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

Vol. 15 | Weekly issue 20 | 20 May 2010

Rapid communications

Research articles

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Steep rise in notified hantavirus infections in Germany, April 2010

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Citation style for this article:
Citation style for this article: Faber MS, Ulrich RG, Frank C, Brockmann SO, Pfaff GM, Jacob J, Krüger DH, Stark K. Steep rise in notified hantavirus infections in Germany, April 2010. Euro Surveill. 2010;15(20):pii=19574. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19574

This article has been published on 20 May 2010

From January to April 2010, 396 hantavirus infections were notified in Germany, a considerable increase compared with previous years (mean: 83 for January–April 2004–2009) including the record-setting year, 2007 (n=232 January–April). Most patients are residents of known Puumala virus endemic areas in southern Germany. The recent increase in notified hantavirus infections is probably due to an increased population density of the main animal reservoir, the bank vole (*Myodes glareolus*).

Introduction

European hantaviruses of the family *Bunyaviridae* cause haemorrhagic fever with renal syndrome. Infection in humans occurs through inhalation of aerosolised virus particles from excreta of chronically infected wild rodents or, rarely, through rodent bites. Infection with Puumala virus – the hantavirus virus species most prevalent in northern and central Europe including Germany – leads to a relatively mild form of disease referred to as nephropathia epidemica. After an incubation period of 5–60 days, patients typically present with abrupt onset of fever and influenza-like symptoms followed by gastrointestinal symptoms. Acute kidney failure requiring temporary haemodialysis may develop.

Puumala virus epidemics in humans occur regularly in several European countries, particularly those in Fennoscandia, and have been linked to cyclic oscillations in the population density of the main animal reservoir, the bank vole (*Myodes glareolus*) [1]. In Germany, typically 150–250 cases have been notified annually since 2001. In 2005 and 2007, however, the annual number of cases peaked at 447 and 1,688, respectively. The outbreak in 2005 mainly affected the federal states of North Rhine-Westphalia and Lower Saxony, including increased numbers of human cases in urban areas [2,3], whereas in 2007, when a record number of hantavirus cases were recorded, most of the cases were reported from the federal states of Baden-Württemberg and Bavaria [4,5].

Methods

Laboratory-confirmed hantavirus infections have been notifiable in Germany since 2001. Serological evidence or detection of viral RNA by reverse transcription-polymerase chain reaction (RT-PCR) is reported to the local public health department by the identifying laboratory. The health department completes and verifies case information according to the national case definition [4]. Information about clinical signs and outcome is obtained either from the patients or their physicians. Case data are anonymised and electronically transmitted to the state health department and from there to the Robert Koch Institute, the national public health institute. For quality assurance, the information in each case report is checked at the Robert Koch Institute for compliance with the case definition and for data consistency. Early transmission of case data based purely on laboratory diagnosis is encouraged: it may take a few days or a few weeks to gather all the information relevant to the case definition and to complete the quality assurance process.

This report describes laboratory-confirmed hantavirus infections with clinical symptoms (according to the national case definition) reported during January to April 2010 for which quality assurance was completed, as of 14 May 2010. An additional 21 notifications in April 2010 currently undergoing quality assurance are not included in this report.

Results

The number of hantavirus cases notified in Germany rose continuously between November 2009 (n=26) and March 2010 (n=69), with a further steep increase in April 2010 (n=166) (Figure 1). As case confirmation is pending for a further 21 notifications in April 2010, the number of cases in April is expected to rise.

From January to April 2010, a total of 396 cases were notified (cumulative incidence: 0.5 per 100,000 population), compared with 13 cases in January – April 2009 and 232 in January – April 2007, the year with the highest number of notified infections so far.

The most common symptoms in cases notified in January to April 2010 were fever, renal impairment, muscle pain and headache (notified for 84%, 74%, 55% and 47% of cases, respectively). Of these, 64% were notified as having been hospitalised. The frequency of

Figure 1

Notified hantavirus infections by year and month of notification, Germany, January 2004 – April 2010 (n=3,269)

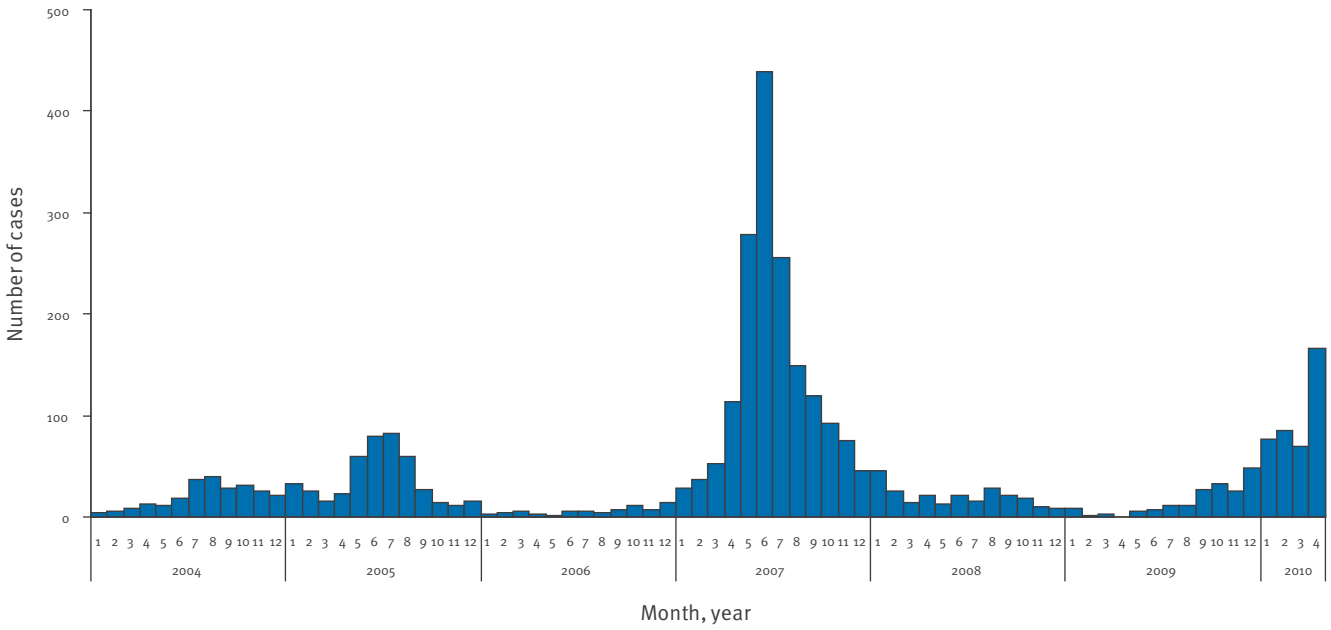
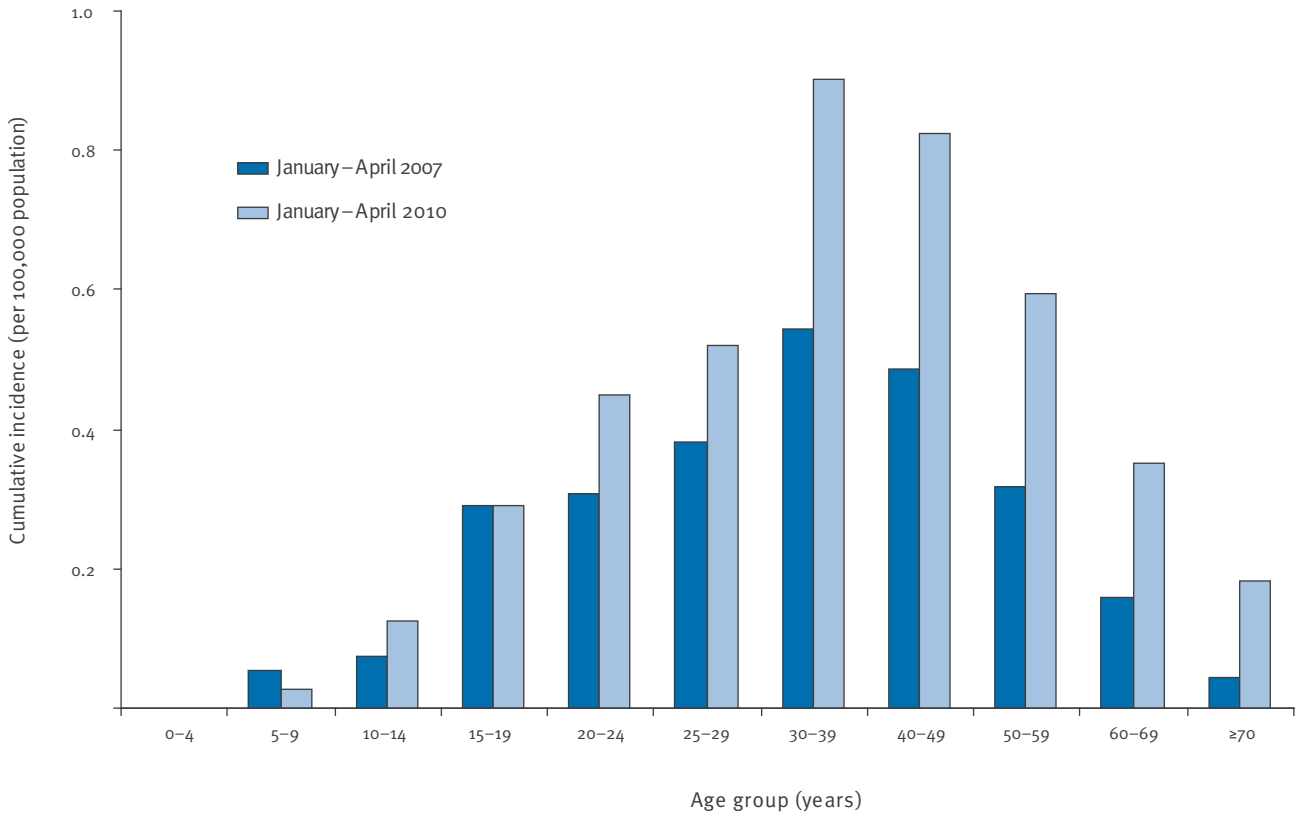


Figure 2

Cumulative incidence of notified hantavirus cases by age group and year, Germany, January – April 2007 (n=232) and January – April 2010 (n=396)



notified symptoms and the hospitalisation rate were comparable with those of previous years.

