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An outbreak of infection with *Bacillus anthracis* in injecting drug users in Scotland

C N Ramsay (colin.ramsay@nhs.net)¹, A Stirling², J Smith², G Hawkins¹, T Brooks³, J Hood⁴, G Penrice², L M Browning¹, S Ahmed², on behalf of the NHS GGC², on behalf of the Scottish National Outbreak Control Teams¹

1. Health Protection Scotland, Glasgow, United Kingdom

2. National Health Service Greater Glasgow and Clyde, Glasgow, United Kingdom

3. Special Pathogens Reference Unit (SPRU) Health Protection Agency, Centre for Emergency Preparedness and Response, Porton Down, Salisbury, United Kingdom

4. Glasgow Royal Infirmary, Glasgow, United Kingdom

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An investigation is currently underway to explore and control an outbreak of *Bacillus anthracis* among drug users (mainly injecting) in Scotland. Contaminated heroin or a contaminated cutting agent mixed with the heroin is considered to be the most likely source and vehicle of infection. Heroin users have been advised of the risk. The risk to the general public is regarded as very low.

Introduction

On 10 December 2009 the National Health Service Greater Glasgow and Clyde (NHS GGC) was informed of two hospitalised injecting drug users (IDUs) with blood cultures positive for *Bacillus* sp. Further testing identified that these cultures were provisionally positive for anthrax on 16 December 2009. One of the patients had died earlier that day. The other patient was stable and responding to a cocktail of antibiotics.

In the following weeks further suspected cases were reported and investigated in Glasgow, Lanarkshire, Tayside, Forth Valley, Fife and other Scottish NHS Board areas. As of 14 January 2010, there were a total of 14 confirmed cases of anthrax infection in Scotland of whom seven have died: seven confirmed cases in the NHS GGC area, four fatal; three cases in Lanarkshire NHS area, one of whom remains in hospital; two fatal cases in Tayside one fatal case in the Forth Valley NHS area, and one surviving case in Fife. All cases reported a history of taking heroin by intramuscular, intravenous or subcutaneous injection and/or by other routes including smoking or snorting.

Epidemiological information

Case definitions were established to classify cases as 'confirmed', 'probable' or 'possible' [1]. Only laboratory-confirmed cases are being reported publicly. The 14 confirmed cases are 10 men and four women* aged between 27 and 55 years for the men and between 39 and 43 years for the women. The mean age of the cases

is 38 years for both men and women. The mean age of the fatal cases is slightly higher at 42 years.

The first confirmed case in Glasgow was admitted to hospital on 7 December 2009; the latest confirmed case was admitted to hospital in Dundee on 6 January 2010 and died on 8 January following a rapid deterioration. Over the five weeks of the outbreak to date, the peak incidence of admissions was in week 3 (six new confirmed cases, week beginning 28 December 2009), dropping to one new confirmed case in week 4 (beginning 4 January 2010). The peak of the outbreak may therefore have already occurred, but it is too early yet to state this with confidence.

There are estimated to be around 55,000 (illegal) drug users in Scotland (not all of whom use heroin) giving a very approximate incidence of 2.5 cases per 10,000 drug users. This is set in the context of approximately 34% of IDUs reporting an injection site wound in any year.

Generally, the cases have presented with inflammation or abscesses related to sites of heroin injection. Symptoms began between one and two days or longer after injection of heroin and admission to hospital generally followed within four days. Localised lesions developed into necrotising fasciitis in a number of cases, some of whom died. The fatal cases in Glasgow (three men and one woman) died between three and seven days after admission. Cellulitis with very marked oedema has been noted in limbs with infection sites in a number of these cases. In a few cases the presentation has been of patients in advance stages of systemic sepsis some of whom died within hours. At least two cases presented with symptoms thought of at initial assessment as suggestive of a sub-arachnoid haemorrhage or haemorrhagic meningitis. Others presented with relatively localised lesions which have not progressed. The range of presentations is therefore wide and inconsistent.

Diagnosis has been confirmed by isolation of *Bacillus anthracis* in early blood cultures in some patients, supported by PCR testing of blood or excised tissues at the Health Protection Agency (HPA) Special Pathogens Reference Unit (SPRU) at Porton Down. In others, no blood cultures were obtained before antibiotic therapy was started and no organism was cultured, but PCR evidence was obtained. In at least one case confirmation was on the basis of finding only significant anti-toxin antibodies on sera following treatment with antibiotics. This raises the possibility that other milder cases may have not been identified who may have antibody evidence of exposure to the organism. Where practical (in the context of the case population), possible cases who have not been confirmed by isolation or PCR will be followed up to obtain convalescent sera, to identify late sero-converters.

Management has consisted of treatment with relevant intravenous antibiotics, with the close involvement of local microbiologists, and surgical debridement where appropriate.

Four cases have been treated with anthrax immunoglobulin (AIG) supplied courtesy of the United States Centres for Disease Control and Prevention (US CDC), under the supervision of CDC staff who were temporarily on site to assist the investigation and have provided advice and guidance in relation to recent US experience with clinical anthrax infection. AIG was provided under the CDC investigational new drug protocol.

Information on injecting drug use, social circumstances and other possible risk factors for developing anthrax has been obtained from these cases wherever possible. A difficulty in this investigation is obtaining reliable accurate histories of recent drug use, given the nature of the situation and the seriousness of illness in some cases. Some cases died before complete histories could be obtained. Information collected to date has indicated that the majority (but not all) had a recent history of injecting heroin, which they had obtained primarily within the Greater Glasgow and Clyde area or neighbouring Lanarkshire. For more recent cases residing outside the Glasgow/Lanarkshire area, the source of their heroin is under investigation. There does not appear to be another common factor for possible anthrax exposure other than the acquisition and taking of heroin by one or more methods. Dissolving agents (mainly citric acid) were purchased at separate locations and are not considered to be implicated as possible vehicles of transmission or contamination.

Response to the outbreak

Initially the outbreak was managed via an Outbreak Control Team (OCT) based in NHS GGC with support from local microbiologists, Strathclyde Police, Health Protection Scotland, and the HPA SPRU (who have acted as the reference laboratory for the confirmation of all cases to date).

The OCT formulated three working hypotheses. Firstly, that there was anthrax in the heroin which may have entered the supply chain at any point from its original source to the final point of acquisition. Secondly, that either the dissolving agent or cutting agent were contaminated with anthrax. Thirdly, that there was an as yet undiscovered link between the cases.

Information was released via the press advising the drug injecting community of the additional risk associated with taking heroin and that they should seek urgent medical advice if they developed an infection. Subsequently specific information leaflets and posters have been developed in collaboration with the Scottish Drugs Forum.

Evidence suggests that subcutaneous and intramuscular routes have been associated with the majority of infections and confirmed cases to date. However, some cases reported multiple routes of administration in sequence. Hence, in contrast to the previous outbreak of *Clostridium novyi* infection (which also affected IDUs in Scotland in 2000) [2,3], it has not been possible to offer advice on harm-minimising methods of taking heroin. Due to the potential risk of inhalational anthrax from smoking (or snorting) heroin, and the potential risk from injecting anthrax spores intravenously, from ingesting or from any other parenteral route of administration, addiction services and pharmacies were alerted to the fact that no 'safe' route of administration of heroin could be advocated. The key harm reduction advice message remains that focused on avoiding the use of heroin if possible and seeking alternatives via drug treatment services, highlighting awareness of the dangers and early symptom identification. General practitioners, hospital departments, and microbiology departments were also alerted. Information has been cascaded across all NHS Boards in Scotland and to specialist community addiction services.

Progress of investigation

Given the confirmation of cases outside the Glasgow conurbation, the outbreak investigation has now been upgraded to a national OCT, coordinated by Health Protection Scotland. Representatives of agencies working with drug users have also been co-opted to the national OCT including the Scottish Drugs Forum and Scottish Drug Deaths Forum. The most likely cause of the outbreak is considered to be exposure by injection (or other routes) to heroin either directly contaminated at the source or contaminated as a result of mixing with other substances contaminated with anthrax at some point in the supply chain. The distribution of cases suggests either that small batches of contaminated heroin may still be circulating in Scotland or that there is a continuing source of contamination in material used to cut (dilute down) the heroin before supply to end users. Further investigations are proceeding to try to trace the supply network and validate the existing hypothesis.

Risk assessments have been undertaken regarding the potential risks to others including health service staff. Police and others involved in searching premises and in handling the cases' belongings. To date there has been no evidence to suggest a risk to the general public or any other parties who have had access to clothing, belongings or the living quarters of cases. No special protective measures are therefore being advised at present and there are no plans to decontaminate any such personal items or premises, on the basis that the risk to date has been confined to an association with personal intake of heroin, not other casual exposures.

Discussion

Although rare, outbreaks or cases of illness among IDUs have been documented in recent years. In 2000, an outbreak among IDUs, involving 60 cases and 20 deaths, occurred in Scotland. The most frequently isolated pathogen among the cases was *C. novyi* and transmission was believed to have occurred via a contaminated batch of heroin [2,3]. Similarly in 2000, a case of 'injectional' anthrax was identified in a heroin-injecting drug user in Norway. A contaminated batch of heroin was believed to be the source of the infection [4].

Between December 2003 and April 2004, reports of *C. histolyticum* from 12 cases of infection in IDUs were identified in England and Scotland. Again, it was believed that the source of the infection was a contaminated batch of heroin distributed across the UK [5].

