the onset of symptoms (Figure 2) and in half of the patients only after four days. This shows that some patients may not treated optimally, according to the recommendations for antiviral treatment [14]. On the other hand, the earlier treatment start reported for non-fatal cases suggests that specific antiviral treatment can reduce untoward outcome. Similar observations have been made in other countries [3,21].

Risk factors

It can be assumed that acute infection interacting with underlying chronic diseases plays a pivotal role in the outcome, as has been described by a number of studies on disease severity of pandemic influenza. Old and newly suggested risk factors, such as obesity, might also impair physiological mechanisms of compensation [22]. This is why it is important to report fatal cases of influenza virus infection even when the contribution of the infection to the detrimental course of disease cannot be quantified precisely.

Most (86.2%) of the reported fatal cases in Germany had an increased likelihood of a severe disease course because of chronic illnesses, including a quarter of patients with more than one underlying disease condition. The proportions of specific underlying conditions vary between different countries or regions, with obesity most frequently observed in California (United States), neurological disorders in England and human immunodeficiency virus (HIV) infections in South Africa [2,3,7]. In our analysis we could show that the relative risk calculated on the basis of population data allows a more precise definition and ranking of risk groups, which might also allow for better comparison between countries. The fifth most frequent underlying disease, showing the highest estimate of risk in our study, was diabetes. As this condition is widely distributed in the European population it has probably been underestimated as a risk factor, so far and further research seems to be warranted. Other studies identified pregnancy as an important risk factor [23,24]. However, due to the small number of deaths in pregnant cases, our results are neither able to confirm nor exclude this for Germany.

Study limitations

Given the high disease awareness during the pandemic in the general population, among medical staff and the reporting authorities, it can be assumed that notified fatal cases with laboratory-confirmed pandemic influenza present a good source of data for the elucidation of underlying medical conditions and other factors related with severe cases of this infection. Nevertheless, artefacts such as underreporting and misclassification of outcome or risk factors are possible and might conceal the real disease burden. Even though case-based information on risk factors was also available for non-fatal cases, analysis showed that reporting was much more complete for patients who died. Therefore, we calculated the relative risk based on a self-reported population survey. In addition, as notification of deaths is mandatory for laboratory-confirmed cases only, such deaths might represent only the tip of the iceberg,

since in the course of the pandemic wave it is estimated that fewer than every tenth case seen by a physician will be laboratory confirmed [25]. Information on other factors for the development of severe illness, such as infectious dose, general immune status (pre-existing immunity), nutrition, access to healthcare or unrecognised comorbidity is lacking and might also influence the risk of death from pandemic influenza.

Acknowledgements

We wish to thank all the physicians who notified their cases to the health authorities and provided adequate information. We also want to thank all German local and regional health authorities, who investigated these cases and submitted the information to the Robert Koch Institute. In addition, we thank the PAE training programme coordinator for her comments on the manuscript and Christina Rafehi for checking and improving the English.

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Response to the 2009 influenza A(H1N1) pandemic in Italy

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Citation style for this article:
Rizzo C, Rota MC, Bella A, Giannitelli S, De Santis S, Nacca G, Pompa MG, Vellucci L, Salmaso S, Declich S. Response to the 2009 influenza A(H1N1) pandemic in Italy. Euro Surveill. 2010;15(49):pii=19744. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19744

Article published on 9 December 2010

In Italy, the arrival of the 2009 pandemic influenza A(H1N1) virus triggered an integrated response that was mainly based on the 2006 National Pandemic Preparedness and Response Plan. In this article we analyse the main activities implemented for epidemiological surveillance, containment and mitigation of the pandemic influenza and the lesson learned from this experience. Overall, from week 31 (27 July – 2 August) of 2009 to week 17 (26 April – 2 May) of 2010, we estimate that there were approximately 5,600,000 cases of influenza-like illness (ILI) who received medical attention (with almost 2,000 laboratory-confirmed cases of pandemic influenza from May to October 2009). A total of 1,106 confirmed cases were admitted to hospital for serious conditions, of whom 532 were admitted to intensive care units. There were 260 reported deaths due to pandemic influenza. Approximately 870,000 first doses of the pandemic vaccine were administered, representing a vaccine coverage of 4% of the target population. One of the possible reasons for the low uptake of the pandemic vaccine in the target population could be the communication strategy adopted, for both the general population and healthcare workers, which turned out to be a major challenge. Active involvement of all health professionals (at local, regional and national level) in influenza pandemic preparedness and response should be encouraged in the future.