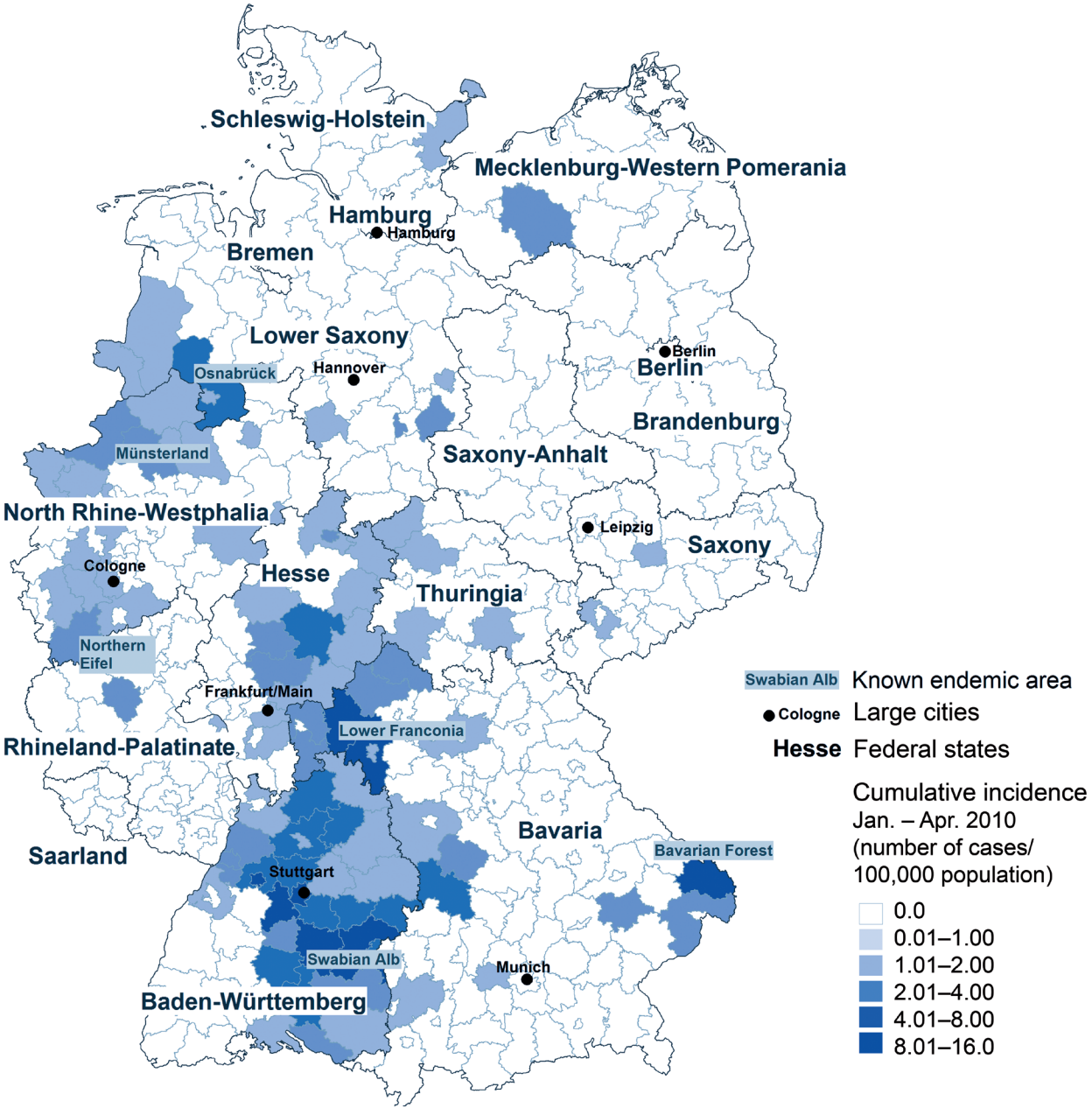
Of the 396 patients, 288 (72%) were male and 275 (69%) were between 30 and 59 years-old. Only one infection occurred in a person younger than 10 years. Compared with the first four months of 2007, the highest increase in incidence was observed in people older than 30 years (Figure 2).

Most hantavirus infections in January to April 2010 (78%) were notified from two states in southern Germany, Baden-Württemberg (64%) and Bavaria (14%). A further 19% were notified from the western states of North Rhine-Westphalia, Hesse and Lower Saxony (7.8%, 5.8% and 5.8%, respectively). No substantial increase of cases was observed in the federal states of Schleswig-Holstein and Mecklenburg-Western Pomerania (Figure 3), which are known for the occurrence of infections caused by Dobrava-Belgrade virus, the second pathogenic hantavirus in Germany, carried by the striped field mouse, *Apodemus agrarius* [6].

Most cases were residents of rural areas known to be endemic for Puumala virus infections, e.g. the Swabian Alb and bordering regions, Lower Franconia, the Bavarian Forest, as well as the Münster and Osnabrück regions. However, in Baden-Württemberg, the percentage of infections having occurred among residents of urban counties rose from 6.5% of the total case load

Figure 3

Cumulative incidence of hantavirus infections by county, Germany, January – April 2010 (n=396) and known endemic areas



in January to April 2007 to 25.1% in the same months of 2010.

Discussion

The high number of hantavirus infections notified in early 2010, the steep increase in April and the early rise of monthly case numbers at the end of 2009 indicate that the case burden of 2010 may exceed figures for 2007. Monthly case numbers also began to rise in the autumn of 2006, peaking at 439 infections notified in June 2007, with a total of 1,688 cases in 2007. On the basis of data from serological investigations and the geographical distribution of cases, the elevated number of cases is likely to be caused by infections with Puumala virus rather than Dobrava-Belgrade virus. Case numbers presented for April 2010 should be regarded as a conservative estimate because they do not include cases with pending quality assurance.

The high number of infections observed in urban environments requires further investigation. Hypotheses include bank voles moving close to human habitats due to an exceptionally cold and snowy winter, increasing presence of the animals in periurban areas used for human recreation (e.g. forests close to urban areas), as reported previously for Cologne in 2005 [2,3], or more basic shifts in the epidemiology of Puumala virus in the bank vole population. The increasing incidence in older age groups cannot be fully explained by available data but is considered to be related to exposure rather than host factors.

Fluctuations in the population size of bank voles and the proportion of infected animals may be one factor explaining the sequence of years with very different numbers of human infections [7]. Several institutions in Germany currently cooperate in an effort to implement an appropriate monitoring system for the rodent reservoir to further study the correlation of host abundance, hantavirus prevalence and frequency of human infections [8]. Initial investigations conducted in selected trapping sites of endemic areas demonstrated a population density of 78 (standard deviation (SD): ±12) bank voles per hectare (10,000 m^2) in April 2010 in North Rhine-Westphalia and 99 (SD: ±51) in Baden-Württemberg (all values are minimum number alive measured by live trapping in three woodlots per state) (J. Jacob, S. Schmidt, U. Rosenfeld, C. Imholt, R.G. Ulrich, unpublished data). Spring vole density in these states was thus close to multi-annual peak densities of 100 voles per hectare [9] and higher than measured previously at comparable sites in the month of April: 44 (SD: ±37) voles per hectare [10].

Prevention

To date, there is no WHO-approved hantavirus vaccine available [11]. Measures should therefore focus on prevention of exposure to rodents and their excreta, particularly in areas known to be endemic for hantavirus infections. This includes keeping houses and their surroundings free from bank voles and using appropriate protection (particle-filtering masks and gloves) when disposing of dead animals. When cleaning sheds, barns, attics or similar rooms where rodents might have nested, virus particles can be stirred up when sweeping or vacuuming. Therefore, surfaces should be moistened before cleaning (e.g. by spraying with a mix of water and household cleaner). The general public in endemic areas and people with an increased risk of occupational hantavirus infection (e.g. forestry workers and construction workers) should be informed about the ongoing, increased risk of infection and appropriate measures should be recommended.

We currently have only limited information on hantavirus infections in countries neighbouring Germany and would welcome feedback on this report from other institutions in Europe.

Acknowledgements

The authors would like to thank local health departments and partners in the networks "Rodent-borne pathogens" and Arbeitskreis "Mäuse im Forst" as well as additional collaborators for their support and Sabrina Schmidt, Ulrike Rosenfeld and Christian Imholt for provision of unpublished data.

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Spotlight on measles 2010: A cluster of measles in a hospital setting in Slovenia, March 2010

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Citation style for this article:
Citation style for this article: Grgic-Vitek M, Frelih T, Ucakar V, Prosenc K, Tomažič J, Petrovec M, Kraigher A. Spotlight on measles 2010: A cluster of measles in a hospital setting in Slovenia, March 2010. Euro Surveill. 2010;15(20):pii=19573. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19573

This article has been published on 20 May 2010

After ten years of being measles free, Slovenia experienced a cluster with secondary transmission in a hospital setting in March 2010. The index case, a resident of Ireland, was hospitalised on the day after his arrival to Slovenia and diagnosed with measles two days later. After his discharge, two cases of measles were notified, a hospital staff member and a visitor to the clinic, suggesting transmission in a hospital setting.

Background

Measles is a highly infectious disease which can be successfully prevented only by vaccination. Notification of measles cases has been mandatory in Slovenia since 1948. According to the Infectious Diseases Act, a case of measles (even a suspected case) has to be reported within three to six hours to the regional Institute of Public Health, responsible for public health interventions and from there immediately to the National Institute of Public Health (NIPH) where data are collected and analysed. In 2005, the European Union case definition [1] for measles was widely publicised and general practitioners and paediatricians were actively encouraged to confirm every possible case of measles (rash fever) with appropriate laboratory diagnosis.

In Slovenia, mandatory vaccination against measles was introduced in 1968 for 12 months old children. In the first years the vaccination coverage was quite low, but already in 1972 (birth cohort 1971) it reached 60%. In 1979 the coverage reached 80% and increased further in the following years. The second dose of measles vaccine was introduced in 1978 for children entering school at the age of seven years (birth cohort 1971), and was replaced by a combined vaccine against measles and mumps in 1979. The coverage for the second dose at seven years of age reached 90% already in the first year, and has been higher than 95% since 1983 (data from annual reports of NIPH) [2]. In 1990, the combined measles-mumps vaccine was replaced by a trivalent vaccine against measles, mumps and rubella (MMR); since then children have been immunised with this vaccine at 12 to 18 months (first dose) and at six years of age (second dose).

After the introduction of measles vaccination the occurrence of measles was substantially reduced compared with the highest reported incidence rate of 407 per 100,000 in 1967, and followed a declining trend (Figure 1). The size of epidemics decreased and inter-epidemic periods lengthened. The last case (indigenous) was reported in 1999. The last reported epidemic started in 1994 and peaked in 1995 when 405 cases (20.4/100,000) were reported, mostly from two regions of Slovenia.

Before the introduction of measles vaccination in Slovenia, measles was a disease of pre-school children. After that, the age distribution of morbidity shifted to older age groups. The average age of reported cases increased gradually from 5.4 years before the vaccination started (1965-1968) to 11.4 years in the 1990s (1989-1998) (unpublished data). However, since 1984, an increased proportion of cases has also been observed among infants under the age of 12 months who are not targeted by MMR vaccination (although only seven, nine and 13 cases were reported in 1996, 1997 and 1998, respectively) (Figure 2).

With regard to susceptibility profiles obtained from serosurveys conducted in Slovenia in 1998 and 2000, the population born before 1960 could be considered immune against measles (the proportion susceptible was 1.5% in those older than 40 years) [3]. Most people borne after 1971 received two doses of measles vaccine. Thus, the cohorts born between 1960 and 1971 would be most at risk of getting measles if the infection was imported to the country.

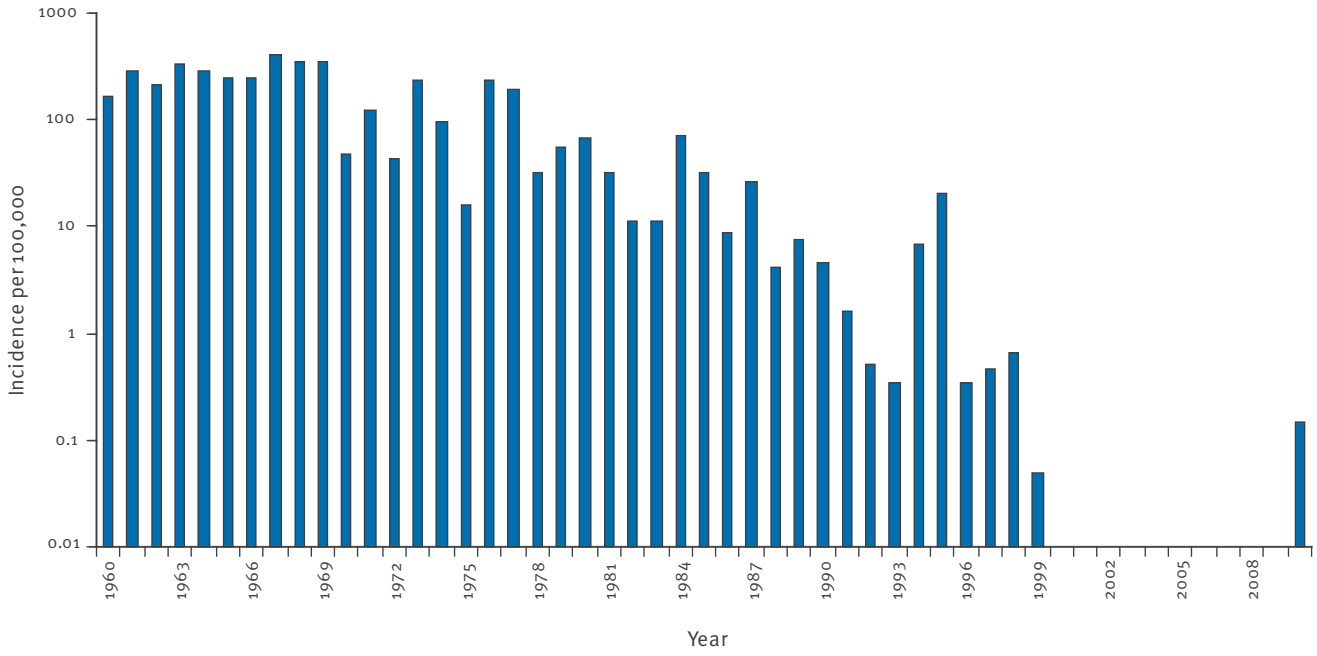
Cluster description

On 11 March the NIPH was notified of a suspected case of measles (Patient 1) in a 19 year old resident of Ireland, who was hospitalised in the Clinic of Infectious Diseases at the University Medical Centre Ljubljana

(CID). On the morning of the same day he was first examined in an emergency outpatient clinic where he presented with an atypical rash (a few abdominal papulae). The patient informed the staff that his brother had been diagnosed with measles a week before and was hospitalised while travelling through Rome, Italy.