Setting an appropriate diagnostic threshold for this outbreak is a challenge in that approximately 34% of IDUs per year report signs of an infected injection site. Hence wound infections in this population are not unusual. However, none of the cases have presented with a classical cutaneous anthrax pattern. It is perhaps surprising given the source and nature of heroin preparation and anecdotal reports that heroin is transported in animal skins, that more cases of infections in heroin users has not been identified before now.

Acknowledgements

The role of CDC in providing advice and support by way of personnel and a supply of the anthrax immunoglobulin (AIG) is gratefully acknowledged, in particular Dr. Nicki Pesik and Dr. Theresa Smith regarding use of the AIG and colleagues Dr. Sean Shadomy and Dr. Kendra Stauffer in support.

* Authors correction: In the original version the sentence read 11 men and three women. This was corrected on request of the authors on 15 January 2010.

References

1. Health Protection Scotland. Anthrax in Drug Users: Case Definitions Version 5.0. 13 January 2010. Available from: <http://www.hps.scot.nhs.uk/anthrax/documents/case-definition-anthrax-outbreak-v5.pdf>
2. McGuigan CC, Penrice GM, Gruer L, Ahmed S, Goldberg D, Black M, et al. Lethal outbreak of infection with *Clostridium novyi* type A and other spore-forming organisms in Scottish injecting drug users. *J Med Micro*. 2002; 51(11):971-7.

3. Taylor A, Hutchinson S, Lingappa J, Wadd S, Ahmed S, Gruer L, et al. Severe illness and death among injecting drug users in Scotland: a case control study. *Epidemiol Infect*. 2005;133(2):193-204.
4. Ringertz SH, Hoiby EA, Jensenius M, Maehlen J, Caugant D, Myklebust A, et al. Injectional anthrax in a heroin skin-popper. *Lancet*. 2000;356(9241):1574-5.
5. Brazier JS, Gal M, Hall V, Morris TE. Outbreak of *Clostridium histolyticum* infections in injecting drug users in England and Scotland. *Euro Surveill*. 2004;9(9):pii=475. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=475>

Preliminary case report of fatal anthrax in an injecting drug user in North-Rhine-Westphalia, Germany, December 2009

D Radun (RadunD@rki.de)¹, H Bernard¹, M Altmann^{1,2,3}, I Schöneberg¹, V Bochat⁴, U van Treeck⁵, R M Rippe⁶, R Grunow⁷, M Elschner⁸, W Biederbick⁹, G Krause¹

1. Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
2. Postgraduate Training for Applied Epidemiology („PAE“, German Field Epidemiology Training Programme) at the Robert Koch Institute, Berlin, Germany
3. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
4. Local Health Department, Aachen, Germany
5. Federal State Health Department, North-Rhine-Westphalia, Duesseldorf, Germany
6. Federal Ministry of Labour, Health and Social Affairs North-Rhine-Westphalia, Duesseldorf, Germany
7. Center for Biological Security, Div. Highly Pathogenic Microorganisms, Robert Koch Institute, Berlin, Germany
8. Friedrich-Loeffler-Institut, Jena, Germany
9. Federal Information Centre for Biological Safety, Robert Koch Institute, Berlin, Germany

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A fatal case of anthrax occurred in an injecting drug user in Germany, in December 2009. A potential link to similar cases in Scotland in the same time period is currently under investigation.

The Robert Koch Institute, in collaboration with the Friedrich Loeffler Institute in Jena, the Federal Research Institute for Animal Health, and the respective local and regional health authorities in the Aachen district, North-Rhine-Westphalia, Germany, are currently investigating a fatal case of anthrax in a 42 year-old male injecting drug user.

The individual was hospitalised on 6 December 2009, complaining of a swelling of his leg following drug injection into the popliteal fossa – reportedly attempting to inject into a vein. He probably injected heroin, however, details are unknown. Following treatment with meropenem and surgical debridement of a subsequent necrotising fasciitis, the patient died with multiorgan failure on 13 December 2009. Anthrax had not been suspected clinically.

Spore-forming bacteria from a wound swab specimen were identified, and on 18 December, the diagnosis of anthrax was confirmed by PCR. The last case of human anthrax in Germany had been reported in 1994, at that time affecting a 66 year-old man [1].

At this point in time, it is not clear whether there is a link between this case and the anthrax outbreak among injecting drug users in Scotland. As far as we know, the deceased had no travel history to Scotland. However, it can be assumed that other drug users in the same area in Germany, or perhaps elsewhere in the country,

have been exposed. In case the hypothesis of a potential link to the Scottish cases proves true, it might well be that also other countries have been supplied with contaminated injectable drugs.

We launched an epidemiological investigation and exchanged information with the colleagues in the United Kingdom and, in particular, Scotland to coordinate the approach.

So far, the following measures have been taken:

- We have distributed information to public health colleagues, medical care facilities and low-threshold facilities in Germany to raise awareness of the event.
- We are collecting information on the case and his contacts, and on the substances consumed.
- We attempt further case finding.
- We aim at a microbiological comparison of isolates to establish a potential epidemiological link with the Scottish cases.

The success of the epidemiological investigation will rely on public health authorities' efforts, alertness amongst clinicians and medical microbiologists, but also on the degree to which drug users themselves can be reached. Therefore, it is of utmost importance to utilise existing communication channels to inform those who might be at risk.

References

1. Robert Koch Institute: Ein Fall von Milzbrand im Land Niedersachsen. [A case of anthrax in Lower Saxony]. Epid Bull. 1994;1:10. German

Epidemiological analysis of mosquito-borne Pogosta disease in Finland, 2009

J Sane (jussi.sane@helsinki.fi)¹, S Guedes^{2,3}, S Kurkela^{1,4}, O Lyytikäinen², O Vapalahti^{1,3,5}

1. Department of Virology, Haartman Institute, Faculty of Medicine, University of Helsinki, Finland

2. National Institute for Health and Welfare (THL), Department of Infectious Disease Surveillance and Control, Helsinki, Finland

3. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, Stockholm, Sweden

4. Department of Virology, Helsinki University Central Hospital Laboratory, Finland

5. Division of Microbiology and Epidemiology, Department of Basic Veterinary Sciences, Faculty of Veterinary Medicine, University of Helsinki, Finland

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Pogosta disease is a viral disease caused by a mosquito-borne alphavirus, Sindbis virus (SINV), and large human outbreaks of SINV infection have emerged in Finland every seven years. After a major outbreak in 2002 an epidemic was expected to take place in 2009. Data from the National Infectious Disease Registry showed a small outbreak in humans in 2009 with a total of 105 reported cases but the seven-year cycle did not recur as anticipated.

Introduction

Sindbis virus (SINV) is a mosquito-borne alphavirus (of the family *Togaviridae*), present in Eurasia, Africa and Oceania [1,2]. Antibodies to SINV are detected in humans in various geographical areas but clinical infections caused by SINV are reported mostly from Finland where SINV is associated with fever, rash and arthritis, known as Pogosta disease [3]. The treatment is symptomatic. Clinically similar diseases are found in Sweden (Ockelbo disease) and in Russia (Karelian fever) [4,5]. The majority of clinical cases occur in Finland during August and September when the primary vectors, the ornitophilic late summer mosquito species *Culex* and *Culiseta*, are abundant. The incidence of Pogosta disease has been highest in the eastern parts of Finland in recent decades [3,6].

Remarkably, outbreaks of Pogosta disease have thus far emerged every seven years since the first outbreak was noted in 1974, and the cause for this phenomenon is yet to be discovered. Tetraonid birds such as grouse, might contribute to this pattern [3]. Grouse have previously shown population cycles with population “crashes” coinciding with SINV outbreaks [7]. Antibodies to SINV have been detected in grouse and migratory birds [3,6].

The last major epidemic in Finland took place in 2002 with almost 600 reported cases and it was anticipated that an outbreak would occur again in 2009. This paper

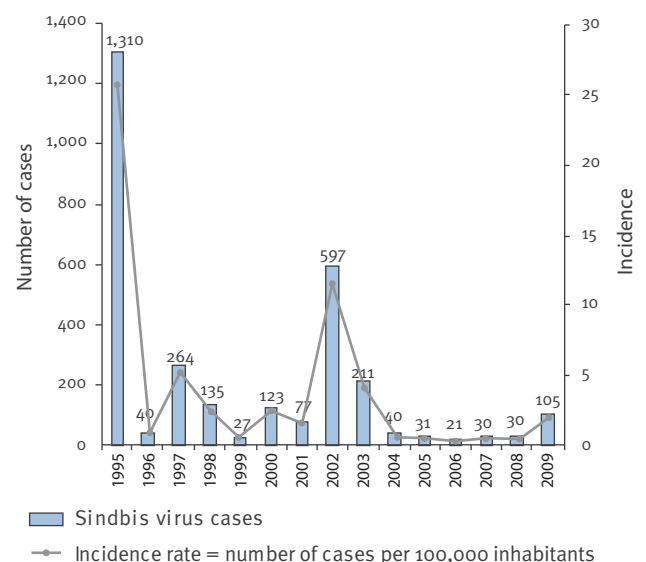
describes the characteristics of the Pogosta disease in Finland from June through October 2009 and discusses the findings in relation with the previous epidemic.