Background

Since the emergence of the avian influenza threat in 1999, the Italian Ministry of Health in collaboration with the Istituto Superiore di Sanità, the national institute of health, started to work on an influenza pandemic preparedness plan. The first National Pandemic Plan for Preparedness and Response was developed in 2003 and subsequently updated in 2006 [1] according to the 2005 recommendations of the World Health Organization (WHO) [2]. The 2006 Plan was aimed at strengthening preparedness and response for an influenza pandemic at both national and local level by improving epidemiological and virological surveillance (identification, confirmation and timely reporting of cases), implementing containment measures at the early stage of a pandemic (e.g. border restrictions, isolation of the first possible, probable and confirmed cases, contact tracing), reducing the impact of the pandemic through the implementation of mitigation measures (pharmaceutical and non-pharmaceutical), ensuring communication strategies to inform healthcare workers, the media and public about decisions, and monitoring the efficiency of the interventions undertaken.

Since 2001, the National Health System has been decentralised and the 21 Italian regions are responsible for organising and delivering health services according to the Ministry of Health recommendations, including the necessary actions to contain and mitigate a pandemic. Each region was requested to produce its own Regional Pandemic Preparedness and Response Plan. This report summarises the response to the 2009 pandemic influenza A(H1N1) in Italy and the lessons learned from this experience.

Initial response strategies

After the first pandemic influenza alert was announced by WHO in late April 2009 [3], a National Crisis Management Committee, headed by the Minister of Health was established, in charge of coordinating the strategies related to preparedness, response and communication during the pandemic.

Enhanced surveillance and data collection

Seasonal Influenza surveillance is based on a nationwide sentinel surveillance network (INFLUNET) combining clinical and virological information. The system is based on sentinel practitioners (general practitioners and paediatricians) covering about 1.5–2% of the general population, with the aim of monitoring the incidence of medically attended influenza-like illness (ILI), identifying the extent of the seasonal epidemics and collecting information on circulating viral strains from week 42 to week 17 of the following year each influenza season. A case of medically attended ILI is defined as a patient attending a sentinel practitioner

with acute onset of fever >38 °C, respiratory symptoms and one of following symptoms: headache, general discomfort or asthenia. Data collected through INFLUNET are also uploaded weekly into the European Influenza Surveillance Network (EISN) database coordinated by the European Centre for Disease Prevention and Control (ECDC) [4].

Immediately after its formation, the National Crisis Management Committee recommended enhancing INFLUNET surveillance, so that it start earlier than usual in order to detect any sudden increase in the number of ILI cases in the community. The committee also decided that an active surveillance system should be set up to detect individuals presenting with ILI with a recent history of travel to the affected areas (Mexico and United States), as well as their close contacts. As previously described [5], individuals coming from affected areas received specific medical advice through the health authorities at airports and seaports to go immediately to a hospital if they developed symptoms of ILI. Any possible, probable or confirmed case of pandemic influenza – defined according to the European Union case definitions [6] – was immediately reported to the Ministry of Health. Moreover, laboratory confirmation of all suspected cases was required. Demographic data and information about symptoms and travel history were collected.

The first 200 confirmed cases of pandemic influenza were thoroughly investigated by local health authorities, using specific online epidemiological investigation forms, within 12 hours after case confirmation. Follow-up information was requested by the local health authorities for each case after 15 days. Data on contacts were also collected including exposure data (e.g. relationship to case, type and date of contact, household information) and subsequent development of illness and/or asymptomatic infection.

Containment measures implemented

Containment measures were implemented in April 2009 and included social distancing measures (early isolation of cases and precautionary closure of schools with more than five ILI cases with at least two confirmed) and antiviral prophylaxis for close contacts of cases. A stockpile of 40 million doses of antiviral drugs (sufficient for a complete treatment for approximately 4% of the whole population) stored by Ministry of Health was distributed to the regions, together with recommendations for their correct use [7]. Any person reporting to have been in close contact with a confirmed case was asked to remain at home for seven to 10 days, thus avoiding contact with others. This recommendation was maintained until the end of July 2009.