Figure 1

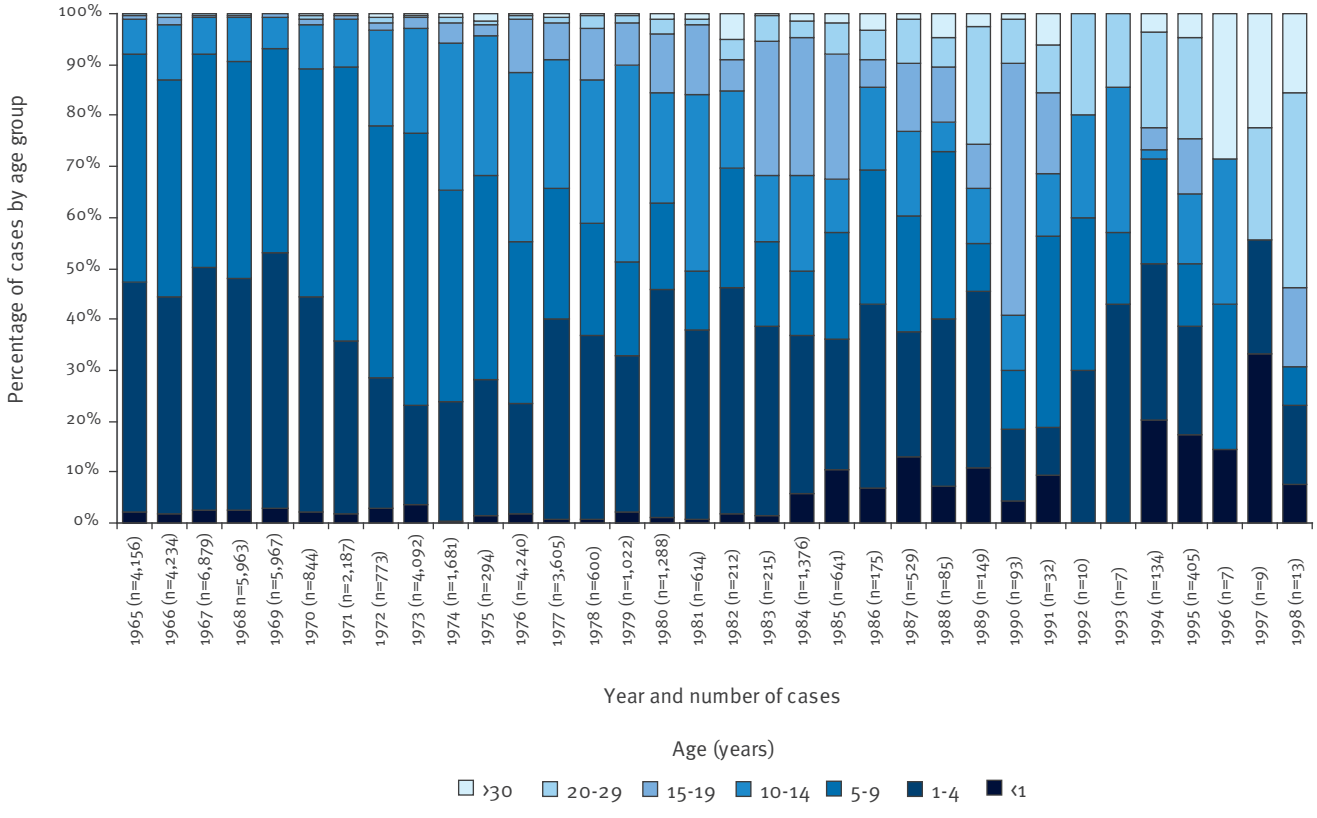
Reported measles incidence rates, Slovenia, 1960-2010



Data as of end April 2010.
Source: National Institute of Public Health of Slovenia.

Figure 2

Age-specific proportions of reported measles cases, Slovenia, 1965-1998



Source: National Institute of Public Health of Slovenia.

The brother did not accompany the family to Slovenia. Patient 1 was therefore transferred to CID in the afternoon of 11 March, where he was isolated with fever, a few abdominal papulae, conjunctivitis, and widespread Koplik spots. A blood sample and throat swab (from Koplik spots) were taken on the same day. The patient's serum was tested for measles-specific IgM and IgG by ELISA (Siemens Enzygnost) and was negative for both. In the swab MV was confirmed by PCR of the nucleoprotein gene, and material from the swab was sent for MV isolation and genotyping to the WHO Regional Reference Laboratory for MMR at the Robert Koch Institute, Berlin. The detected MV belonged to genotype D4 and was most similar to MV detected in the UK in 2009. The rash became typical for measles on 12 March and measles-specific IgM resulted positive in another blood sample on 13 March, while IgG was still negative. In the following days the patient's condition worsened and he developed pneumonia. He was discharged from hospital on 19 March fully recovered. In the last specimens taken on that day the IgM titre became lower and specific IgG antibodies appeared (Table).

The patient came to Slovenia with his family in the evening of the day before he was admitted to the hospital. He had no contact with local people as he and his family were sleeping in a caravan. He did not know if he had been vaccinated against measles. According to his statement he was a member of the Irish Traveller community [4] and originating from Limerick, Ireland where an outbreak of measles was ongoing in early 2010.

On 24 March the NIPH was notified of another suspected case of measles (Patient 2) in a healthcare worker who had been in contact with the index case at his admission. The patient had fever, sore throat, muscle aches, vomiting, photophobia, but no typical rash (only a few papulae in the face). At first she was classified as a probable case of measles. She reported to have been vaccinated at least once (as she was born after 1971 she was supposed to have received two doses). Serum specimens taken on 23 and 25 March were tested with ELISA. Both were negative for IgM and positive for IgG antibodies (400 IU/mL). A throat swab taken on 24 March tested negative for measles with PCR. An archived serum sample taken from this patient six months earlier showed the same titre of measles-specific IgG (400 IU/mL) as in the current sera.

Patient 2 was ruled out as a case of measles and therefore was not part of this cluster. Serological evidence (IgG) indicated that the patient was fully protected against measles after being vaccinated as a child, probably with two doses, and her symptoms and signs must have been due to a different viral infection.

Another suspected case (Patient 3) was notified on 1 April in a healthcare worker involved in the care of the index case. According to her self-reported vaccination status she was vaccinated once and was thus allowed to care for Patient 1. When in contact with patients she was always wearing a mask. She was tested for immunity to measles on 16 March (together with other staff members exposed to the index case at his admission) and was found IgG-negative. Nevertheless, she was not excluded from work. She was not vaccinated against measles at that time because she had mild conjunctivitis and herpes labialis (already on 15 March).

On 23 March Patient 3 reported fever, cough and coryza. She noticed a few papulae on her neck and forehead on

TABLE

Patients notified to the National Institute of Public Health of Slovenia as suspected measles cases, Slovenia, March 2010 (n=4)

Patient	Status/case classification	Sex, age	Onset of illness	Laboratory results (date of sample taken)
1	Index case, confirmed	Male, 19	11 March	IgG neg, IgM neg (11 March)IgG neg, IgM pos (13 March) IgG pos, IgM pos (19 March) PCR pos (11 March) Genotype D4
2	Not confirmed, excluded	Female, 30	23 March	IgG pos, IgM neg (23 March) IgG pos, IgM neg (25 March) PCR neg (23 , 24 and 25 March)
3	Secondary case, confirmed	Female, 39	23 March	IgG neg (16 March) IgG pos, IgM borderline (27 March) PCR neg (8 April)
4	Secondary case, confirmed	Male, 54	23 March	IgM pos, IgG pos (1 April) PCR pos (1 April) Genotype D4

25 and 26 March and some abdominal papulae on 27 March. A sample taken on 27 March resulted positive for measles-specific IgG (8,800 IU/mL) and borderline for IgM. She stayed at home for a week from 29 March to 2 April. Throat swab and urine specimens taken on 8 April were PCR-negative (Table).

On 2 April, NIPH was notified of a man in his 50s (Patient 4) diagnosed with measles at CID on 1 April. He had visited his physician on 23 March with high fever and malaise. As his condition did not improve he returned on 30 March and was referred to CID due to high gamma glutamyltransferase levels, high levels of C-reactive protein and elevated liver transaminase levels, where he presented on 31 March. Measles was suspected on 1 April, when a typical rash appeared. He had noticed the rash on his neck already on 30 March but not payed attention to it. It was assumed from his age that he was not vaccinated against measles and he did not recall having had the disease as a child. The diagnosis was confirmed by serology (positive IgM and IgG) and by positive PCR of the throat swab taken on 1 April. Genotyping was performed at the RKI and showed 100% agreement with the sequence from the MV of Patient 1 (Table).

Between 12 and 21 March (after the isolation of Patient 1), this patient had been visiting twice a day a relative who was hospitalised on the same ward as the index case. He did not travel during or shortly before the incubation period and had no known contact with measles cases. He lives with his wife who had measles in childhood; other members of the family were vaccinated against measles according to the vaccination programme.

An alert was issued on 13 March through the Early Warning and Response System (EWRS) following the diagnosis of the index case. On 2 April the NIPH informed paediatricians and general practitioners about the outbreak through regional epidemiologists; information about measles cases was also published at NIPH website. Guidance for healthcare workers was prepared; an algorithm for the management of measles cases was published on the NIPH website (http://sm146.slohosting.com/Planet/?ni=150&pi=5&_5_Filename=1246.pdf&_5_MediaId=1246&_5_AutoResize=false&pl=150-5.3.).

Discussion

We describe a nosocomial cluster in a highly vaccinated population of Slovenia. Different manifestations of measles were observed, depending on the vaccination status of the patients.

Fortunately, measles in the index case was suspected even before the typical clinical picture appeared. Thus, control measures could have been implemented in time. However, despite this, transmission to two individuals occurred in the hospital setting. The index case was placed in a single room with anteroom in droplet isolation. No air condition was in place. All healthcare workers who were exposed to the index case at admission were tested for immunity against measles and offered vaccination if measles-specific IgG test was negative, but they were not excluded from work. Documented evidence of measles vaccination was not available for all healthcare workers.

It is obvious that Patient 3 was infected by the index case. As she reported to be vaccinated once, but tested negative for measles-specific IgG, she should have been considered a vaccine failure case (primary or secondary) Nevertheless, she was not excluded from work despite her susceptibility and exposure history. The observed rapid IgG antibody response could have been due to secondary immune response [5,6]. Rising measles-specific IgG in the absence of IgM in vaccinated cases has been described before [7]. Due to clinical presentation (mild measles) and antibody dynamics, Patient 3 was classified as a case of measles due to vaccine failure. According to some authors, most measles cases in a highly vaccinated population represent vaccine failure and are vaccine-modified cases with a lower transmission potential [8,9]. Although it is not very clear whether individuals with a mild illness who do not display the full range of clinical signs of measles are capable of transmitting the virus to susceptible persons, early detection of measles cases especially in healthcare workers is important so that appropriate infection control measures can be implemented in time to reduce the risk of nosocomial transmission.