Methods

Since 1995, all confirmed diagnoses of SINV infection have been reported to the National Infectious Disease Registry (NIDR) at the National Institute for Health and Welfare (THL). Notifications include information on date of sample collection, date of birth, sex, and on place of treatment. Multiple notifications of persons with the same date of birth, sex and place of treatment received within a 12-month period were combined as one case. The place of treatment refers to the health care center or hospital (in particular hospital district) where the diagnosis has been made. Data were analysed by sex, age, week and month of disease onset

FIGURE 1

Number and incidence rates of laboratory confirmed Sindbis virus cases, Finland, 1995-2009 (n=3,041)



and by hospital district of treatment. Finland has a population of 5.3 million and is divided into 20 hospital districts. Laboratory diagnosis is based on enzyme immunoassays (EIA) and/or in some cases a haemagglutination inhibition test (HI) (5).

Results

From June through October 2009, a total of 105 laboratory confirmed cases were reported to the NIDR and the

incidence of SINV infection was two cases per 100,000 inhabitants per year (Figure 1). Most of the cases occurred in September ($n=60$) followed by August ($n=33$). Sixty percent ($n=63$) of the cases were females. The highest incidence (4.6/100,000/year) was among persons aged 50-59 years. Only two of the cases were aged under 18 years.

FIGURE 2

Number and incidence rates of laboratory confirmed Sindbis virus cases, by health care districts, Finland 2009 ($n=105$) and 2002 ($n=597$)

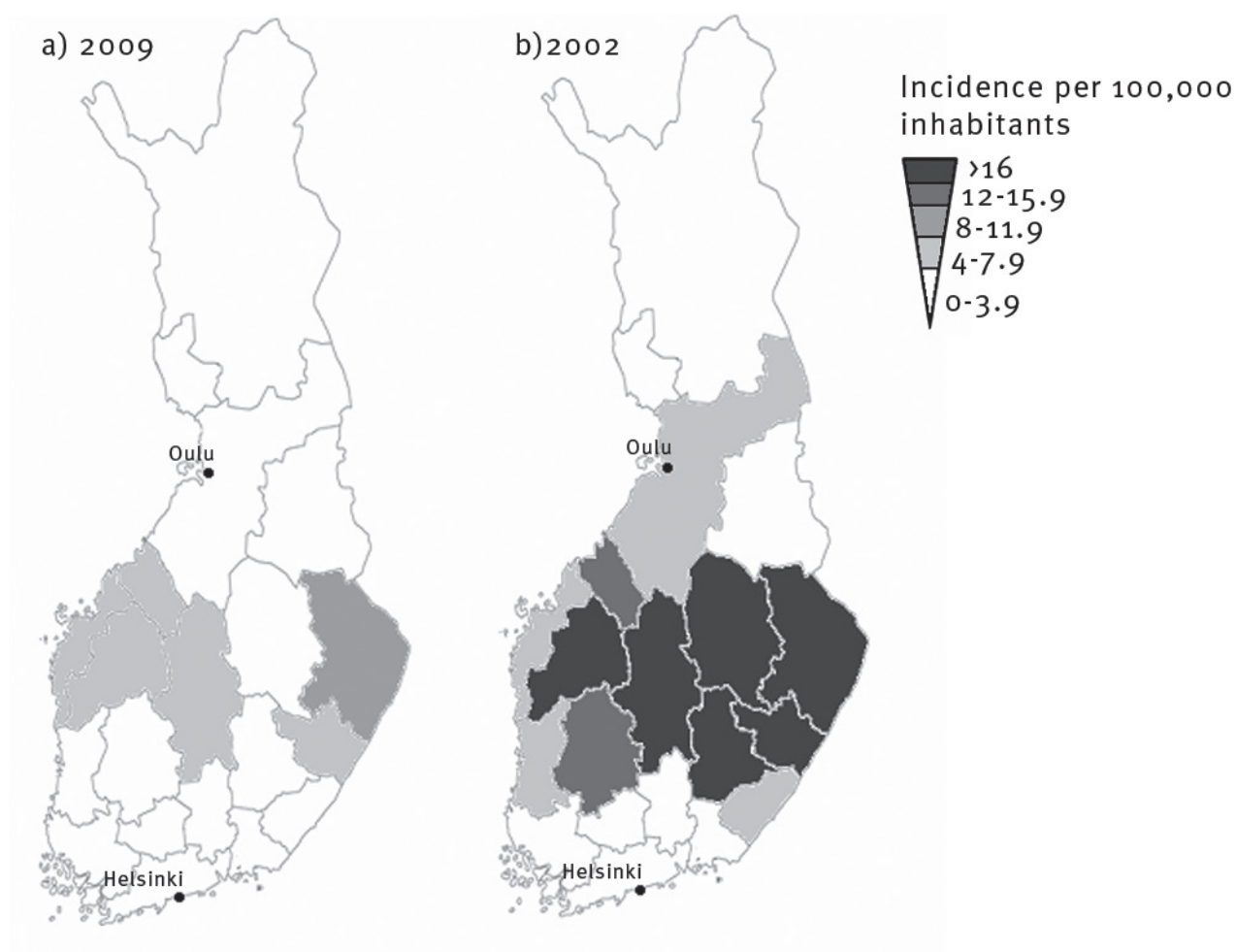
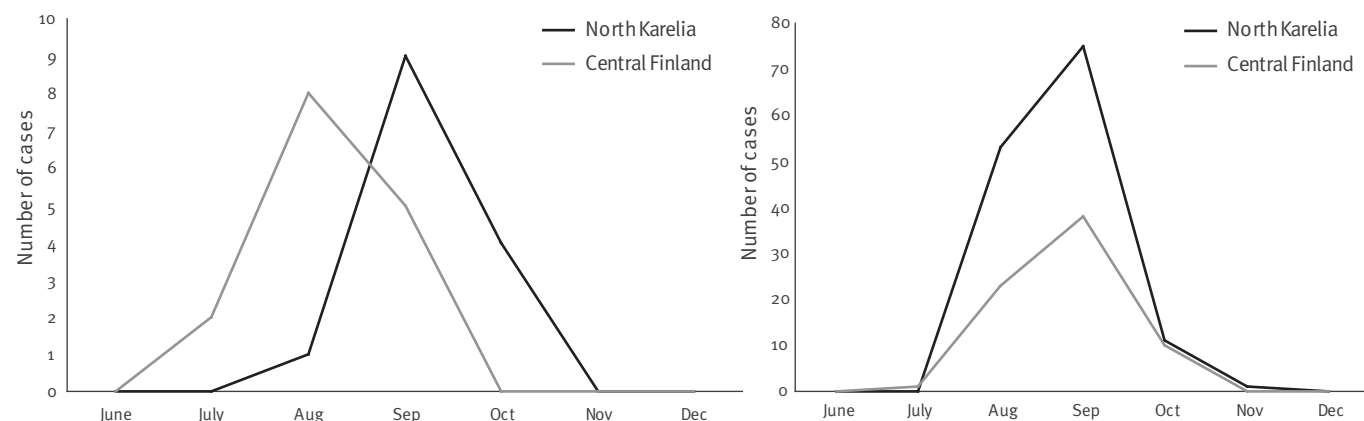


FIGURE 3

Sindbis virus cases in north Karelia and central Finland, 2009 ($n=29$) and 2002 ($n=212$)



The incidence was highest in north Karelia, followed by east Savo, central Ostrobothnia and central Finland together with southern Ostrobothnia (Figure 2). The incidence rates in 2009 were considerably lower than those in 2002.

The number of cases was highest in central Finland (n=15). The majority of the cases (n=10) in central Finland occurred in July-August whereas only one case was reported from north Karelia during this time period (Figure 3). On the contrary, 13 cases were reported from north Karelia and five from central Finland during the months of September-October. In 2002, cases peaked in September in both of the hospital districts.

Discussion

A major Pogosta disease outbreak has occurred every seven years in Finland since 1974, with hundreds or even thousands of patients. Following this pattern, another outbreak was expected for 2009. However, the number of cases was substantially lower than in previous epidemics in 1995 and 2002 when 1301 and 597 cases were reported respectively [6]. The 105 cases reported in 2009 exceed the average number of cases (n=57) in the non-epidemic years during 1995-2009. However, in some intermediate years, 1997-1998, 2000 and 2003, the number of cases exceeded the number reported in 2009. In comparison, five SINV infections were reported in Sweden in 2009 (Sirkka Vene, personal communication, 1 December 2009).

The factors behind the puzzling cycles in the epidemiology of Pogosta disease are unclear but recently attention has focused on tetraonid birds. In the epidemic years of 1974 and 1981, grouse population crashed in north Karelia [4]. Further, detection of SINV antibodies in one quarter of grouse examined in the year following the 2002 epidemic, indicated vast exposure of grouse to SINV, and suggested that the virus may have an endemic cycle in tetraonid birds [6]. The density of grouse was above average in 2007 but the population crashed in 2008. The recovery of grouse population can be rapid and was anticipated to occur in 2009. However, the density of their population continued to decline to an all time low (since the measurements from 1980s) [8]. Hence, it is plausible that grouse play a significant role in the human epidemiology of SINV. It is possible that the continuing decline in the grouse population in 2009 diminished the role of grouse as amplifying hosts and that therefore, a milder outbreak than expected was observed.