Modelling disease spread

As soon as the pandemic threat emerged, it was crucial for national policymakers to have early predictions on the possible spread of the pandemic virus. Since the early phase of the epidemic in Italy, real-time analysis was undertaken to provide weekly advice, together with epidemiological data, to the National Crisis Management Committee. Since the National Health Authorities request relevant information to tailor containment and mitigation measures to be implemented in the population and to understand the possible scenarios of the pandemic influenza burden in case of disease spread at the national level, a reference scenario on the spatio-temporal spread of the pandemic virus was provided, using mathematical modelling, and the effectiveness of mitigation measures, both pharmaceutical and non-pharmaceutical (such as school closure and social distancing measures), was assessed. Briefly, a stochastic, spatially explicit, individual-based simulation model was used. Individuals are explicitly represented and can transmit the infection to household members, to school or work colleagues and in the general population (where the force of infection is assumed to depend explicitly on geographical distance). The national transmission model was coupled with a global homogeneous mixing Susceptible Exposed Infected Removed (SEIR) model accounting for the worldwide pandemic, which was used for determining the number of cases imported over time. The transmission model used was parameterised, based on the existing evidence, derived from the analysis of data from the national surveillance system until 17 June 2009 and on estimates of key epidemiological parameters available at that time [8].

Fine-tuning surveillance

On 11 June 2009, the WHO Director-General raised the pandemic level to level 6 [3]. In July 2009, WHO made changes in the reporting requirements for pandemic influenza, because of the worldwide spread of the disease [9]. The Italian Ministry of Health modified the previous requirements: regions were required to report weekly an aggregate number of probable, possible and confirmed cases, confirmed hospitalised cases and deaths due to pandemic influenza [8].
In addition, the following pre-existing surveillance systems were expanded.

- A web-based emergency room hospital admissions and hospitalisations sentinel surveillance system had been in place since 2008. In August 2009, the system was enhanced, by increasing the number of emergency rooms surveyed. A network was established among Italian emergency services that had an automatic recording system for admissions. Of the 21 Italian regions, 12 identified at least one emergency service that would send data for surveillance; to date, these constitute the reporting units of the system. Data from the previous year, were used when available to estimate the number of weekly admissions. Epidemic thresholds were calculated using a Poisson regression model.
- A surveillance system of drug purchase – collecting data from a representative sample of 2,500 public and private pharmacies in Italy on the purchase of antibiotics (belonging to the Anatomical

Therapeutic Chemical (ATC) Classification System (ATC J01), painkillers (ATC N02B) and antiviral drugs (ATC J05AH) – was incorporated into pandemic surveillance activities. All data refer to prescribed drugs except painkillers, which are also available in Italy over the counter. The system had been in place since January 2005.

In addition, the following surveillance systems were set up during the pandemic.

- A web-based data collection form for surveillance of severe confirmed hospitalised cases and deaths due to pandemic influenza was set up in mid-September 2009. Forms were filled in by regional and local authorities and data were analysed daily at the national level (by the Istituto Superiore di Sanità and the Ministry of Health).
- To monitor vaccination coverage, in October 2009 a specific web-based data collection form was developed to be filled in by local health authorities (with details of the number of vaccine doses administered weekly to the target population, by age, risk conditions and region). Moreover, denominators for each target groups were also requested for each region in order to calculate vaccination coverage. The data were subsequently aggregated at the national level. Vaccination coverage reported always refers to the target population.

Communication of data

In order to inform the public about the pandemic in Italy and abroad, and to minimise conflicting information from different sources, communication to the public through the media was centralised at the national level and daily reports were published on the Ministry of Health website. When all surveillance activities were well established, a weekly report – including data and trends of ILI cases, vaccination coverage, emergency room admissions for acute respiratory syndromes, purchase of painkillers, antibiotics and antiviral drugs, and mortality – was released, in both Italian and English [10].