It is not clear how Patient 4 was infected. To our knowledge, he had no direct contact with the index case. It is not very probable that Patient 3 was the source of infection because the illness in both cases was reported to start almost simultaneously. There is a possibility of indirect transmission from the index case.

In case of suspected measles in a hospital setting it is important to identify susceptible staff (without evidence of vaccination with two doses or laboratory evidence of immunity) who should be excluded from contact with suspected cases. Screening of immunity should be considered. Only staff with documented measles immunity should provide care to a suspected measles case.

Conclusion

This small outbreak clearly demonstrated the importance of implementing all appropriate control measures in healthcare settings. In addition, high measles vaccination coverage and strong surveillance remain critical to prevent future outbreaks.

Acknowledgements

We would like to thank Annette Mankertz and Sabine Santibanez from the Robert Koch Institute, Berlin for their generous support, confirming promptly the index case and providing us with all information and control material needed.

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Update: A food-borne outbreak of hepatitis A in the Netherlands related to semi-dried tomatoes in oil, January-February 2010

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Citation style for this article:
Citation style for this article: Petrignani M, Harms M, Verhoef L, van Hunen R, Swaan C, van Steenbergen J, Boxman I, Peran i Sala R, Ober HJ, Vennema H, Koopmans M, van Pelt W. Update: A food-borne outbreak of hepatitis A in the Netherlands related to semi-dried tomatoes in oil, January-February 2010. Euro Surveill. 2010;15(20):pii=19572. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19572

This article has been published on 20 May 2010

Between 31 December 2009 and 10 February 2010, 13 patients were infected by an identical hepatitis A virus strain not previously detected in the Netherlands. They had not been abroad and were widely distributed over the Netherlands. A case-control study including 12 cases and 44 controls identified semi-dried tomatoes in oil as the source of the outbreak (odds ratio: 20.0; 95% confidence interval: 1.5-274). The virus was not detected in any of 81 tested food samples. International trace-back is still ongoing.

Introduction

On 12 February 2010, five patients with acute hepatitis were detected in the Netherlands through our enhanced molecular surveillance programme and found to harbour an identical strain of hepatitis A virus (HAV, Hu/Netherlands/RIVM-006/2010). These patients had not been abroad and did not cluster geographically. Although the number of reported HAV cases was normal for the time of the year, finding five identical HAV strains was unusual and triggered an outbreak investigation [1]. Because the nucleotide sequence of a fragment of the VP1-2A region of HAV isolated from patients was identical to that found in patients involved in an outbreak in 2009 in Australia [2], and because the sequences were unique in the HAV database at our institute, a relation between these two outbreaks was suspected. The outbreak of hepatitis A in Australia was epidemiologically associated with the consumption of semi-dried tomatoes. To find a possible common source for the Dutch cluster, an investigation was conducted. The main goals were to identify any potential source among the food products consumed by the patients, specifically those containing semi-dried tomatoes. This article describes the results of the case-control study and food sample analysis.

Methods

Case-control study

The outbreak investigation focused on reported cases of hepatitis A with patients who contracted their infection in the Netherlands. Hepatitis A is notifiable in the Netherlands when a person has clinical symptoms of jaundice and/or fever combined with an elevated level of hepatitis A IgM in their serum (confirmed HAV patient) or combined with an epidemiological relation to a confirmed HAV patient (probable HAV patient). A nationwide project in which all laboratories were asked to send in the serum samples of patients for sequence analysis was already ongoing at the time of this outbreak [3].

A case-control study was initiated. Cases were defined as all reported persons with hepatitis A infection between 10 December 2009 (week 50) and 13 April 2010 (week 15) confirmed to have a primary infection with a genotype 1B HAV strain with identical sequence in a 460 nt fragment of the VP1-2A part of the genome, Hu/Netherlands/RIVM-006/2010 [4]. Cases related to primary cases and with onset of disease two weeks or more after the primary case were regarded as secondary cases. All primary cases were approached for inclusion.

To facilitate rapid source identification, controls were selected by three methods. The first group consisted of unrelated hepatitis A cases with onset of illness in the same time period. These unrelated cases were people who contracted their infection in the Netherlands,

but had a different HAV strain or were epidemiologically related to patients confirmed to be infected with a different strain. The second group of controls were found among non-household contacts of the cases and a third group by taking a sample in the same geographical area and of the same age range as the cases. Partners and family members were excluded to be controls since they could have been immunised as part of the outbreak control activities.

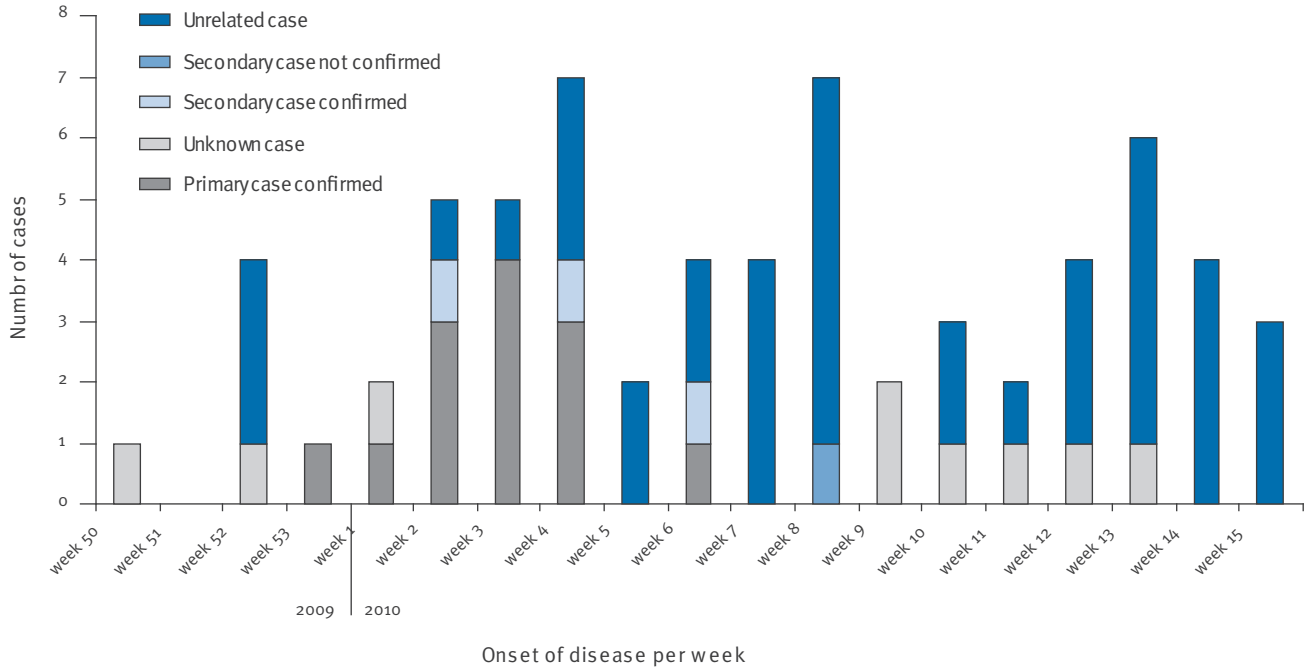
The cases and non-household contacts were asked to answer a web-based or telephone questionnaire. The controls that were selected from the same geographical region got the questionnaire and a letter asking for their participation in the study sent by post.

The questionnaire covered personal information such as age, gender, place of residence, country of birth, vaccine status, symptoms, contact with other infected persons, and a detailed food history. The food history specifically included fresh produce and fruits that are eaten unpeeled and/or uncooked (including: cabbage lettuce, iceberg lettuce, other lettuce, raw spinach, raw endives, other raw vegetables, sandwiches, dried tomatoes, semi-dried tomatoes in oil, tapenade, raspberries, blackberries, berries, strawberries, dates, figs and other fruit), as well as shellfish and other products that are normally eaten uncooked (clams, oysters, other shellfish, other raw products and other ready-made products). The participants were asked to indicate the degree of certainty of their answers as 'surely', 'possibly', 'not' or 'don't remember'. They were asked to name the places where the products were purchased and where they normally went shopping.

Because the power of analysis of the different control groups separately was limited due to low numbers of cases and controls, all three control groups were combined. Data were analysed univariately with a Fisher's exact test for non-random association between factors, the corresponding odds ratio was adjusted for age, sex and the different control groups, using appropriate dummy variables. After univariate testing all variables with a p value under 0,2 were used in a forward stepwise selection method to fit a multivariate model. Analyses were done in R (version 2.10).

Figure

Cases of hepatitis A contracted in the Netherlands between 10 December 2009 and 13 April 2010 (n=66)



Table

Odds ratios of risk factor for infection with the HU/Netherlands/RIVM-006/2010 strain in the Netherlands, 10 December 2009 – 13 April 2010 (n=56)

Consumed semi-dried tomatoes in oil	Total respondents		Cases		Controls		
	n	Percentage	n	Percentage	n	Percentage	Odds ratio[a]
Not	24	43%	2	4%	22	39%	1.0
Surely and possibly	22	39%	8	14%	14	25%	20.0 (1.5-274.1)
Missing information	10	18%	2	4%	8	14%	11.6 (0.4-312)
Total	**56**	**100%**	**12**	**22%**	**44**	**78%**	

[a] Odds ratio adjusted for age, sex and control groups.

Source tracing and sampling for laboratory analyses

Semi-dried tomatoes were implicated from the beginning of the investigation because the same strain was identified in an outbreak in Australia linked to semi-dried tomatoes [2]. In order to identify a common source of the semi-dried tomatoes consumed by the patients, the Food and Consumer Product Safety Authority performed trace back investigation on national and international suppliers of semi-dried tomato products. International trace-back information was exchanged via the Rapid Alert System for Food and Feed (RASFF) and Infosan. Initially, only little information was available on the brands of the products containing semi-dried tomatoes that had been consumed by the patients. For this reason, inspectors of the Food and Consumer Product Safety Authority collected a wide range of products at the stores used by the patients, and when national trace back information became available, samples were taken at the identified suppliers or warehouses located in the Netherlands.

All samples were analysed for the presence of HAV RNA at least in duplicate using an in-house method including an extraction process control and an external HAV RNA standard to control for inhibition of the PCR signal.

Results

Background information

As of 21 April 2010, a total of 66 cases were notified that had contracted their HAV infection in the Netherlands (Figure). Of these, 13 primary cases were confirmed to be infected by the same strain with onset of disease between 31 December 2009 and 10 February 2010 (one of them a British tourist). Four secondary cases were reported to be epidemiologically related to the confirmed primary cases (partners and family members), three of whom were infected by the Hu/Netherlands/RIVM-006/2010 strain. For the fourth contact no serum was obtained for sequencing. Of the 13 confirmed primary cases, eight were male and five were female, with a median age of 42 years (range: 20-63 years). Nine cases with onset of disease between 10 December 2009 and 2 April 2010 and unknown transmission route could not be genotyped due to negative RT-PCR (n=4) or lack of serum samples (n=5) and were considered as 'unknown' cases. Of these nine unknown cases four were male and five were female, with a median age of 44 years (range: 6-69 years).

In the same period, 40 unrelated cases were reported who also contracted their infection in the Netherlands, but either had a different HAV strain or were epidemiologically related to patients confirmed to be infected by a different strain. Of the unrelated cases 16 were male and 24 were female, with a median of 20 years (range: 2-69 years).

Case-control study

13 primary confirmed cases and 262 controls were approached for inclusion. One case did not agree to participate in the study for unknown reasons. In total 61 controls filled out the questionnaire. Of the responding controls, 17 were excluded for returning an incomplete questionnaire. All further analysis was done based on a sample of 12 primary cases and 44 controls of which 12 were unrelated cases, 10 were non-household contacts of the patients and 22 were selected from the same geographical area.

For the univariate analysis the answers 'surely' and 'possibly' were taken together and 'don't remember' was classed as missing. Odds ratios were adjusted for age, sex and possible differences between control groups by adding two dummy variables to the model, which made it possible to differentiate between the three different control groups and see whether any of the groups had an effect on the model individually.