Similar to previous findings, the incidence of SINV was highest in the hospital district of north Karelia. The difference in incidence of this hyperendemic region with other hospital districts was not, however, as prominent as previously. In 2009 many of the hospital districts with high incidence were located in central and north-western parts of Finland. These observations may point towards a geographical shift in the incidence of SINV virus infection. The relatively low incidence in north Karelia compared to the epidemic in 2002 may also

reflect the increased human seroprevalence towards SINV which indicates immunity. The district of Kainuu had no cases, which was surprising since previous studies showed high seroprevalence in that area [6]. This could be attributable to significant underdiagnosis or acquired immunity, which may result from high number of cases during the 1970s and 1980s.

Most cases in central Finland occurred in August whereas in north Karelia the number of cases peaked in September. This could reflect the variations in mosquito activity and population size due to differences in weather conditions in these areas. The month of May was drier than normally in Joensuu (the largest city in north Karelia) but the rainfall in June-July was considerably higher than on average [9]. Perhaps the dry May in Joensuu contributed to fewer cases in July-August but the high rainfalls in June and July created better environmental conditions for mosquito development and thus, more human cases of SINV occurred in September-October. Weather conditions are also likely to influence human outdoor activities, and thereby exposure to SINV.

In summary, a limited outbreak of SINV in humans took place in Finland in late summer and autumn of 2009 but the expected seven-year cycle did not recur. The data suggest a geographical shift in disease incidence. It is likely that fluctuations in grouse populations play a major role in the occurrence of SINV epidemics. To further elucidate the role of tetraonid birds and other factors, such as weather and climate variations, more epidemiological studies and proper mathematical modeling of SINV epidemics is needed.

References

1. Taylor RM, Hurlbut HS, Work TH, Kingston JR, Frothingham TE. Sindbis virus: a newly recognized arthropod-transmitted virus. *Am J Trop Med Hyg.* 1955 Sep;4(5):844-62.
2. Hubalek Z. Mosquito-borne viruses in Europe. *Parasitol Res.* 2008;103 Suppl 1:S29-43.
3. Brummer-Korvenkontio M, Vapalahti O, Kuusisto P, Saikku P, Manni T, Koskela P, et al. Epidemiology of Sindbis virus infections in Finland 1981-96: possible factors explaining a peculiar disease pattern. *Epidemiol Infect.* 2002;129(2):335-45.
4. L'vov DK, Skvortsova TM, Gromashevskii VL, Berezina LK, Iakovlev VI. [Isolation of the causative agent of Karelian fever from *Aedes* sp. mosquitoes]. [Russian]. *Vopr Virusol.* 1985 May-Jun;30(3):311-3.
5. Skogh M, Espmark A. Ockelbo disease: epidemic arthritis-exanthema syndrome in Sweden caused by Sindbis-virus like agent. *Lancet.* 1982;1(8275):795-6.
6. Kurkela S, Ratti O, Huhtamo E, Uzategui NY, Nuorti JP, Laakkonen J, et al. Sindbis virus infection in resident birds, migratory birds, and humans, Finland. *Emerg Infect Dis.* 2008 Jan;14(1):41-7.
7. Lindén H. Characteristics of tetraonid cycles in Finland. *Finnish Game Research.* 1989;46:34-42.
8. Finnish Game and Fisheries Research Institute. [Internet]. Helsinki: Metsäkanalinnut 2009. [Finnish]. Available from: http://www.rktl.fi/riista/riistavarat/metsakanalinnut_2009/.
9. Finnish Meteorological Institute. [Internet]. Helsinki: Kuinka tilaan säätilastoja tai säähavaintosarjoja. [Finnish]. Available from: www.fmi.fi. Accessed 6 November 2009.

Surveillance of Hospitalisations for 2009 Pandemic Influenza A(H1N1) in the Netherlands, 5 June – 31 December 2009

T M van 't Klooster (tessa.van.t.klooster@rivm.nl)¹, C C Wielders^{1,2}, T Donker¹, L Isken¹, A Meijer¹, C C van den Wijngaard¹, M A van der Sande¹, W van der Hoek¹

1. Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

2. Pallas health research and consultancy B.V., Rotterdam, the Netherlands

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We analysed and reported on a weekly basis clinical and epidemiological characteristics of patients hospitalised in the Netherlands for the 2009 pandemic influenza A(H1N1) using information from the national mandatory notification system. The notification criteria changed on 15 August 2009 from all possible, probable and confirmed cases to only laboratory-confirmed pandemic influenza hospitalisations and deaths. In the period of comprehensive case-based surveillance (until 15 August), 2% (35/1,622) of the patients with pandemic influenza were hospitalised. From 5 June to 31 December 2009, a total of 2,181 patients were hospitalised. Of these, 10% (219/2,181) were admitted to an intensive care unit (ICU) and 53 died. Among non-ICU hospitalised patients, 56% (961/1,722) had an underlying medical condition compared with 70% (147/211) of the patients in ICU and 46 of the 51 fatal cases for whom this information was reported. Most common complications were dehydration among non-ICU hospitalised patients and acute respiratory distress syndrome among patients in ICU and patients who died. Children under the age of five years had the highest age-specific hospitalisation rate (62.7/100,000), but relatively few were admitted to an ICU (1.7/100,000). Characteristics and admission rates of hospitalised patients were comparable with reports from other countries and previous influenza seasons. The national notification system was well suited to provide weekly updates of relevant monitoring information on the severity of the pandemic for professionals, decision makers, the media and the public, and could be rapidly adapted to changing information requirements.

Introduction

On 30 April 2009, the first case of human infection with the 2009 pandemic influenza A(H1N1) was reported in the Netherlands, and on 5 June 2009 the first patient was hospitalised [1]. From 15 August 2009, only patients with a laboratory-confirmed pandemic

influenza infection who were hospitalised and/or died because of the severity of their illness were notifiable. This was in line with international consensus that registration of all cases of pandemic influenza A(H1N1) is not efficient anymore when there is widespread community transmission and that surveillance efforts should focus on severe disease to enable mitigating the impact of the pandemic [2-3]. The World Health Organization (WHO) suggested surveillance of severe acute respiratory illness (SARI) in a number of sentinel hospitals, with a case definition of sudden onset of fever ($\geq 38^{\circ}\text{C}$) and cough or sore throat in the absence of other diagnoses, shortness of breath or breathing difficulty, and requiring hospital admission [4]. As it was not a realistic option to establish and validate such a novel surveillance system in the Netherlands in a very short time, it was decided to modify the nationwide mandatory notification system and limit this system to hospital admissions and/or deaths due to laboratory-confirmed pandemic influenza virus infection. Reports from the southern hemisphere give important information on the impact of the first wave of the pandemic. However, such data cannot be transferred directly to Europe because of the differences in population composition, health systems, notification systems, climate and the prevalence of other infectious diseases that can all affect the spread and impact of an epidemic.

In this report, we analyse the clinical and epidemiological characteristics of the first patients hospitalised and deceased in the Netherlands with a confirmed 2009 pandemic influenza A(H1N1) virus infection and we discuss the mandatory notification system for all hospital admissions.

Methods

Notification system

From 30 April to 14 August 2009 all possible, probable and confirmed cases of 2009 pandemic influenza A(H1N1) were notifiable. On 15 August, the notification

criteria changed, and from that date only cases who were admitted to hospital or died because of the severity of a laboratory-confirmed pandemic influenza virus infection had to be notified. Within a few days a new questionnaire was developed, which had to be as short

TABLE 1

Characteristics of patients hospitalised for 2009 pandemic influenza A(H1N1), the Netherlands, 5 June–31 December 2009 (n=2,186)

Characteristic	No. (%) of hospitalised patients (non-ICU) (n=1,962)	No. (%) of patients admitted to ICU (n=219)	No. (%) of deaths (n=53)
Sex ^a			
Male	918 (47.3)	110 (50.2)	29 (54.7)
Female	1024 (52.7)	109 (49.8)	24 (45.3)
Age group ^b			
0–4 years	565 (29.1)	16 (7.3)	5 (9.4)
5–14 years	350 (18.0)	34 (15.5)	9 (17.0)
15–24 years	216 (11.1)	16 (7.3)	2 (3.8)
25–34 years	165 (8.5)	17 (7.8)	1 (1.9)
35–44 years	173 (8.9)	31 (14.2)	6 (11.3)
45–54 years	203 (10.4)	41 (18.7)	10 (18.9)
55–64 years	153 (7.9)	44 (20.1)	13 (24.5)
65–74 years	70 (3.6)	15 (6.8)	5 (9.4)
75–84 years	41 (2.1)	5 (2.3)	1 (1.9)
≥ 85 years	8 (0.4)	0 (0.0)	1 (1.9)
Pneumonia ^c	508 (29.5)	153 (74.3)	31 (67.4)
Mechanical ventilation ^d	Not applicable	126 (63.3)	21 (42.9)

ICU: intensive care unit.

^a For 20 hospitalised patients sex was unknown.

^b For 18 hospitalised patients the age group was unknown.

^c For 240 hospitalised patients, for 13 of the patients admitted to an ICU and for seven of the patients who died, information on pneumonia was not available.

^d For 20 of the patients admitted to an ICU and for four of the patients who died it was unknown whether they had received mechanical ventilation.