Mitigation measures implemented

Since 22 July 2009, the Ministry of Health recommended the use of antiviral drugs only for severe cases of pandemic influenza and for symptomatic patients with underlying medical conditions. In September 2009, the Ministry of Health started a health education campaign targeted at the general population recommending the adoption of basic non-pharmaceutical measures, such as staying at home if ill and covering noses or mouths with tissues, handkerchiefs or elbows when sneezing or coughing. Moreover, a specific hotline was set up to give advice and information regarding pandemic influenza prevention to both the general population and healthcare professionals.

Also in September 2009, according to the National Pandemic Preparedness and Response Plan before the pandemic vaccine became available, the Ministry of Health on 30 September 2009 identified the priority categories to be vaccinated, in a stepwise manner:

Table

Vaccination coverage for first dose of pandemic influenza vaccine by target group, Italy, October 2009 to May 2010

Target groups	Number of first doses administered	Number of persons in target group	Vaccine coverage (%)
Healthcare personnel	165,562	1,069,264	15.5
Essential services personnel (e.g. police, firefighters, military corps)	72,181	1,228,155	5.9
Blood donors	6,329	742,349	0.8
Pregnant women in their second and third trimesters	23,016	189,915	12.1
Women who delivered in the previous 6 months or person who take cares of the baby	8,170	237,594	3.4
Individuals with at least one chronic underlying condition aged 6 months–65 years	549,167	4,309,466	12.7
Individuals with at least one chronic underlying condition aged >65 years	13,562	710,862	1.9
Children aged >6 months attending day-care centres	4,618	89,394	5.2
Children aged <18 years resident in long-term care facilities	1,120	10,155	11.0
Children aged <24 months born pre-term	1,595	20,657	7.7
Healthy children and adolescents aged 6 months–17 years	20,307	7,671,581	0.3
Healthy individuals aged 18–27 years	5,650	4,642,188	0.1
Total	**871,277**	**20,921,580**	**4.2**

1. healthcare personnel and essential services personnel (e.g. police, firefighters, military corps) including blood donors;
2. pregnant women in their second and third trimesters and women who delivered in the previous 6 months or persons who take care of the baby;
3. individuals with at least one chronic underlying condition aged 6 months–65 years putting them at high risk of severe or fatal complications due to pandemic influenza and children aged <24 months born pre-term;
4. children aged >6 months attending day-care centres
5. healthy children and adolescents (aged between 6 months and 17 years);
6. healthy individuals aged 18–27 years;
7. individuals with at least one chronic underlying condition aged >65 years.

The Table shows the vaccination coverage for the first dose of the pandemic vaccine during October 2009 to May 2010.

Agreements with pharmaceutical companies regarding the availability of pandemic vaccine according to the WHO indications [11] on the pandemic strain were signed by the Ministry of Health in 2005. On these bases and with the support of mathematical modelling showing that vaccinating 40% (24 million) of the Italian population (60 million) was adequate to mitigate the pandemic, the Ministry of Health decided to buy 24 million doses of adjuvated (MF59) vaccines from only one supplier. The selected company delivered half of the purchase to the Ministry of Health central storage from where vaccines have subsequently been distributed to the 21 Italian regions (since 12 October 2009) through the network of the Italian Red Cross.

Evaluation of the pandemic in Italy

Active surveillance of imported pandemic cases

In Italy, the first imported confirmed case of pandemic influenza was detected on 24 April 2009 (week 17) [12]; by the end of July 2009 approximately 250 imported confirmed cases had been reported, with more than 2,000 suspected cases being investigated. In August 2009 the total number of medically attended ILI cases reached 5,000, of whom approximately 2,000 (40%) were laboratory confirmed. Since then the number of autochthonous clusters increased, suggesting sustained transmission in Italy, supported by the schools re-opening in mid-September. By mid-October 2009 (week 43) approximately 14,000 ILI cases had been reported.