Univariately three variables showed a p value of less than 0.2: dates, raw vegetables and semi-dried tomatoes in oil. Of these variables, dates were a protective factor and after multivariate analysis only semi-dried tomatoes in oil turned out to significantly improve the null model. Of the 10 respondents who answered this question, eight (80%) confirmed having consumed semi-dried tomatoes in oil, compared to 14 of the 36 controls (39%), giving an adjusted odds ratio of 20.0 (95% confidence interval: 1.5-274.1) (Table).

Eight of the cases confirmed eating semi-dried tomatoes in oil, two did not remember and two denied having eaten them. Of these last four cases, two ate mixed salads that very likely contained semi-dried tomatoes, one case had surely consumed dry semi-dried tomatoes and the remaining case also had consumed mixed salads and often ate take-away food from restaurants.

Source tracing and analyses of semi-dried tomato products

In total 81 samples were collected between 23 February and 1 April 2010. These were semi-dried tomatoes in oil either marinated or not (n=36), dried tomatoes without oil (n=17), marinated semi-dried tomatoes (n=16), tapenade or raw materials for tapenade containing semi-dried tomatoes (n=20) and salads or dried salad mixes containing semi-dried tomatoes (n=8). Five of these samples were collected as opened packages at the patients' homes (semi-dried tomatoes in oil (n=2), dried tomatoes (n=1), tapenade (n=1) and dried salad mix containing semi-dried tomatoes (n=1). In none of the 81 samples analysed, HAV RNA could be detected by two-step real-time RT-PCR. The products collected and specifically remembered by the patients were diverse and from different brands. Trace-back by Dutch food safety inspectors showed a complex product chain, involving multiple companies, and leading to international importers in different countries. Until now no common source could be identified, but we are still awaiting feedback from international trace-back through RASFF and Infosan.

Discussion

The case-control study confirmed food products containing semi-dried tomatoes in oil as a risk factor for the hepatitis A cluster. Nearly all patients ate semi-dried tomatoes while only relatively few of the controls did. This is true for all three control groups and provides strong epidemiological evidence that semi-dried tomatoes were the source of the outbreak. Semi-dried tomatoes have not been described before as a cause of food-borne outbreaks of hepatitis A. When patients are asked what raw products they have consumed, it is likely that they will not mention semi-dried tomatoes spontaneously. Therefore we recommend keeping this product in mind when implementing a food questionnaire in the investigation of a suspected food-borne outbreak.

In our study, controls were not selected according to a standardised epidemiological study design, nor were all controls selected by the same method, which may have introduced selection bias. This choice was made for practical reasons to enable rapid conclusions for source tracing. As preliminary analysis of individual groups showed comparable results, we considered it justified to analyse the controls as one group to increase power.

Our results could not be confirmed by food testing as all samples tested negative for HAV RNA. Several factors associated with food analyses in general and with virus testing in particular may have lead to the negative test results. Food testing for viruses is not done routinely and there are at present no accepted validated routine methods available, but most importantly: only part of the samples were taken from the product type associated with the highest risk in our investigation and most likely these were collected too late. Often, leftovers from the batch implicated in a food-related event have been discarded by the time samples are being taken, as a consequence of the long incubation period of hepatitis A. In the present study, sampling started only from mid-February 2010, whereas many of the confirmed patients had probably been exposed to the source already in December 2009. Other factors in general are the potential non-homogeneous distribution of (low amounts of) virus in the food, low efficiency of the method to extract the virus from the food, co-isolation of inhibitory agents from the food that interfere with the test method, or insufficient sensitivity of the detection method.

Unfortunately, the products remembered by the patients were of diverse origin, involving many companies and requiring international trace-back. Around ten companies in different countries have been identified that supply (marinated) semi-dried tomatoes in oil to the stores where patients purchased their products. The source of this outbreak remains obscure, and given the diffuse pattern of distribution of cases is likely to be a contamination event higher up in the food production chain. One hypothesis could be that contaminated water was used during cultivation of the tomatoes as has been described for green onions [5].

We are still waiting for international responses through the RASFF and Infosan systems about possible relationships between the different companies. Therefore, a common source cannot be ruled out and we cannot be certain that the outbreak has ended. It is possible that some of the contaminated products have been frozen and not been consumed yet. HAV can survive for several months in frozen produce as has recently been described for spinach leaves, berries and herbs [6,7]. Alternatively, there could still be a risk of contamination at the farm where the tomatoes originated from. Therefore, surveillance through sequence analysis of patient sera will remain necessary for several months at least.

Acknowledgements

We would like to thank Geke Hägele and Nathalie te Loeke for analyses of the food samples, Jeroen Cremer and Bas van der Veer for technical assistance on human sera, Joanne Bruins, Jolanda Rensink and Marlies van Dam for assisting the outbreak team. Furthermore, we would like to thank the Municipal Health Services for their help in including the patients, the Food and Consumer Product Safety Authority food inspectors for product sample collection and their back office for technical assistance as well as the medical microbiological laboratories involved for sending in the patient sera.

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Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010

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Citation style for this article:
Citation style for this article: Pebody RG, McLean E, Zhao H, Cleary P, Bracebridge S, Foster K, Charlett A, Hardelid P, Waight P, Ellis J, Bermingham A, Zambon M, Evans B, Salmon R, McMenamin J, Smyth B, Catchpole M, Watson JM. Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Euro Surveill. 2010;15(20):pii=19571. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19571

This article has been published on 20 May 2010

This paper describes the epidemiology of fatal pandemic influenza A(H1N1) cases in the United Kingdom (UK) since April 2009 and in particular risk factors associated with death. A fatal case was defined as a UK resident who died between 27 April 2009 and 12 March 2010, in whom pandemic influenza A(H1N1) infection was laboratory-confirmed or recorded on the death certificate. Case fatality ratios (CFR) were calculated using an estimated cumulative number of clinical cases as the denominator. The relative risk of death was estimated by comparing the population mortality rate in each risk group, with those not in a risk group. Across the UK, 440 fatal cases were identified. In England, fatal cases were mainly seen in young adults (median age 43 years, 85% under 65 years), unlike for seasonal influenza. The majority (77%) of cases for whom data were available (n=308) had underlying risk factors for severe disease. The CFR in those aged 65 years or over was nine per 1,000 clinical cases (range 3–26) compared to 0.4 (range 0.2 to 0.9) for those aged six months to 64 years. In the age group between six month and 64 years, the relative risk for fatal illness for those in a risk group was 18. The population attributable fractions in this age group were highest for chronic neurological disease (24%), immunosuppression (16%) and respiratory disease (15%). The results highlight the importance of early targeted effective intervention programmes.

Introduction

Seasonal influenza is responsible for excess winter all-cause mortality and hospitalisations – particularly amongst the elderly, the very young and those with underlying high-risk conditions such as chronic heart and lung disease [1]. The extent of any observed excess mortality varies each year and depends upon various factors including the predominant circulating influenza strain [2].

Since the emergence of pandemic influenza A(H1N1) in April 2009 and initial concerns about the risk of severe respiratory illness, much effort has been devoted to rapidly understanding the severity and impact of this novel influenza virus. Early work in various settings has demonstrated that the overall case fatality ratio (CFR) is generally low [3-5], with similar risk factors for severe disease as seasonal influenza, although in addition, individuals who are obese or pregnant are reportedly at high risk of severe outcome [6-8].

By 12 March 2010, more than 400 deaths had been reported across the United Kingdom (UK) by the Chief Medical Officer and health protection organisations in Wales, Scotland and Northern Ireland [9]. Information on which groups are at higher risk of death is key to healthcare planning – in particular the development and evaluation of the pandemic influenza A(H1N1) vaccination programme. The vaccination programme in the UK started in October 2009 and initially targeted individuals at higher risk of severe disease, including pregnant women [10]. In December 2010, vaccination for all children from six month to five years of age began.

Using surveillance data collected during the pandemic in the UK, this paper aims to describe the epidemiology of fatal pandemic influenza A(H1N1) cases. It sets out to estimate various mortality indicators by age and clinical risk group to inform the implementation of prevention and control programmes for pandemic influenza.

Methods

The methods initially outline the case definitions, how cases were ascertained and what additional epidemiological data, including risk factor information, was gathered. The descriptive section (time and place) covers the entire UK (England, Wales, Scotland and Northern Ireland). The analytical section (the

population mortality rates, CFRs and population attributable fractions) only covers England.

Case definition

A fatal case was defined as a resident in the UK who died after 27 April 2009, in whom pandemic influenza A(H1N1) virus infection was confirmed by a laboratory ante- or post-mortem (either by RT-PCR or serology) or by any mention on the death certificate and was reported up to 12 March 2010.

Case ascertainment

Fatal cases in England were ascertained by the Health Protection Agency (HPA) over this period from several different reporting sources: Firstly, local healthcare providers reported fatal pandemic influenza cases to HPA-run local Health Protection Units (HPUs). Secondly, the immunisation department of the HPA Centre for Infections followed up laboratory-confirmed pandemic influenza cases with general practitioners (GPs) as part of monitoring the pandemic influenza vaccination programme. This follow-up included ascertainment of outcome status. Thirdly, hospital clinicians reported confirmed hospitalised cases of pandemic influenza to a web-based hospital surveillance system for pandemic influenza A(H1N1) infection. This included ascertainment of outcome status. Fourthly, the Office for National Statistics (ONS) shared each week individual death registrations with the HPA Centre for Infections of any death with a mention of influenza (ICD-10 codes J09, J10 and J11).

Individual fatal cases were reconciled and de-duplicated using available personal identifiers. All fatal cases were verified as laboratory-confirmed by matching to laboratory records of confirmed pandemic influenza held by the HPA or by any mention of influenza on the death certificate from ONS. They were confirmed as deceased either through the NHS Patient Demographic Service or through death certificate from ONS. Deaths were also compared with fatal cases collected by the Office of the Chief Medical Officer in England [3].

Fatal cases outside England were identified by the Boards of Health by Health Protection Scotland and through their equivalents in Wales and Northern Ireland.

The work was carried out under NHS Act 2006 (section 251), which provides statutory support for disclosure of such data by the NHS, and their processing by the HPA, for purposes of communicable disease control. Ethical approval was not required and informed consent was not sought.

Case follow-up

Clinical and demographic data and information on underlying risk conditions were gathered from the local HPU, the hospital physician or the general practitioner using a standard questionnaire. For those fatal cases for whom such data were not available, risk factor information was extracted from the death certificate, if available.

Risk factor definition

The seasonal influenza risk groups used throughout this paper were those defined by the UK Department of Health (DH) for the seasonal influenza vaccination programme in 2008-9: chronic respiratory disease, including asthma treated in the last three years; chronic heart disease, chronic liver disease, chronic renal disease, chronic neurological disease, stroke/transient ischaemic attack, and immunosuppression through disease or treatment and diabetes.

The risk groups for pandemic influenza in addition included pregnancy and obesity, which are presented separately.

Population mortality rates

Age-specific population mortality rates for pandemic influenza were calculated using the mid-2008 population for England (Source: ONS).

Seasonal influenza deaths

Death registrations between 2 January 2001 and 2 February 2009 with an ICD-10 code for influenza (ICD-10 J09, J10 and J11) in England were also identified to compare the epidemiology of fatal pandemic influenza with fatal seasonal influenza. Information on whether the person suffered from underlying risk conditions was not specifically gathered for these fatal cases; deaths were classified into DH standard risk groups as above, based on available text information recorded for cause of death on the certificate. The distribution of DH-defined risk groups for severe disease amongst deaths with laboratory-confirmed pandemic influenza A(H1N1) and deaths with any mention of seasonal influenza were compared using age-adjusted Mantel-Haenszel odds ratios (OR). To calculate the population mortality rate for seasonal influenza deaths, the denominators were the cumulative mid-year annual population estimates for England for the period from 2001 to 2008 (source: ONS).