TABLE 2

Cumulative incidence for hospitalisation, admission to an ICU and deaths due to 2009 pandemic influenza A(H1N1) per 100,000 population by age group, the Netherlands, 5 June–31 December 2009 (n=2,186)

Age group	Population (n)	Incidence of hospitalisation (non-ICU) (per 100,000)	Incidence of ICU admission (per 100,000)	Incidence of death (per 100,000)
0–4 years	926,993	62.7	1.73	0.54
5–14 years	1,988,047	19.3	1.71	0.45
15–24 years	2,013,827	11.5	0.79	0.10
25–34 years	1,996,248	9.1	0.85	0.05
35–44 years	2,505,006	8.1	1.24	0.24
45–54 years	2,449,226	10.0	1.67	0.41
55–64 years	2,138,141	9.2	2.06	0.61
65–74 years	1,373,058	6.2	1.09	0.36
75–84 years	840,788	5.5	0.59	0.12
≥ 85 years	290,171	2.8	0.00	0.34
Total	16,521,505	13.1	1.33	0.32

ICU: intensive care unit.

as possible in order not to overburden the municipal health services and physicians. In the Netherlands, the attending medical doctor and the head of the involved microbiology laboratory both have to report the name and clinical characteristics of the hospitalised patient to the municipal health service. Notifications are entered by the municipal health services into a national anonymous and password-protected web-based database, including information on underlying medical conditions (co-morbidity), vaccination status, treatments, complications such as pneumonia, and admission to an intensive care unit (ICU).

Laboratory confirmation

In the Netherlands, initially the National Influenza Centre (NIC, consisting of the National Institute for Public Health and the Environment (RIVM), Bilthoven and the Erasmus Medical Centre, Rotterdam) and later the 11 laboratories of the Outbreak Assistance Laboratories Network tested nose and throat samples for pandemic influenza A(H1N1) virus [5]. When the pandemic was evolving, additional peripheral and hospital laboratories also performed diagnosis of pandemic influenza using molecular diagnostic tests made available by the NIC in conjunction with an external quality assurance programme. The Centre for Infectious Disease Control at RIVM acted as central confirmation laboratory.

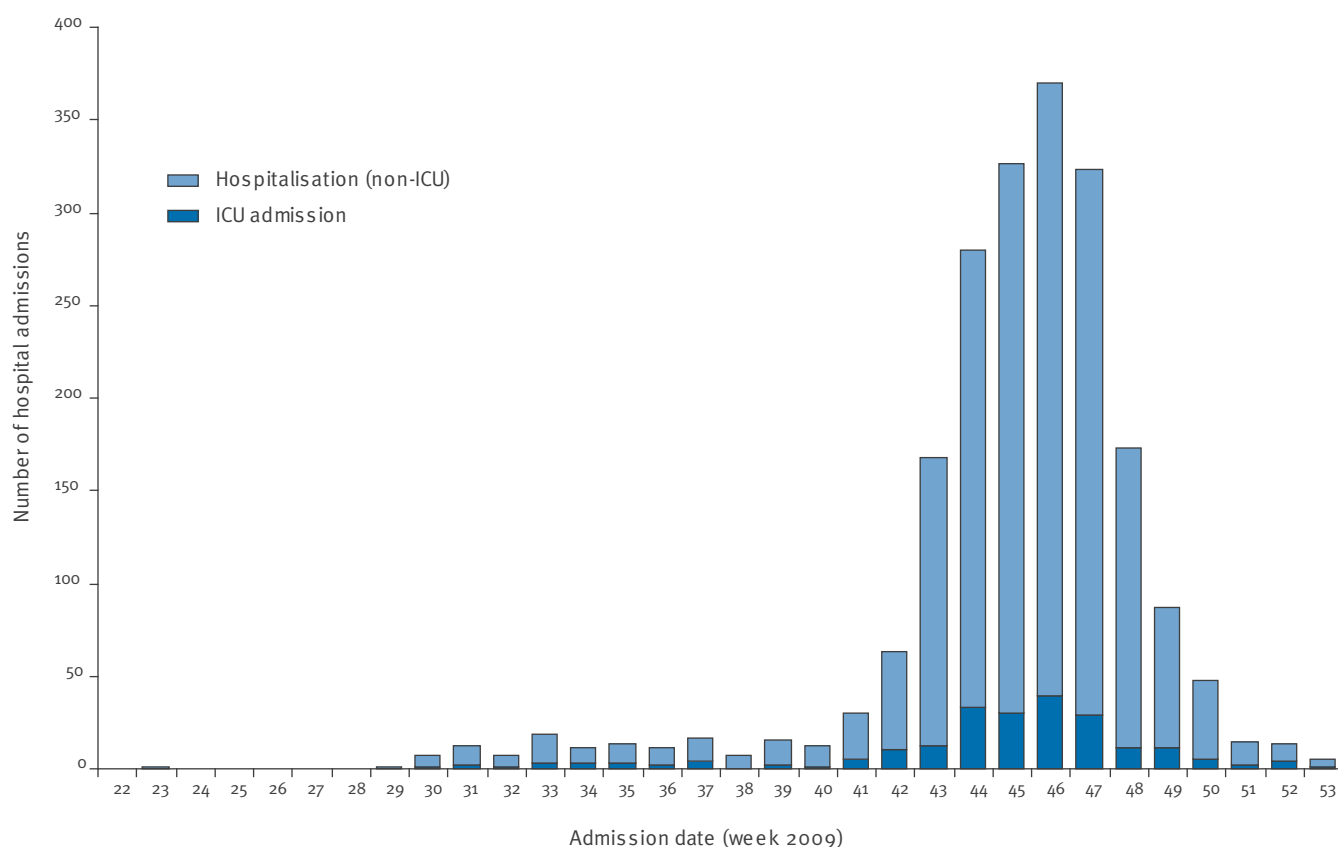
For diagnostics, real-time RT-PCR assays for general detection of influenza virus type A and specific detection of pandemic influenza A(H1N1) virus were used with a confirmation by sequencing [5].

Dissemination

Weekly reports summarising new and cumulative numbers of hospitalisations by age and by underlying conditions were prepared for discussion by the multidisciplinary response team of RIVM. In these reports, notification data were linked to data from the sentinel surveillance of influenza-like illness (ILI),

FIGURE 1

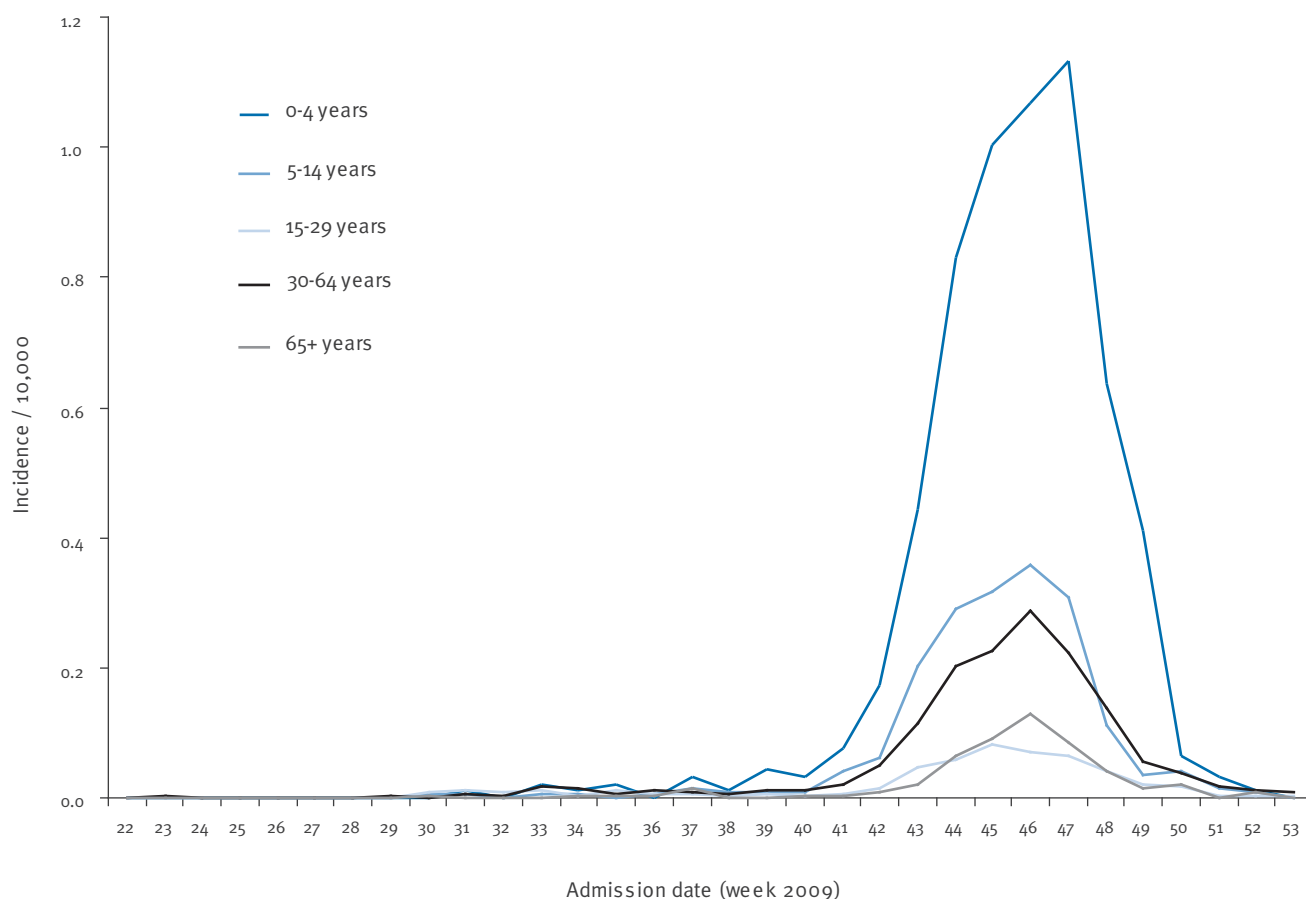
Hospital admissions (ICU and non-ICU) due to laboratory confirmed 2009 pandemic influenza A(H1N1) by week of hospitalisation, the Netherlands, 5 June–31 December 2009 (n=2,034 with a reported admission date)



ICU: intensive care unit

FIGURE 2

Incidence of hospital admissions (non-ICU) due to 2009 pandemic influenza A(H1N1) by age group and week of hospitalisation, the Netherlands, 5 June–31 December 2009 (n=1,962)



crude mortality registers, and virological surveillance. Implications were discussed with decision makers at the Ministry of Health following these weekly meetings. Results were disseminated online every week, followed by a press briefing.