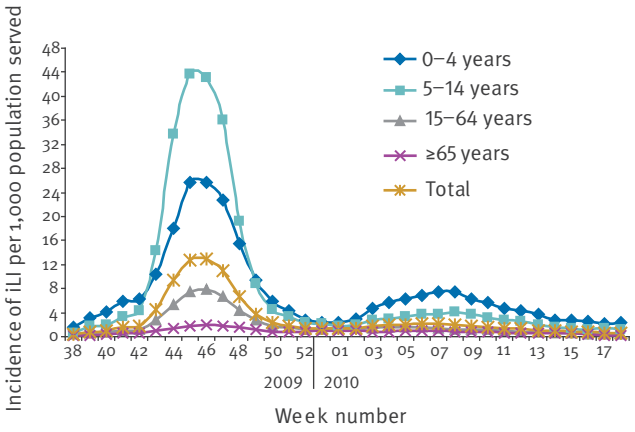
INFLUNET sentinel surveillance system

Even though the INFLUNET surveillance system had been in place from week 17 of 2009, no significant signals of increased influenza activity were detected until week 43, when an incidence of 4.5 cases per 1,000 served population of each reporting physician was observed. Two weeks later (week 45), the epidemic curve reached its peak, with a total incidence of 12.9 per 1,000 served population (Figure 1).

From week 31 of 2009 to week 17 of 2010, there were an estimated of approximately 5,600,000 medically attended ILI cases. The ILI incidence observed during the 2009–10 influenza season was 97 cases per 1,000 served population. This incidence estimate is similar to that described during the 2004–05 season, when the incidence rate reached the highest value ever described in Italy (116 cases per 1,000 served population). However, during the 2009–10 season, the number of ILI cases in the age group 0–14 years (270 cases per 1,000 served population) was the highest ever reported since the beginning of the INFLUNET surveillance system (which began in the 1999–2000 influenza season).

Figure 1

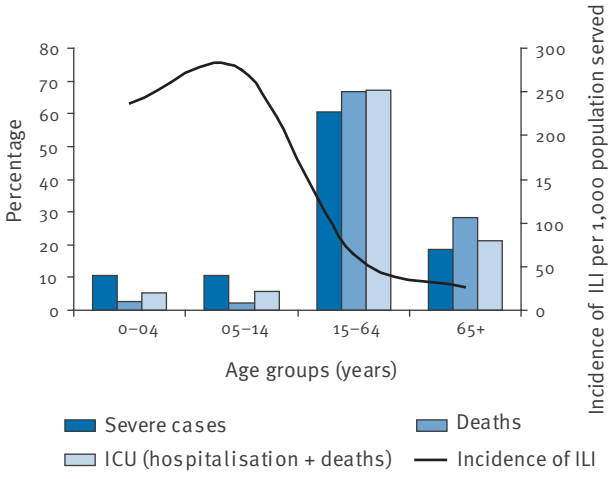
Incidence of influenza-like illness by age group, Italy, week 38 of 2009 to week 17 of 2010



ILI: influenza-like illness.
Source: INFLUNET data.

Figure 2

Proportion of severe cases, admission to intensive care unit and deaths and incidence of influenza-like illness[a], by age group, Italy



ICU: intencive care unit; ILI: influenza-like illness.
[a] Source: INFLUNET.

In contrast, incidence in the age group >64 years was very low (26 cases per 1,000 served population).

Surveillance of the first 200 confirmed pandemic influenza cases

The epidemiological investigations of the first 200 confirmed pandemic influenza cases were collected using an online database established at the end of April 2009 after the first Italian laboratory confirmed imported pandemic influenza cases in the country. By the last week of October 2009, a total of 1,286 cases had been included in the database, with reported symptom onset dates from 24 April to 31 October 2009. Details of approximately 3,900 contacts were also included in the database. Most (1,093 of 1,286; 85%) of the reported cases were notified by local health authorities within 12 hours after laboratory confirmation. Follow-up data were available for 1,040 of 1,286 (81%) of the cases. In the later stage of the surveillance of the first 200 confirmed cases (end of September 2009 to November 2009), the proportion of cases that were followed-up decreased because the number of cases increased dramatically.

Surveillance of laboratory-confirmed severe cases

Approximately 1,100 cases were admitted to hospital for serious conditions, of whom 532 were admitted to intensive care units, 49 needed extracorporeal membrane oxygenation, 166 were diagnosed with acute respiratory distress syndrome and 166 required oro-tracheal intubation. A total of 260 deaths due to complications arising from pandemic influenza were reported. In total, 476 of 1,100 (43%) of hospitalised cases with available information were reported to have an underlying risk factor for severe disease, including pregnancy and obesity. Proportional distribution by age group of severe cases, number of cases who were admitted to an intensive care unit and number of deaths is shown in Figure 2. Data are compared with INFLUNET and clearly show that the incidence of ILI cases was higher in the children aged less than 14 years, while disease severity and fatal outcomes were concentrated in those aged over 15 years, with a mean of 43 years.