Population prevalence of specific risk factors in England

The prevalence of specific high risk conditions (excluding pregnancy and obesity) in the English population were derived from the DH influenza vaccine uptake monitoring system [11]. All GPs in England are requested to extract data on registered patients from their health information systems each season using standard queries. This system was used to determine the total number of people registered with a general practice in England and the number of those older than six months eligible for seasonal influenza vaccine by age group and by individual risk group. These risk groups did not include pregnancy or obesity, as these are not DH-defined target groups for the seasonal influenza vaccination programme [11]. For people aged between six months and 64 years a breakdown by individual

DH-defined seasonal influenza risk group was available (based on data provided by 96.2% of all English GP practices) in two age groups: six months to 15 years and 16 years and over [12]. For those aged 65 years and over information on the number in any DH-defined risk group was available and was extrapolated from data provided by 79.4% of GP practices (provisional data provided by the DH). Using this approach, as people may fall into more than one risk group, the sum of all the individual risk groups will exceed the total number in the population [11].

The point prevalence of pregnant women was calculated using the estimated English mid-2008 female population aged 15 to 44 years (source: ONS) as the denominator. According to ONS, an estimated 676,236 maternities (live and still births) occurred in England in 2008 [13]. Assuming 4% of the female population of child-bearing age (15 to 44 years) experience a miscarriage or abortion in any given year [14] and using the mid-2008 estimate of the female population aged 15 to 44 years (10,532,500), an annual figure of 421,300 miscarriages/abortions was calculated. To calculate the number of women who were pregnant at any one time, 9/12 of the annual number of maternities (assuming these pregnancies have a duration of nine months) was added to 3/12 of the annual number of miscarriages/abortions (assuming these pregnancies have an average duration of three months). A final figure of 612,502 pregnancies (5.8% of the female population aged 15 to 44 years) was reached.

Case fatality ratios for clinical pandemic influenza in England

The CFRs were calculated overall and by age and risk group. The numerator was fatal cases in England and the denominator was the estimated cumulative number of clinical cases in England from the beginning of the pandemic to 21 February 2010. This includes a three week lag. This lag incorporates the observed median delay from disease onset to report of death (see results section). The estimated number of clinical cases was calculated by the HPA using a statistical model which relies on data from various surveillance systems: the primary care-based QSurveillance scheme, sentinel virological surveillance schemes and data from the National Pandemic Flu Service (NPFS) [15].

The estimated number of clinical cases consulting health services by age group were calculated using age group-specific data from the various surveillance systems (available in the following age groups: <1 year, 1-4, 5-14, 15-24, 25-44, 45-64 years and ≥65 years). To estimate the number of clinical cases in each DH-defined risk group, the proportion of people aged between six months and 64 years in each risk group from the GP vaccine uptake survey described above was applied to the cumulative number of cases estimated by the HPA in the same age group. This assumes that those in a clinical risk group are as likely to have symptomatic infection as those not in a clinical risk group.

It was assumed that babies aged under six months represent half the infant (aged under one year) clinical cases. To estimate the number of pregnant clinical cases, the point prevalence of pregnancy (as described above) was applied to half of the estimated number of clinical cases aged 15 to 44 years (assuming an equal distribution of influenza infection between males and females).

The HPA's estimate of clinical case numbers is subject to uncertainties particularly regarding consultation behaviour. A lower and upper estimate was calculated to allow for this. A sensitivity analysis was undertaken: the overall and the age- and risk group-specific CFRs were calculated using the central estimate for the number of clinical cases, and for the low and high estimates. A 95% exact binomial confidence interval (CI) was calculated around each case fatality estimate. The range incorporating the 95% CI around the CFRs calculated from the low and high estimated number of clinical cases is presented.

Relative risk of fatal pandemic influenza in England

The relative risk (RR) of fatal pandemic influenza for each risk group was calculated by comparing the population mortality rate in each individual risk group with the rate in those who did not fall into any risk group. For those aged under 65 years, Mantel-Haenszel age-adjusted RR, with corresponding exact 95% CI were calculated for each risk group using the two available age groups (from six months up to 15 years and from 16 to 64 years). For those aged 65 years and over, information was only available overall for any risk group to calculate RR of fatal infection.

Population attributable fractions for fatal pandemic influenza in England

The population attributable fraction (PAF) of each individual risk group to fatal pandemic influenza was estimated. The PAF was calculated by dividing the difference in the overall population mortality rate (PMR) and the PMR in the non-exposed by the overall PMR. The unexposed group were people without that particular risk factor (i.e. all other cases, who may fall into other risk groups), which is different to that used to calculate the RR (people with no risk factor at all). The PAF takes into account the prevalence of the exposure in the population and is interpreted as the proportion of the total number of deaths which would be averted, if the exposure were completely removed.

Laboratory methods

Laboratory confirmation of pandemic influenza A(H1N1) virus was performed using respiratory swabs collected into virus transport medium. All samples were tested either at the Respiratory Virus Unit of the HPA Centre for Infections, London or at the HPA Regional Microbiology Network Laboratories, using real-time RT-PCR assays for detection of influenza A, and subtyped for pandemic influenza A(H1N1) viruses [16,17]

Figure 1

Number of deaths from confirmed pandemic influenza A(H1N1) by week and country of death, June 2009–February 2010 (n=436, date of death missing in four cases) with estimated number of clinical cases in England (HPA)

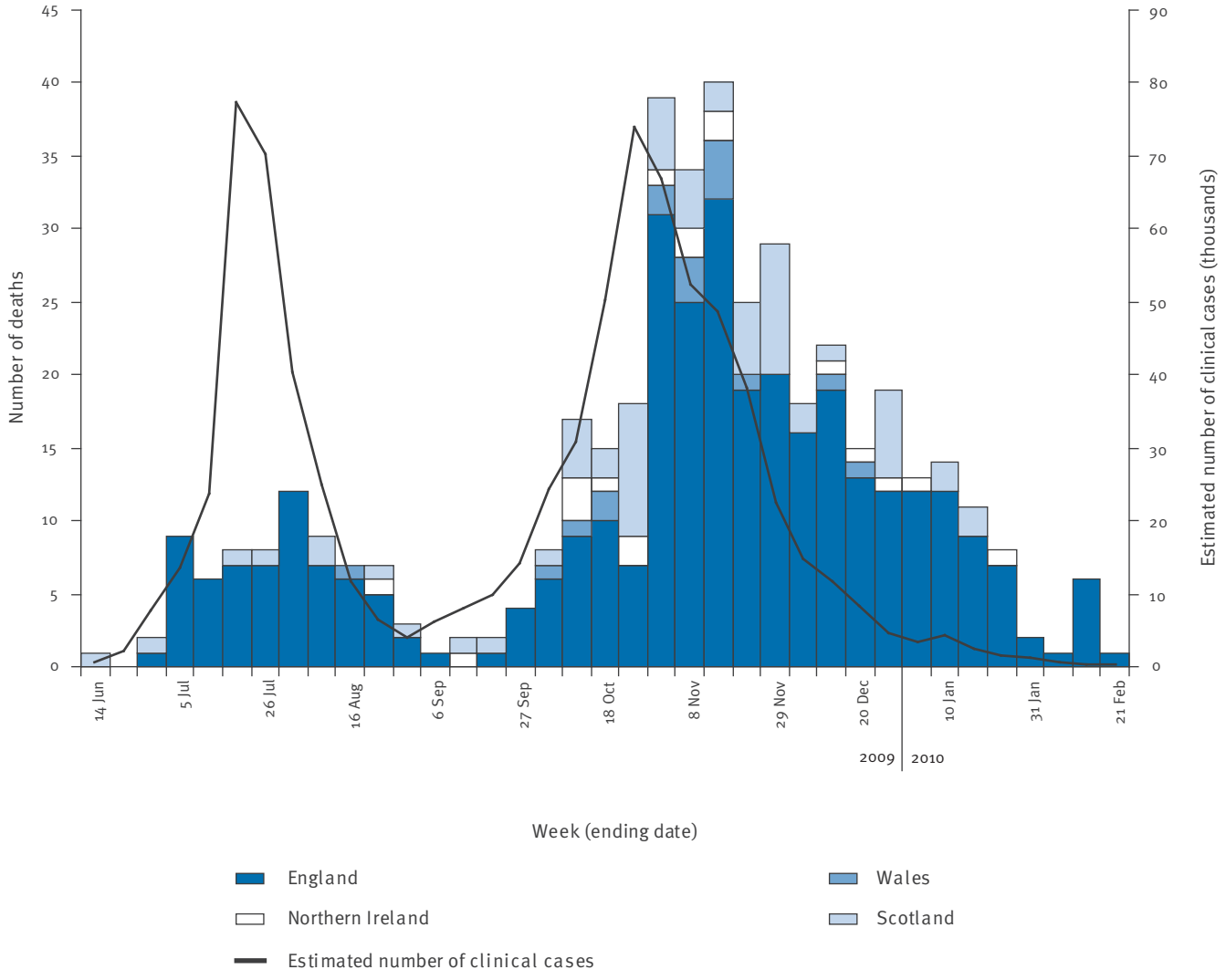
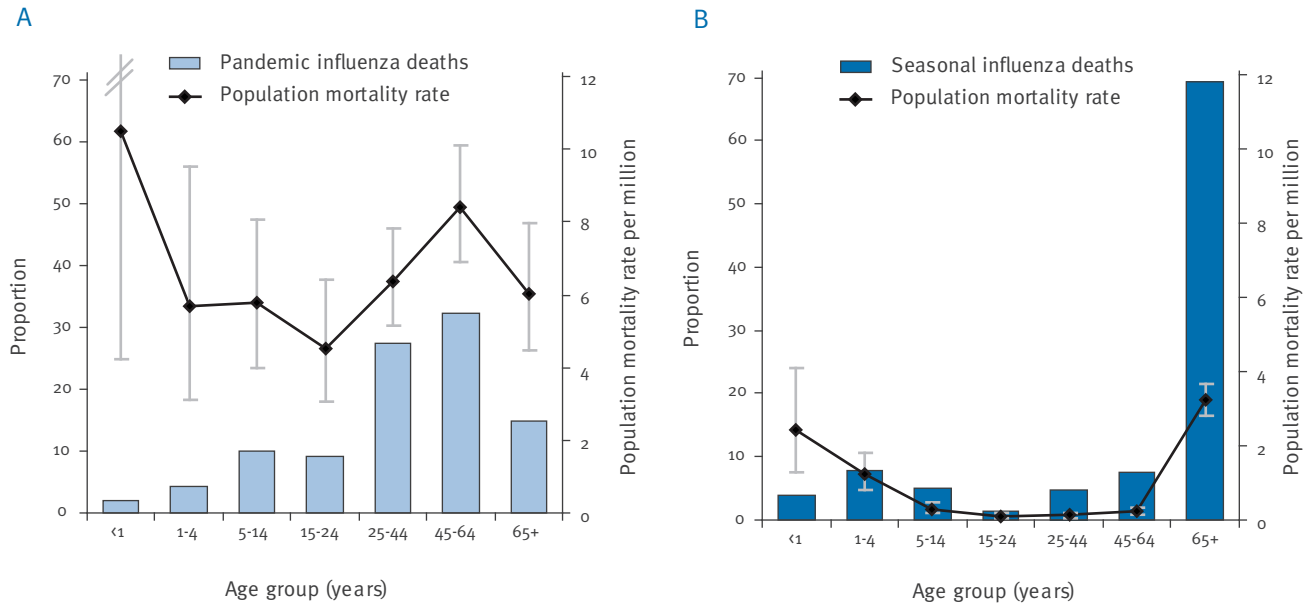


Figure 2

Age distribution of (A) pandemic influenza deaths, England, until February 2010 (n=336[a]), with cumulative population pandemic influenza mortality rate, and (B) seasonal influenza deaths, England, January 2001–February 2009) (n=334), with average annual population mortality rate (2001–2008)



[a] Age not available for one fatal pandemic influenza case.

Results

Fatal pandemic influenza cases by time and place in the United Kingdom

Individual information on 440 fatal pandemic influenza cases fulfilling the case definition was collated by the HPA from across the UK up to 12 March 2010: 337 deaths occurred in England, 65 in Scotland, 21 in Northern Ireland and 17 in Wales. Of the 440 deaths, 387 (88%) were laboratory-confirmed and 53 were only confirmed by mention of influenza on the death certificate.