Data analysis

We calculated descriptive statistics for all study variables. For categorical variables percentages were reported and for continuous variables the median (with range). Only laboratory-confirmed cases were included in the analysis. We categorised patients according to age groups. All descriptive statistics were calculated for non-ICU hospitalised patients, patients admitted to an ICU and deceased patients. All statistical analyses were conducted using SAS version 9.1 (SAS Institute).

Results

Clinical characteristics

From 5 June to 14 August 2009, the period before the notification criteria changed, 2.2% (35/1,622) of the notified patients with a confirmed pandemic influenza infection were admitted to a hospital [1]. From 5 June to 31 December 2009, a total of 2,181 patients were hospitalised for severe laboratory-confirmed infection with pandemic influenza. Of these, 10.0% (219/2,181) were admitted to an ICU. In the same period, a total of 53 patients died due to laboratory-confirmed infection with pandemic influenza, five of whom died without hospital admission.

Epidemiological characteristics

The median age of non-ICU hospitalised patients was 17 years (range 0-89 years). For patients admitted to an ICU the median age was 42 years (range 0-82 years), and for patients who died the median age was 52 years (range 0-85 years) (Table 1). Incidence of non-ICU hospitalisations peaked in the group of 0-4 year-olds and thereafter declined with age. Incidence of ICU admissions and deaths, however, showed a second peak in the group of 55-64 year-olds (Table 2). The highest incidence for ICU admission overall was observed in patients aged between 55 and 64 years (2.06 per 100,000 population), whereas the highest incidence for non-ICU hospitalisation was among children under the age of five years (62.7 per 100,000 population).

Of the non-ICU hospitalised patients 29.5% (508/1,722) had pneumonia, while among the patients who were admitted to an ICU, 74.3% (153/206) had pneumonia and 63.3% (126/199) needed mechanical ventilation. Pneumonia was reported for 31 of 46 fatal cases for whom this information was available and 21 of 49 patients who died had received mechanical ventilation.

From week 40 to week 46 2009, we observed an exponential rise in the number and incidence of hospital admissions (non-ICU) and ICU admissions due to pandemic influenza (Figures 1-3), but this did not give rise to changes in the distribution of age groups among hospitalised patients. After week 46, the number and

FIGURE 3

Incidence of ICU admissions due to 2009 pandemic influenza A(H1N1) by age group and week of hospitalisation, the Netherlands, 5 June–31 December 2009 (n=219)

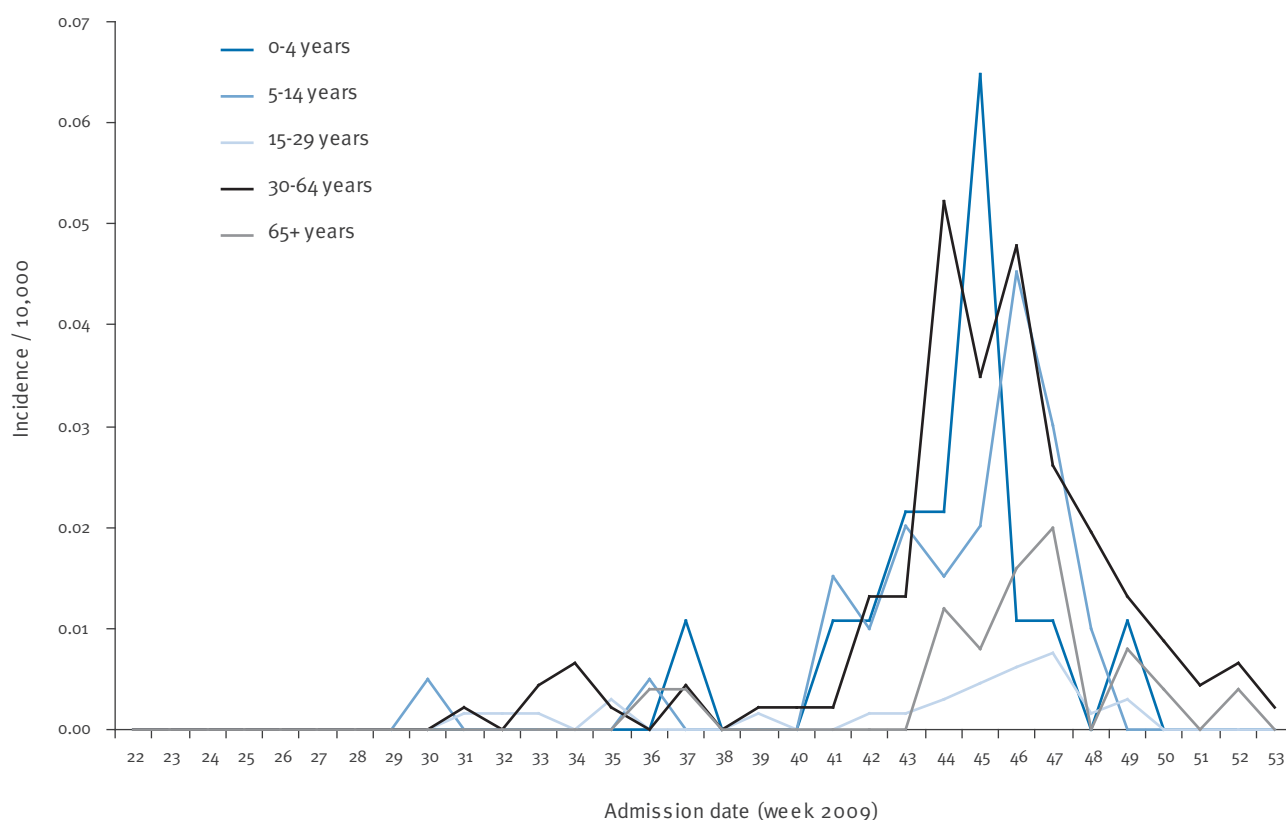
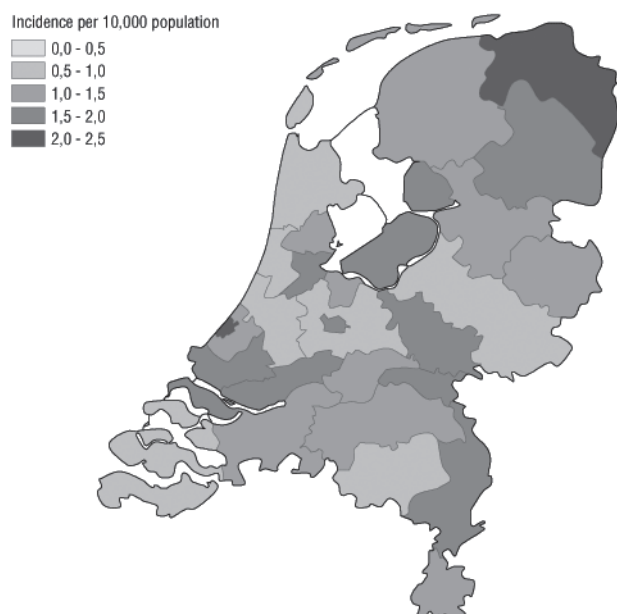


FIGURE 4

Incidence of hospital admissions (ICU and non-ICU) due to 2009 pandemic influenza A(H1N1) by municipal health service region, the Netherlands, 5 June–31 December 2009 (n=2,181)



ICU: intensive care unit.

Source: GGD-Osiris, RIVM.

incidence of non-ICU hospitalisations and ICU admissions for pandemic influenza by week decreased. There was only limited geographical variation in the incidence of hospital admissions (ICU and non-ICU) due to pandemic influenza by municipal health service region in the Netherlands (Figure 4).

Underlying medical conditions

An underlying medical condition was reported for 961 (55.8%) of the 1,722 non-ICU hospitalised patients for whom this information was available (Table 3). Of these, 6.2% (60/961) were pregnant, most of them in the third trimester. Nine of the pregnant patients also had another underlying medical condition. The most common conditions were chronic pulmonary diseases (48.6%; 467/961), especially asthma and chronic obstructive pulmonary disease (COPD). Of the patients admitted to an ICU, 69.7% (147/211) had an underlying medical condition. 5.4% (8/147) of these patients were pregnant, mainly in the third trimester. The most common medical condition for ICU-admitted patients were chronic pulmonary diseases (43.5%; 64/147), especially asthma and COPD. Underlying medical conditions were present in 46 of the 51 patients who died and for whom this information was available.