Figure 3

Regions participating in the sentinel emergency room surveillance system, Italy, August 2009 to May 2010

Emergency room admissions

The emergency room admission system collates data from 73 major, representative hospitals in 13 regions (Figure 3). Data reported during the week 43 of 2009 showed that (3,269/43,335) 7.5% of all people who visited hospital emergency rooms were diagnosed with acute respiratory infection. Of these 653 (20%), were admitted to hospital after being in an emergency room, with the baseline for admissions reached for the first time for all age groups. During week 45 of 2009, the peak was reached, with 12.2% of acute respiratory infection cases among emergency room visits (4,995 of 41,037); of these 863 (17.3%) were hospitalised (Figure 4).

Drug purchase

A first peak in the purchase of antiviral drugs was registered in weeks 28 (6–12 June) to week 31 (July 27 to 2 August) of 2009, corresponding to the first pandemic wave registered in some northern European countries. In week 45, when the first peak of the ILI cases reported by INFLUNET in Italy was reached, a 90% increase in the purchase of antiviral drugs, and a 41% increase of antibiotics and a 95% increase of painkillers purchases were recorded, compared with the same week in 2008. Antiviral drug purchases reached 47 items per 100,000 inhabitants, more than double the amount bought the previous week, in line with the increase in the incidence of ILI.

Mathematical modelling

Simulations obtained by mathematical modelling were in agreement with the INFLUNET data in the early phase of the epidemic (April 2009 to September 2010), when containment measures were implemented. Briefly, by assuming isolation of confirmed cases, antiviral treatment and prophylaxis to 90% of symptomatic cases until 8 July 2009, and 33.3% natural immunity in the population aged more than 59 years, the peak of the ILI cases in Italy was expected on week 44 (95% confidence interval: 44 to 45). Estimates were consistent with the INFLUNET data showing that the peak in Italy was reached in week 45-46 [8].

Vaccine administration

The pandemic vaccine was administered mostly by vaccination services; however, some regions also involved general practitioners and paediatricians in the pandemic vaccination campaign. Overall, 871,277 first doses and 52,723 second doses were administered (giving a total of 924,000 vaccine doses) and a national coverage among the target population of 4% (Table). Coverage was 15% of healthcare workers, 12% of pregnant women, 13% of persons aged under 65 years at high risk, and 11% of institutionalised individuals aged under 18 years old.