The first reported death occurred in the week ending on 14 June 2009 (Figure 1). The number of deaths by date of death climbed to a peak in the week ending on 2 August, with the onset of the school summer holidays and declined to baseline levels by the beginning of September. This pattern reflects the summer pandemic wave as illustrated by the weekly estimated number of clinical cases of pandemic influenza in England. A small number of deaths continued to be reported each week throughout September, followed by an increase from October onwards coinciding with a second increase in pandemic influenza activity in the autumn. This second larger peak of deaths occurred in mid-November and decreased to low levels by the end of January 2010. The final reported death included in this analysis occurred in the week ending on 21 February 2010. Seventy-three (17%) of the 440 fatal cases in the UK occurred during the summer wave (until end August 2009) and 367 (83%) during the autumn/winter wave (from the beginning of September 2009 to February 2010).

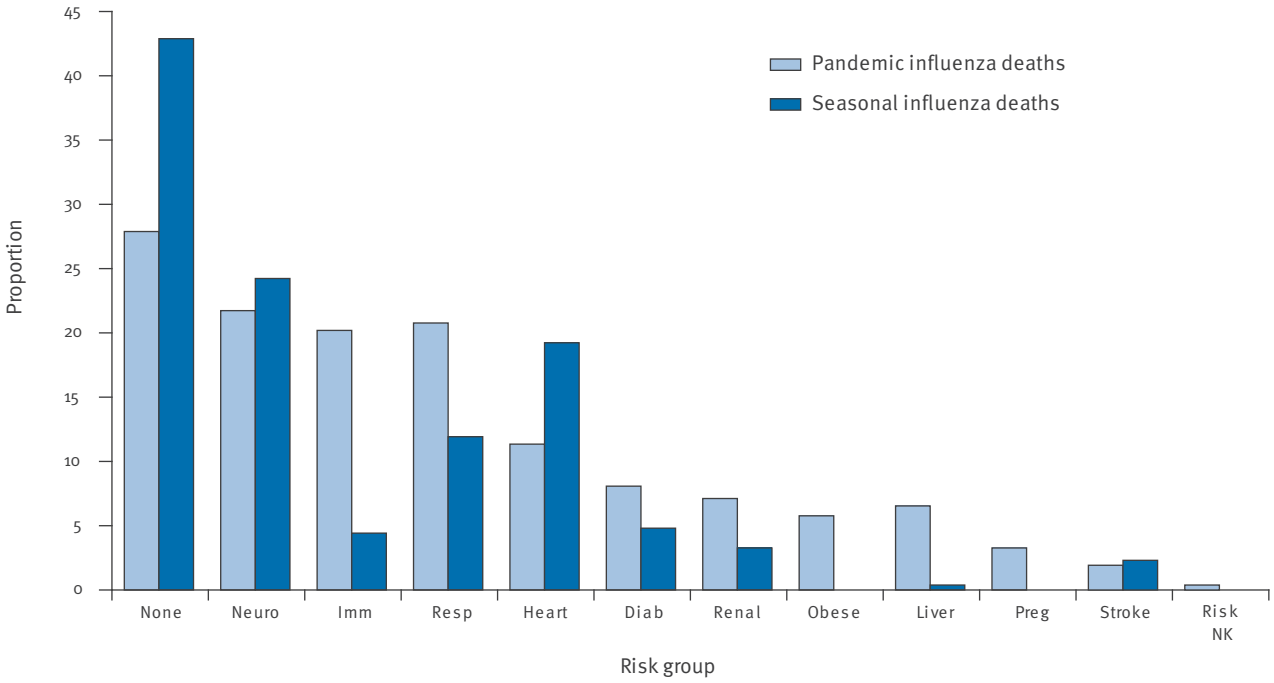
Age distribution of fatal pandemic and seasonal influenza cases in England

Of the 336 pandemic fatal cases in England with information on age, the median age of fatal pandemic cases was 43 years (interquartile range (IQR): 24–57) and the mean was 41 years (standard deviation (SD): 22). The population mortality rate from pandemic influenza was higher in the under one-year-olds than in other age groups (Figure 2A). Only four (1%) of 336 fatal pandemic cases were reported in children under six months of age. Population mortality rates were not elevated in 1-4 year olds compared to older age-groups.

A total of 334 fatal seasonal influenza cases were collated from death certificates for the period between 2 January 2001 and 2 February 2009 in England. The seasonal influenza deaths occurred mainly in people aged 65 years or over (Figure 2B), with 232 (69%) of 334 seasonal influenza deaths compared to 50 (15%) of 336 pandemic influenza deaths (Fisher's exact test, $p<0.0001$). There was no evidence of a significant difference in the proportion of deaths in children younger than six months from pandemic influenza compared to seasonal influenza (Fisher's exact test, $p=0.24$). The average age was higher in fatal seasonal influenza cases compared to fatal pandemic influenza, with

Figure 3

Distribution of pandemic influenza A(H1N1) deaths (2009-2010, n=308[a]) and seasonal influenza deaths (2001–2009, n=334) by reported underlying risk factor, England



Risk groups: chronic neurological disease (Neuro), chronic respiratory disease including asthma (Resp), immunosuppression through disease or treatment (Imm), chronic heart disease (Heart), diabetes (Diab), chronic renal disease (Renal), obesity (Obese), chronic liver disease (Liver), pregnancy (Preg) and stroke/transient ischaemic attack (Stroke), no risk group including pregnancy and obesity (None).

Cases may fall into more than one risk group.

[a] Excluding cases with no available information on risk group.

a median of 81 years (IQR: 53–89) and a mean of 66 years (SD: 32).

Distribution of underlying risk factors amongst pandemic influenza and seasonal influenza fatal cases in England

Data on risk group were missing for 29 (9%) of 337 cases. Information was more likely to be missing in young children (p=0.004, 36% in the 1–4-year-olds compared to all other age groups in the range of 0–15%) and in the autumn wave (p=0.028, 2% in the summer wave versus 10% in the autumn wave). Of the 308 fatal pandemic influenza cases in England with available data, 222 (72%) fatal cases had an underlying risk factor for severe influenza and fell into DH-defined risk groups recommended for the 2008-9 seasonal influenza vaccine (excluding pregnancy and obesity). Twenty-eight people had these latter underlying conditions, 15 of whom (nine obese and six pregnant fatal cases) did not have any other underlying risk factor. Including these 15, this gives a total of 77% (237 of 308) of fatal pandemic influenza cases in a risk group. The majority (n=171, 72%) of the 237 fatal cases with an underlying risk factor had only one risk factor, however, 43 fatal cases suffered from two underlying conditions, 20 from three, and three from four or five risk factors.

The distribution of fatal cases of pandemic influenza by reported underlying risk factor is shown in Figure 3. Chronic neurological disease, respiratory disease and immunosuppression were the most common reported risk factors. A similar pattern in the distribution of individual risk factors was observed for seasonal influenza deaths, although, after adjusting for age, fatal cases of pandemic influenza were more likely to be associated with a risk factor than fatal cases of seasonal influenza (age-adjusted OR: 2.8; 95% CI 1.7–4.5; p<0.0001). For fatal seasonal influenza cases, 57% (191 of 334) had an underlying risk factor (excluding pregnancy and obesity). The most common risk factors were chronic neurological and cardiac disease (Figure 3). There was evidence that immunosuppression (age-adjusted OR: 4.3; 95% CI: 2.4–7.8) and chronic renal disease (age-adjusted OR: 2.7; 95% CI: 1.2–6.2) were more common in pandemic influenza deaths than seasonal deaths.

The distribution of individual risk factors in the English pandemic fatal cases is shown in Table 1. The most commonly reported underlying risk factor in children (aged under 16 years) was neurological disease,

Table 1

Distribution of risk factors for fatal pandemic influenza A(H1N1), England only, April 2009–February 2010 (n=308)

Underlying risk factor	Total (%[a])
Chronic neurological disease	**67 (22%)**
Cerebral palsy/developmental delay	22
Neuro-musculoskeletal disorders	10
Down's syndrome	7
Epilepsy	9
Chronic respiratory disease	**63 (20%)**
Chronic obstructive pulmonary disease	20
Asthma	19
Immunosuppression	**62 (20%)**
Leukaemia/lymphoma	20
Myeloma	14
Solid tumour	8
Organ/bone marrow transplant	9
Chronic heart disease	**35 (11%)**
Congenital	9
Diabetes	**25 (8%)**
Chronic renal disease	**22 (7%)**
Chronic liver disease	**20 (6%)**
Alcohol-related	12
Obesity	**18 (6%)**
Pregnancy	**10 (3%)**

Cases may fall into more than one risk group and suffer from more than one disorder within each risk group.

[a] Proportion of all cases with known risk group status (n=308).

Table 2

Proportion of fatal pandemic (n=308a) and seasonal (2001-2009, n=334) influenza cases with risk factors compared to the general population, by age group, England

	Population			Pandemic influenza deaths (April 2009-February 2010)				Seasonal influenza deaths (2001-2009)			
Age group	**Risk group**	**Total**	**%**	**Risk group**	**Total**	**%**	**p[b]**	**Risk group**	**Total**	**%**	**p[b]**
<6 months	N/A	333,800	N/A	4	4	100.0%	N/A	4	8	50.0%	N/A
<6 months - 15 years	535,933	9,225,079	5.8%	32	44	72.7%	<0.0001	28	49	57.1%	<0.0001
16-64 years	4,043,312	34,724,600	11.6%	145	215	67.4%	<0.0001	29	45	64.4%	<0.0001
65 years and over	4,233,686	8,285,300	51.1%	41	45	91.1%	<0.0001	130	232	56.0%	0.148
Total	**8,812,931**	**52,568,779**	**16.8%**	**222**	**308**	**72.1%**	**<0.0001**	**191**	**334**	**57.2%**	**<0.0001**

N/A: not applicable.

[a] Of those with known risk group status (excluding pregnancy and obesity).

[b] p value for Fisher's exact test of difference in proportions.

Table 3

Estimated case fatality ratios, population mortality rate, relative risk and population attributable fractions, by risk group, England, April 2009–February 2010

	Population (in thousands)	Estimated number of cases (central estimate)	Number of deaths	CFR (per 1,000 cases)	95% CI[a]	Population mortality rate (per 100,000)	95% CI	Relative risk[b]	95% CI	PAF (%)[c]
65 years and over only										
No risk factor	4,051	2,643	4	1.5	0.2 – 8.1	0.1	0.03 – 0.3	baseline (for RR)		
Any risk factor	4,234	2,762	41	14.8	5.1 – 42.2	1.0	0.7 – 1.3	9.8	3.5 – 27.4	81.8
Total[d]	**8,285**	**5,405**	**50**	**9.3**	**3.3 – 25.6**	**0.6**	**0.4 – 0.8**			
Over six months to 64 years only										
No risk factor	39,370	693,259	82	0.1	0.05 – 0.3	0.2	0.2 – 0.3	baseline (for RR)		
Any risk factor	4,579	80,634	177	2.2	0.9 – 5.4	3.9	3.3 – 4.5	17.9	13.8 – 23.2	64.7
Chronic renal disease	183	3,219	15	4.7	1.2 – 16.1	8.2	4.6 – 13.5	36.3	20.9 – 63.2	5.4
Chronic heart disease	688	12,110	23	1.9	0.6 – 6.0	3.3	2.1 – 5.0	15.2	9.6 – 24.1	7.4
Chronic respiratory disease	2,016	35,498	48	1.4	0.5 – 3.8	2.4	1.8 – 3.2	11.3	7.9 – 16.1	14.6
Chronic liver disease	139	2,455	20	8.1	2.4 – 26.3	14.3	8.8 – 22.2	63.3	38.6 – 103.7	7.4
Diabetes	1,010	17,793	21	1.2	0.4 – 3.8	2.1	1.3 – 3.2	9.2	5.6 – 14.9	5.9
Immunosuppression	373	6,574	44	6.7	2.3 – 18.9	11.8	8.6 – 15.8	52.8	36.3 – 76.6	16.3
Stroke/transient ischaemic attack	177	3,119	3	1.0	0.1 – 5.9	1.7	0.3 – 5.0	7.5	2.3 – 23.7	0.8
Chronic neurological disease	254	4,469	64	14.3	5.3 – 38.3	25.2	19.4 – 32.2	115.3	84.3 – 157.6	24.3
Total[d]	**43,950**	**773,894**	**282**	**0.4**	**0.2 – 0.9**	**0.6**	**0.6 – 0.7**			
All age groups										
Total	**51,446**	**782,271**	**337**	**0.4**	**0.2 – 1.0**	**0.7**	**0.6 – 0.7**			

CFR: case fatality ratio; CI: confidence interval; PAF: population attributable fractions; RR: relative risk.