TABLE 3

Underlying medical conditions of hospitalised patients (non-ICU), patients admitted to ICU and deaths due to 2009 pandemic influenza A(H1N1), the Netherlands, 5 June–31 December 2009 (n=1,062 with an underlying medical condition)

Medical condition	No. (%) of hospitalised patients (non-ICU) (n=961 ^a)	No. (%) of patients admitted to ICU (n=147 ^a)	No. (%) of deaths (n=46)	Prevalence in general population ^b (%)
Asthma	246 (25.6)	12 (8.2)	4 (8.7)	7.7 ^B
COPD or other chronic pulmonary disease (other than asthma)	221 (23.0)	52 (35.4)	14 (30.4)	
Heart disease	88 (9.2)	21 (14.3)	5 (10.9)	1.7 ^B
Cancer	56 (5.8)	16 (10.9)	12 (26.1)	1.0 ^B
Diabetes	83 (8.6)	16 (10.9)	0 (0.0)	3.9 ^B
Kidney disease	35 (3.6)	7 (4.8)	0 (0.0)	Unknown
Obesity	16 (1.7)	11 (7.5)	1 (2.2)	11.1 ^b
Immune disorder/AIDS	24 (2.5)	3 (2.0)	2 (4.3)	0.2 ^c
Muscular or nerve disorder	22 (2.3)	6 (4.1)	3 (6.5)	Unknown
Physical and/or mental retardation	38 (4.0)	10 (6.8)	10 (21.7)	Unknown
Epilepsy	33 (3.4)	5 (3.4)	6 (13.0)	Unknown
Pregnancy^d	60 (6.2)	8 (5.4)	0 (0.0)	1.1^b
1st trimester	3 (5.6)	1 (14.3)	N/A	Unknown
2nd trimester	15 (27.8)	1 (14.3)	N/A	Unknown
3rd trimester	36 (66.7)	5 (71.4)	N/A	Unknown
Other	201 (20.9)	19 (12.9)	6 (13.0)	Unknown

COPD: chronic obstructive pulmonary disease; AIDS: acquired immunodeficiency syndrome; ICU: intensive care unit; N/A: not applicable.

^a The total number of medical conditions is higher than the total number of patients with underlying medical conditions because one patient can have more than one underlying medical condition

^b Source: Statistics Netherlands: <http://statline.cbs.nl/statweb/>

^c Prevalence of HIV. Source: National Institute for Public Health and Environment (RIVM): <http://www.rivm.nl/bibliotheek/rapporten/210261005.pdf>

^d For six pregnant hospitalised patients and for one pregnant ICU patient the trimester was unknown.

Complications

For 15.7% (309/1,962) of the non-ICU hospitalised patients it was unknown whether they had complications. Specific complications were reported for 365 (21.1% of the remaining 1,653) patients, with dehydration as the most common complication (Table 4). For 14.2% (31/219) of ICU-admitted patients information on complications was not available. Among the remaining 188, 123 (65.4%) had a complication, mostly acute respiratory distress syndrome (ARDS) (36.6%; 45/123). Among the 53 patients who died, 30 had a complication reported and for nine no information was available.

Discussion and conclusion

The data reported in this paper are based entirely on the routine national infectious disease notification system. This system made it possible to provide weekly updates of relevant pandemic monitoring information on severe pandemic influenza for dissemination to professionals, decision makers, the media, and the public. Changes in the web-based notification system were communicated by the Centre for Infectious Disease Control and implemented rapidly by municipal health services, physicians and heads of medical microbiology laboratories. Nevertheless, a nation-wide mandatory notification system puts restrictions on the amount of information that can be requested from hospital and public health physicians. Therefore, it was not possible to provide information on the reason for hospital admission, other than that it was for laboratory-confirmed pandemic influenza. Also, follow-up of patients by the municipal health service, for example to obtain information on date of discharge from the hospital, was not considered feasible.

The highest age-specific rates of hospital admission were seen in the age group of 0-25 year-olds. In absolute numbers and in incidence, most admissions occurred in the age group of the 0-4 year-olds, but only 3% (16/581) of them were admitted to an ICU. Of the

admitted patients older than 45 years, 18% (105/580) were admitted to an ICU. Infants might have been admitted to hospital for observation even in the absence of signs of respiratory distress or other complications, or for supervised oseltamivir therapy, although personal communications from a number of paediatricians suggested that the majority of small children admitted with laboratory-confirmed pandemic influenza were admitted because of serious illness.

The observed hospitalisation, ICU and mortality rates are compatible with data reported from other countries [6-10]. Hospitalisation rates from countries in the southern hemisphere ranged (by country) from 2.0 to 31.8 per 100,000 population, and mortality rates ranged from 0 to 3.6 per 100,000 population [8]. In the Netherlands, hospitalisation rates due to pandemic influenza by age group ranged from 2.8 to 62.7 (overall 13.1) per 100,000 population and mortality rates ranged from 0.05 to 0.61 (overall 0.32) per 100,000 population. High rates of hospitalisation in the age group of 0-4 year-olds were also reported for Queensland and New South Wales (Australia), Ireland and other European countries [6-7,10-11]. While in seasonal influenza epidemics, the highest incidence of severe morbidity and deaths is expected in the oldest age groups, we observed the declining incidence in ICU admissions and deaths in patients older than 65 years following a peak in the age group of 55-64 year-olds, which could be compatible with a reported protection of those exposed to influenza A(H1N1) before 1957.

The majority of severe cases were people with pre-existing underlying medical conditions: 55.8% (961/1,722) of the hospitalised patients, 69.7% (147/211) of the cases admitted to ICU, and 46 of the 51 deceased patients. Asthma was the most common underlying condition, followed by other chronic lung disease and cardiovascular disease. This is in line with reports from other countries [6-7,11]. However,

TABLE 4

Specific complications of hospitalised patients (non-ICU), patients admitted to an ICU and deaths due to 2009 pandemic influenza, the Netherlands, 5 June–31 December 2009 (n=473 with specific complications reported)

Complication	No. (%) of hospitalised patients (non-ICU) (n=365 ^a)	No. (%) of patients admitted to ICU (n=123 ^a)	No. (%) of deaths (n=30)
Dehydration	110 (30.1)	8 (6.5)	3 (10.0)
ARDS	18 (4.9)	45 (36.6)	9 (30.0)
Low saturation	10 (2.7)	1 (0.8)	0 (0.0)
Worsening asthma / COPD or other respiratory complaints	89 (24.4)	30 (24.4)	9 (30.0)
Otitis	23 (6.3)	0 (0.0)	0 (0.0)
Sepsis	16 (4.4)	13 (10.6)	3 (10.0)
Other bacterial infections	24 (6.6)	11 (8.9)	5 (16.7)
Diarrhoea	6 (1.6)	3 (2.4)	3 (10.0)
Other	104 (28.5)	32 (26.0)	9 (30.0)

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit.

^a The total number of complications is more than the total number of patients with complications because one patient can have more than one complication

compared with other countries, obesity was reported for very few hospitalised patients and was not a risk factor in the Netherlands. However, no systematic data was collected on length and weight of the hospitalised patients not reported to be obese, which may have resulted in underreporting as obesity is likely to have been a subjective assessment of the attending physician.

A further limitation of this study is the fact that the Dutch notification system does not provide specific data on SARI. The reported cases include patients admitted for severe influenza illness with other complications than respiratory distress. Therefore, the Dutch SARI cases that are reported to the WHO and the European Centre for Disease Prevention and Control (ECDC) are laboratory-confirmed pandemic influenza cases, in contrast to some other countries that report all clinical SARI cases. Also, we could not determine why no complications were reported for 65 of 188 patients who were admitted to an ICU. It is possible that the attending physicians did not consider ARDS as a specific complication or that patients with respiratory distress did not fulfil all the diagnostic criteria for ARDS.

Comparison of the severity of the current epidemic with previous influenza seasons can not be based on direct analyses of hospital-based surveillance data, as there are no reliable historical records of hospital admissions and deaths related to laboratory-confirmed influenza, but will need to rely on the ongoing ILI sentinel surveillance among general practitioners (GPs). We recently related this GP ILI surveillance to retrospective respiratory hospitalisation rates over the years 1999 to 2005 [12-14]. So far, the admission rates in 2009 seem similar to the estimates over the period 1999-2005, although the admission rates for children and adults seem among the highest rates compared with the 1999-2005 influenza seasons, whereas the admission rates for the elderly (≥ 65 years of age) seem among the moderate or lowest rates compared with 1999-2005. Analyses as in [13] on trends in ILI GP consultations by age or in [14] on hospitalisations and mortality for respiratory diseases versus ILI GP consultations including 2009, could allow comparing the severity of the current epidemic with previous influenza seasons. A surveillance system with real-time availability of SARI cases would have made such analyses possible during the ongoing epidemic, but only if data on SARI cases (or similar clinical diagnosis) had also been available for earlier seasons, which is not the case in the Netherlands.