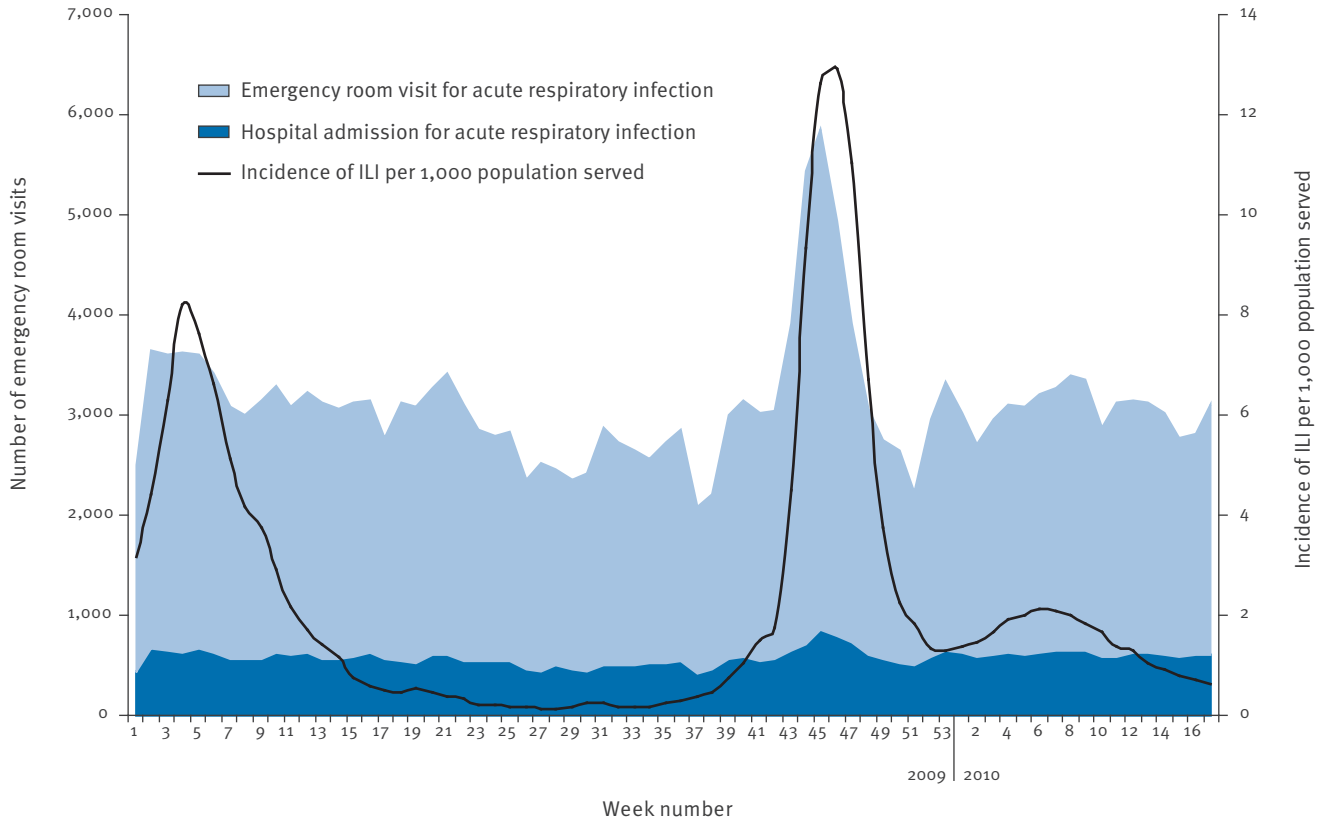
Lessons learned

When the pandemic virus emerged in late April 2009, reliable epidemiological data on the new circulating virus were limited and not available in a timely manner [13]. Consequently, uncertainty regarding the pathogenicity and severity of the pandemic virus, at the very beginning of its appearance, led advisors of decision-makers to consider the worst-case scenario. The combination of uncertainty and urgency to implement containment and mitigation measures in a short time made it difficult to fine-tune measures already included in the 2006 National Preparedness and Response Plan and to produce real-time modelling analysis with different scenarios of the possible impact of the mitigation measures. The WHO 11 June 2009 pandemic level 6 declaration supported the worst-case scenario approach. Therefore, on the basis of epidemiological data available in April 2009, only the actions listed in the 2006 Plan that were considered relevant to the situation at that time were performed. Among the activities undertaken, planning and coordination, situation monitoring and assessment, and containment and mitigation measures appeared to be efficient in the first containment phase (April- July 2009), in accordance with modelling results [8]. In fact, our experience suggests that the early response phase may have contributed to delaying and reducing the impact of the pandemic during spring and summer. This was facilitated also by school closure from early June to mid-September.

By contrast, the communication strategy adopted in Italy turned out to be a major problem. While at the beginning, the fast worldwide spread of the pandemic generated among the general population the feeling of a threat that was able to disrupt social life. Given the WHO pandemic level-6 declaration in June 2009, it was quite clear that the 2009–10 pandemic was caused by a virus able to spread effectively between humans. The uncertainty of the data (regarding disease severity and real number of affected individuals and of deaths) between April and October 2009 caused a high degree

Figure 4

Influenza-like illness incidence[a] and emergency room visits for acute respiratory infections, Italy, week 1 of 2009 to week 17 of 2010



ILI: influenza-like illness.

[a] Source: INFLUNET.

of disconcertion among healthcare workers and the public. This heavily influenced the vaccination campaign, in which the communication strategy plays a crucial role. The low vaccination uptake led to coverage of only 4% of the target population: 15% of the healthcare personnel and 1.5% of the general population [10].