[a] 95% CI represents range incorporating 95% CIs of CFRs using high and low estimates of total clinical cases.

[b] Age adjusted ratio of population mortality rates presented for all except the age-group 65 years and older which are crude population rate ratio.

[c] PAF ((rate in overall population - rate in unexposed) / rate in overall population) is calculated comparing the risk in the exposed (e.g. each risk group) with that of all people not exposed to that risk (e.g. all others, not just those not falling into any risk group).

[d] Totals include people with missing information on risk group; To ensure comparability with seasonal influenza, cases that would not have been eligible for the 2008-9 seasonal influenza vaccine (e.g. pregnant or obese) were excluded from the total number in a risk group and presented separately, unless they fell into another group.

whereas in adults (aged 16 years or over), immunosuppression was the most common. There were also 71 other fatal cases that had no reported underlying risk factor for severe disease. Adults aged 25-44 years had the highest proportion without an underlying reported risk factor for severe disease (28/87, 32%).

The mean duration of time from illness onset to death amongst fatal pandemic influenza cases was 12 days, the median was 9.5 days (IQR: 5–17, range: 0–45 days) (n=116 on whom such information was known).

Prevalence of underlying risk factors for severe disease in the general population and in fatal cases of seasonal and pandemic influenza in England

The prevalence of any risk factor for severe disease in the general population of England between six months and 64 years of age was 10%, whereas it was 51% for people aged 65 years or over (Table 2).

There was strong evidence in all age groups for a significant difference ($p<0.0001$) between the people who died with pandemic influenza and the general population regarding the proportion with at least one risk factor (excluding obese and pregnant fatal cases). A similar pattern was seen for deaths due to seasonal influenza (Table 2).

Case fatality ratios for pandemic influenza A(H1N1) in England by risk factor

The overall estimated symptomatic CFR was 0.4 per 1,000 clinical cases. The 95% confidence limits around CFR estimates, using low and high estimates for the cumulative number of clinical cases, gave a range of 0.2 to 1 per 1,000 clinical cases. There was evidence of differences in the age-specific CFRs, with a higher CFR in those over 65 years of age (CFR: 9; range: 3–26 per 1,000 clinical cases) compared to those aged six months to 65 years (CFR: 0.4; range: 0.2–0.9 per 1,000 clinical cases).

The estimated CFR for clinical cases aged between six months and 64 years in a risk group (excluding obese and pregnant cases) was 2 per 1,000 cases compared to 0.4 per 1,000 case for those not in a clinical risk group (Table 3). The CFR for clinical cases aged 65 years or over in a clinical risk group was estimated to be 15 per 1,000 clinical cases compared to 1.5 per 1,000 for those aged 65 years or over who were not in a risk group.

The estimated CFR also varied by individual risk group (Table 3). In particular a much higher CFR was observed amongst clinical cases with underlying immunosuppression, chronic liver disease or chronic neurological disease.

The CFR for pregnant women was 0.9 per 1,000 clinical cases (95% CI: 0.2–3.5 per 1,000).

Population mortality rate and relative risk of fatal illness in England by risk group

In the age group between six months and 64 years of age, the population mortality rate by risk group was highest for those with underlying chronic neurological disease, chronic liver disease and immunosuppression (Table 3). The population mortality ratio for pregnant women was 1.6 per 100,000 (95% CI: 0.8–3.0 per 100,000).

The RR of fatal illness from pandemic influenza A(H1N1) virus infection was highly elevated for those with a risk factor in all age groups (Table 3). In the age group of six months to 64 year-olds, the highest risk group-specific age-adjusted RR of fatal illness was found in those with immunosuppression, chronic liver disease and chronic neurological disease.

The RR of fatal illness for pregnant women was also elevated (RR: 7; 95% CI: 3–15) compared with women of child-bearing age with no risk factor (15-44 years).

Population attributable fraction for fatal pandemic influenza in England

The PAF was 82% for any risk factor in fatal cases aged 65 or over and 65% for those aged six months to 64 years. This means that 65% of the pandemic influenza deaths in the English population aged six months to 64 years could potentially be prevented by protecting all those in a clinical risk group.

The highest risk group-specific PAFs for those aged six months to 64 years were for chronic respiratory disease, immunosuppression and chronic neurological disease (Table 3).

Discussion

After the summer and autumn/winter waves of pandemic influenza (H1N1) 2009, more than 400 fatal cases had been reported across the UK. Unlike seasonal influenza, where deaths occur mainly amongst the elderly, the majority of the pandemic influenza deaths were among young and middle-aged adults. Most fatal pandemic influenza cases had underlying risk factors for severe illness and although the overall CFR has been low, it was significantly higher amongst those in clinical risk groups. The RR and population attributable fractions for fatal pandemic influenza were particularly high for groups with underlying chronic neurological disease, chronic respiratory disease, chronic liver disease and immunosuppression. Pandemic influenza in pregnancy has also been demonstrated to be a risk factor for death.

There are several limitations to this study. Firstly, the CFR estimates rely on estimated numbers of clinical cases consulting health services in the population. There is considerable uncertainty about these denominators. If the number of symptomatic cases has been underestimated, then the CFR will have been overestimated. An indication of the uncertainty is captured by

including the upper and lower limits of the estimated number of cases in the CFR calculations. Secondly, fatal case ascertainment may be incomplete. To minimise this, data has been reconciled from several independent sources. Thirdly, data on risk factors are missing for 9% of pandemic fatal cases. Fourthly, we did not have information on trimester at time of death for pregnant women. Consequently, to derive our denominator of pregnant women we used an estimate for all pregnancies including those that had a miscarriage. If the risk of death is greatest in the later stages of pregnancy, this may have led to an under-estimation of the risk of fatal disease amongst pregnant women. Fifthly, the results of the comparison between seasonal and pandemic influenza should be interpreted cautiously, as the method of collection of risk group information in the two datasets was different. Finally, some of the cases had severe underlying medical conditions, with influenza as a contributing cause of death. We do not know what proportion of these deaths could have been prevented by protecting against influenza.

Several hundred fatal pandemic influenza A(H1N1) cases have been reported in the UK since spring 2009. Laboratory-confirmed fatal cases have been identified in all age groups, mainly amongst younger adults, with only a minority of deaths in those aged over 65 years. Although the population mortality rate for pandemic influenza virus infection was low in the elderly, the CFR of pandemic influenza in this group was high. A very different picture was apparent for seasonal influenza, where the majority of deaths based on death certificate analysis were in those in 65 years or older. This is illustrated by excess mortality at the population level during seasonal influenza seasons, with the excess normally occurring amongst the elderly [18]. The observation that few confirmed pandemic influenza deaths occurred amongst those aged 65 years or older suggests that this part of the population is at least partially protected from the infection. This concurs with cross-sectional seroprevalence data from the United States (US) and the UK, which show that a substantial proportion of the birth cohort born before 1957 have cross-reactive antibodies to the pandemic influenza A(H1N1) virus [19,20]. This would be consistent with exposure to influenza A(H1N1) viruses circulating in the population in the period from 1918 to 1957 and explains the relatively low disease burden in these older cohorts during the present pandemic.

We report an overall CFR of 0.4 per 1,000 cases of pandemic influenza. This CFR is consistent with earlier published work from the UK by Donaldson *et al*. [3], but also from the US [5] and from reports from the southern hemisphere [21]. This figure also fits with the clinical picture associated with pandemic influenza virus infection that continues to be a generally mild disease for most cases. The observed CFR is much lower than observed in previous pandemics [3]. This low case fatality is in agreement with data from the routine excess mortality surveillance system operating in England and Wales, where no excess all-cause mortality was observed until the end of December 2009 either overall or in any individual age group based on daily and weekly mortality returns from the General Registry Office and the ONS. However, a small excess in all-cause mortality was observed in weeks 52 and 53 of 2009. This occurred at a time when there was little pandemic influenza circulation and is therefore unlikely to be attributable to pandemic influenza [9]. Other European countries have also developed real-time systems to monitor excess mortality as part of an EU-funded network, EuroMoMo. This network has reported a slight excess in cumulative mortality in young children which could possibly be attributed to pandemic influenza activity [22].

We report that the majority of fatal cases of confirmed pandemic influenza had an underlying risk factor for severe influenza disease. Similar findings have been reported earlier in the UK [3] and the US [23]. The risk factor distribution for pandemic influenza deaths was very similar to that seen for seasonal influenza deaths, except that the latter group had a larger proportion with no reported clinical risk group according to data obtained from death certificates. This discrepancy could be related to under-reporting of clinically relevant material on the death certificate for seasonal influenza, particularly in the older age groups among whom the prevalence of underlying risk conditions is likely to be high. The measures of risk and impact of pandemic influenza were particularly high for those with underlying neurological disease, respiratory disease, immunosuppression and liver disease. This highlights the importance of implementing effective, targeted prevention measures, although a significant minority of younger adults had no underlying risk factor.

A number of points can be raised regarding specific clinical risk groups:

Those with underlying neurological disease were the largest recognised group of deaths with an underlying risk factor. This group had the highest CFR and the largest population attributable fraction. Successfully targeting this group provides potential to reduce overall pandemic deaths. The majority of these cases were children and young adults with neuro-developmental problems such as cerebral palsy or neuro-muscular-skeletal problems such as muscular dystrophy. The US Centers for Disease Control and Prevention have reported that 92% of the children who died with laboratory-confirmed infection and who had an underlying risk factor had neuro-developmental conditions [24]. This population (particularly under 16 years) is not large in the UK and is often clustered in residential special school settings, further increasing their vulnerability. They have been recognised as a group at higher risk of severe disease from seasonal influenza [25]. Our findings highlight the importance of delivery of pandemic influenza A(H1N1) vaccine to this group. In addition, these individuals should have rapid access

to antiviral drugs to modify the clinical course of their infection and should be considered for prophylaxis if exposed.

Those with underlying respiratory disease were the second largest group of deaths with an underlying risk factor. However, as this population, which includes people with asthma and chronic obstructive airways disease, is large, the CFR is considerably lower than for other risk factors such as neurological disease. Asthma and other chronic respiratory diseases have long been recognised as important risk factors for severe illness from influenza infection [26,27], and targeting people with these risk factors with vaccination and early antiviral treatment can prevent a significant number of deaths.

Pregnant women were overrepresented amongst fatal cases in the UK compared with the general population and are at increased risk of death. These observations are similar to what has been seen in the US [7], with reports of deaths usually in the third trimester of pregnancy. Deaths amongst pregnant women have also been observed in other countries [6] e.g. South Africa [28]. More recent work from the US has also shown the benefit of early antiviral treatment [8], and these findings reinforce the importance that pregnant women remain a priority group for the UK pandemic influenza A(H1N1) vaccine programme.

The findings from this paper, and in particular the information from the RRs and population attributable fractions show that the most vulnerable groups for fatal pandemic influenza virus infection are younger adults with chronic neurological, immunosuppressive and respiratory diseases. Assuming causality, the results suggest that many deaths can be prevented if risk groups are targeted early with effective prevention programmes such as pandemic influenza vaccination. The success of such prevention programmes is contingent upon them achieving rapid high coverage.

Acknowledgements

The authors wish to acknowledge all colleagues throughout the Health Protection Agency Centre for Infections and HPA Local and Regional Services who contributed to data collection, colleagues in the HPA Regional Microbiology Network and Respiratory Virus Reference Unit who undertook laboratory investigation of respiratory samples from suspect cases, colleagues in Health Protection Scotland, National Public Health Service for Wales and Public Health Agency Northern Ireland who undertook investigation and reporting of cases, and finally the medical staff of the Chief Medical Officer in England.

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