In addition, the pandemic vaccines used during the 2009 pandemic were licensed by the European Medicines Agency (EMA) based on a mock-up vaccine procedure and were used on the basis of clinical data supporting the safety and effectiveness of vaccines developed using the influenza A(H5N1) strain, which had been thought would cause the next pandemic [14]. The way in which the pandemic vaccines were licensed was one of the main reasons of concern among healthcare workers and the general population. Another reason for concern was that this vaccine was a vaccine containing an adjuvant (MF59-squalene) and was recommended for risk groups (such as children and pregnant women) that differed from those included in the seasonal vaccination recommendations (elderly people and persons with underlying conditions older than 18 years) [15]. Concern was also raised by media regarding the risk of Guillain–Barré syndrome, related to the pandemic vaccine that was associated with 'swine influenza' vaccine that was administered in the United States in 1976–77 [16,17]. However, surveillance of adverse effect of pandemic influenza vaccination in Italy showed no particular evidence with respect to previous years [18].

These issues were mainly of concern to healthcare workers (e.g. general practitioners, paediatricians, specialists and nurses), who were supposed to liaise between the national and regional health authorities and the community. An Italian survey conducted in October 2009 among physicians and nurses, which investigated attitudes and behaviours towards preventive measures against the pandemic influenza, showed that: 70% of the 1,360 females (mainly nurses) in the sample and 51% of the 600 males would not get vaccinated against pandemic influenza [19].

Given this, many general practitioners and paediatricians were not able to disseminate the correct message, not even to the risk groups. Healthcare workers should have been timely informed about vaccine safety and involved in specific health education programmes in order to correctly inform the general population, but it was impossible to set up specific training before the end of December 2009, due to the overload of activities to be carried out during the pandemic. Indeed, concerns about vaccine safety should have been addressed first with general practitioners, using specific educational communication programmes. The fact that pandemic vaccine recommendations and prioritisation were based on risk rather than age strategies, coupled with the shortage of pandemic vaccines before the pandemic peak, vaccine dosage uncertainties, and the milder impact of the epidemic, concurred in discouraging the population to seek vaccination and probably had an important role in the failure of the vaccination campaign. This was the unfortunate consequence of the high level of uncertainties that informed most decisions during the period from July to September 2009.

As a result of the low vaccination coverage at national level, vaccine stock levels at the Ministry of Health warehouse remained high. In December 2009, a vaccine order was revised, 2,4 million doses were donated to WHO for developing countries, but the one-year validity of the vaccine doses forced the government to recall the doses and they will probably be discarded [20].

Enhanced epidemiological surveillance implemented in Italy during the pandemic substantially improved the quality and completeness of the epidemiological data collected. The integration of different data sources (i.e. incidence, mortality, severe cases, hospitalisation, emergency room visits, drugs purchases, pandemic vaccine coverage), allowed a weekly description of the burden of the 2009 pandemic influenza. This weekly epidemiological report (available also in English), disseminated through various official websites (Ministry of Health, Istituto Superiore di Sanità/National Centre for Epidemiology Surveillance and Health Promotion (Epicentro) and ECDC), has been a useful tool in informing and updating the media and health workers about the pandemic in Italy.

The intrinsic unpredictable characteristics of an influenza pandemic made every attempt of preparedness difficult and required flexibility in decision-making. However, the surveillance efforts made during this pandemic have provided a unique opportunity to validate influenza integrated surveillance, at both regional and national level. This surveillance, together with the established INFLUNET sentinel surveillance, will be maintained during the next influenza seasons. The underestimation of deaths could have been a weakness of the enhanced surveillance system adopted, because not all cases were laboratory confirmed.

The communication problems experienced during the pandemic also turned out to be valuable in generating a constructive discussion and building awareness of the importance of the active involvement of all health professionals (at local, regional and national level) in influenza pandemic preparedness.

In Italy responsibility for public health is shared between health authorities at national and regional level. Because of the threat posed by the pandemic, the regional health authorities implemented local pandemic plans. Thus, logistics issues, especially those concerning the distribution of vaccines within each region, as well as the strategy for the vaccinations at vaccination services or at the practices of general practitioners, were designed locally. Therefore, the response to the pandemic threat in Italy may have not been uniform and homogeneous, but it has strengthened the collaboration between central and peripheral levels.

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