In conclusion, the national notification system was well suited and could rapidly be adapted to changing information requirements, although a national notification system puts restrictions on the amount of information that can be requested. While we could not confirm an association with obesity, other reported characteristics of hospitalised patients with confirmed pandemic

influenza in the Netherlands were in line with those reported by other countries, including countries in the southern hemisphere. This report is based on the 2009 phase of the pandemic in the Netherlands. Numbers, distribution by age group and characteristics could still change when the pandemic develops further, thus continuing surveillance and vigilance is essential.

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References

1. Vriend HJ, Hahné SJM, Donker T, Meijer A, Timen A, Osterhaus A, et al. Epidemiologie van Nieuwe Influenza A(H1N1) in Nederland, 30 april–15 augustus 2009. [Epidemiology of the new influenza A(H1N1) in the Netherlands, 30 April–15 August 2009.] *Ned Tijdschr Geneesk* 2009;153:A969. Dutch.
2. World Health Organization. Pandemic (H1N1) 2009 – update 73. [Accessed 9 November 2009]. Available from: http://www.who.int/csr/don/2009_11_06/en/index.html
3. European Centre for Disease Prevention and Control (ECDC). Pandemic (H1N1) 2009. Issue 18. 9 November 2009. Available from: [http://www.ecdc.europa.eu/en/healthtopics/Documents/091109_Influenza_A\(H1N1\)_Weekly_Executive_Update.pdf](http://www.ecdc.europa.eu/en/healthtopics/Documents/091109_Influenza_A(H1N1)_Weekly_Executive_Update.pdf)
4. World Health Organization. Pandemic (H1N1) 2009. Human infection with pandemic (H1N1) 2009 virus: updated interim WHO guidance on global surveillance. 10 July 2009. Available from: http://www.who.int/csr/disease/swineflu/guidance/surveillance/WHO_case_definition_swine_flu_2009_04_29.pdf
5. Meijer A, Beerens A, Claas E, Hermans M, de Jong A, Molenkamp R, et al. Preparing the outbreak assistance laboratory network in the Netherlands for the detection of the Influenza virus A(H1N1) variant. *J Clin Virol*. 2009;45(3):179-84.
6. New South Wales public health network. Progression and impact of the first winter wave of the 2009 pandemic H1N1 influenza in New South Wales, Australia. *Euro Surveill*. 2009;14(42):pii=19365. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19365>
7. Cullen G, Martin J, O'Donnell J, Boland M, Canny M, Keane E, et al. Surveillance of the first 205 confirmed hospitalised cases of pandemic H1N1 influenza in Ireland, 28 April – 3 October 2009. *Euro Surveill*. 2009;14(44):pii=19389. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19389>
8. Baker MG, Kelly H, Wilson N. Pandemic H1N1 influenza lessons from the southern hemisphere. *Euro Surveill*. 2009;14(42):pii=19370. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19370>
9. Baker MG, Wilson N, Huang QS, Paine S, Lopez L, Bandaranayake D, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. *Euro Surveill*. 2009;14(34):pii=19319. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19319>
10. State Population Health Emergency Operations Centre. Queensland Government. Pandemic (H1N1) 2009. Influenza in Queensland 2009 Weekly Report for Week 41. 12 October 2009. Registered document no. CH003112. Available from: <http://www.docstoc.com/docs/16058979/Influenza-in-Queensland-2009-Weekly-Report-12-October-2009>

11. European Centre for Disease Prevention and Control (ECDC). ECDC Risk Assessment. 2009 influenza A(H1N1) pandemic. Version 6. 6 November 2009. Available from: http://www.ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_Risk_Assessment.pdf
12. van Gageldonk-Lafeber AB, Bogaerts MA, Verheij RA, van der Sande MA. Time trends in primary-care morbidity, hospitalisation and mortality due to pneumonia. *Epidemiol Infect.* 2009;137(10):1472-8
13. Dijkstra F, Donker GA, Wilbrink B, de Jong JC, van Gageldonk-Lafeber AB, van der Sande MAB. Long-time trends in influenza-like illness and associated determinants in the Netherlands. *Epidemiol Infect.* 2009;137(4):473-9.
14. van den Wijngaard CC, van Asten L, Meijer A, van Pelt W, Nagelkerke NJD, Donker GA et al. Detection of Increased Severity of Influenza Infections: Associating Respiratory Hospitalizations and Mortality with Influenza-Like-Illness in Primary Care. *Am J Public Health* (in press).

Severe hospitalised 2009 pandemic influenza A(H1N1) cases in France, 1 July-15 November 2009

C Fuhrman (c.fuhrman@invs.sante.fr)¹, I Bonmarin¹, A C Paty¹, N Duport¹, E Chiron¹, E Lucas¹, D Bitar¹, A Mailles¹, M Herida¹, S Vaux¹, D Lévy-Bruhl¹

1. Institut de veille sanitaire, Saint-Maurice, France

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From 1 July 2009 to 15 November 2009, 244 patients with 2009 pandemic influenza A(H1N1) were admitted to intensive care units (ICU) and were compared with 514 cases hospitalised in medical wards in France until 2 November 2009. Detailed case-based epidemiological information and outcomes were gathered for all hospitalised cases. Infants and pregnant women are overrepresented among cases admitted to ICU with seven per cent for both groups respectively, and twenty per cent of ICU cases did not belong to a risk group. Chronic respiratory disease was the most common risk factor among cases but obesity (body mass index ≥ 30 Kg/m²), chronic cardiac disease and immunosuppression were risk factors associated with severe illness after adjustment for age and for other co-morbidities.

Introduction

On 1 May 2009, the first two cases of 2009 pandemic influenza A(H1N1) were identified in France [1]. At this time, hospitalisation of all cases was required, irrespective of their clinical presentation. After the virus had spread more widely and community transmission had increased, systematic hospitalisation was discontinued on 1 July. At the same time, a national hospital-based surveillance system of hospitalised 2009 pandemic influenza cases was set-up by the National Institute for Public Health Surveillance (Institut de veille sanitaire, InVS). The surveillance of hospitalised pandemic influenza cases was restricted to patients with severe disease on 2 November when there had been a sharp rise in the total number of cases requiring hospital admission.

In this paper we describe the characteristics and outcome of severe cases of pandemic influenza hospitalised in metropolitan France between 1 July and 15 November, 2009 and identify risk factors for severe outcome and death, respectively.

Methods

In France, a nationwide hospital-based surveillance system was implemented on 1 July 2009. Clinicians were requested to report to InVS all hospitalised cases

of pandemic influenza through a standardised notification form available on the InVS website. Patients to be notified included (i) those with a positive RT-PCR performed on a nasal swab, (ii) patients with a severe clinical influenza, likely to be caused by 2009 pandemic influenza virus according to the clinician, even in the absence of laboratory confirmation, and (iii) patients with an epidemiological link with a confirmed case of pandemic influenza. Two levels of severity of disease were defined: non-severe (hospitalised in medical wards for at least 24 hours) and severe (admitted to ICU or death while hospitalised).

Follow-up data for cases were collected weekly by telephone contact between InVS staff (epidemiologists or physicians) and physicians in charge of the patient until discharge or death. At discharge, clinicians were invited to return a second notification form also available on the InVS website. The forms received were cross-checked with individual positive PCR results coming from the network of all laboratories performing the RT-PCR for the 2009 pandemic influenza virus.

Descriptive statistics included frequency analysis (percentages) for categorical variables and median and interquartile ranges (IQR) for continuous variables. The differences in characteristics according to outcomes were tested using chi-squared test for categorical variables and Mann-Whitney rank sum test for continuous variables. A p-value under 0.05 was considered statistically significant. Two types of comparison were made. First, the clinical characteristics of patients with severe disease were compared with those of patients admitted to medical wards until 2 November 2009. Second, clinical characteristics of surviving severe cases discharged before 15 November, were compared with those of fatal cases. Odds ratios (OR), including 95% confidence intervals (CI), were calculated through multivariate logistic regression analysis. We included in the analysis the presence or absence of each of the following underlying medical conditions/ potential risk factors: chronic respiratory disease, pregnancy, diabetes, obesity (body mass index ≥ 30 Kg/m²), immuno-

suppression and chronic cardiac disease as categorical variables. The analysis was performed with Stata V9.

Results

From 1 July to 15 November and 2 November 2009 respectively, 244 severe cases of 2009 pandemic influenza and 514 cases hospitalised in medical wards were reported to InVS. The number of hospitalisations increased sharply from week 41 (Figure 1). Almost all cases (98%) were laboratory confirmed as 2009 pandemic influenza A(H1N1), the 2% non-laboratory confirmed cases were patients with clinical influenza and/or patients with an epidemiological link with a confirmed case.

Clinical characteristics

Among the 244 severe cases, 48 (20%) were children under 15 years of age, the male/female ratio was 1.1 (Table 1). The age-specific incidence of admission to ICU was highest among infants (children under one year of age, 2.03 cases per 100,000 of the age group and lowest among those 65 years of age or older (0.18 cases/100,000 of the age group).

Underlying conditions were present in 188 (80%) patients. This proportion was 67% among children.

Chronic respiratory diseases were the most common underlying condition, both in adults and children. Of the 117 women, 18 were either pregnant, mainly in the second (n=5) and third trimester, or had recently delivered (i.e. within a week) (n=11). Among these 18 women, 61% had an underlying medical condition.

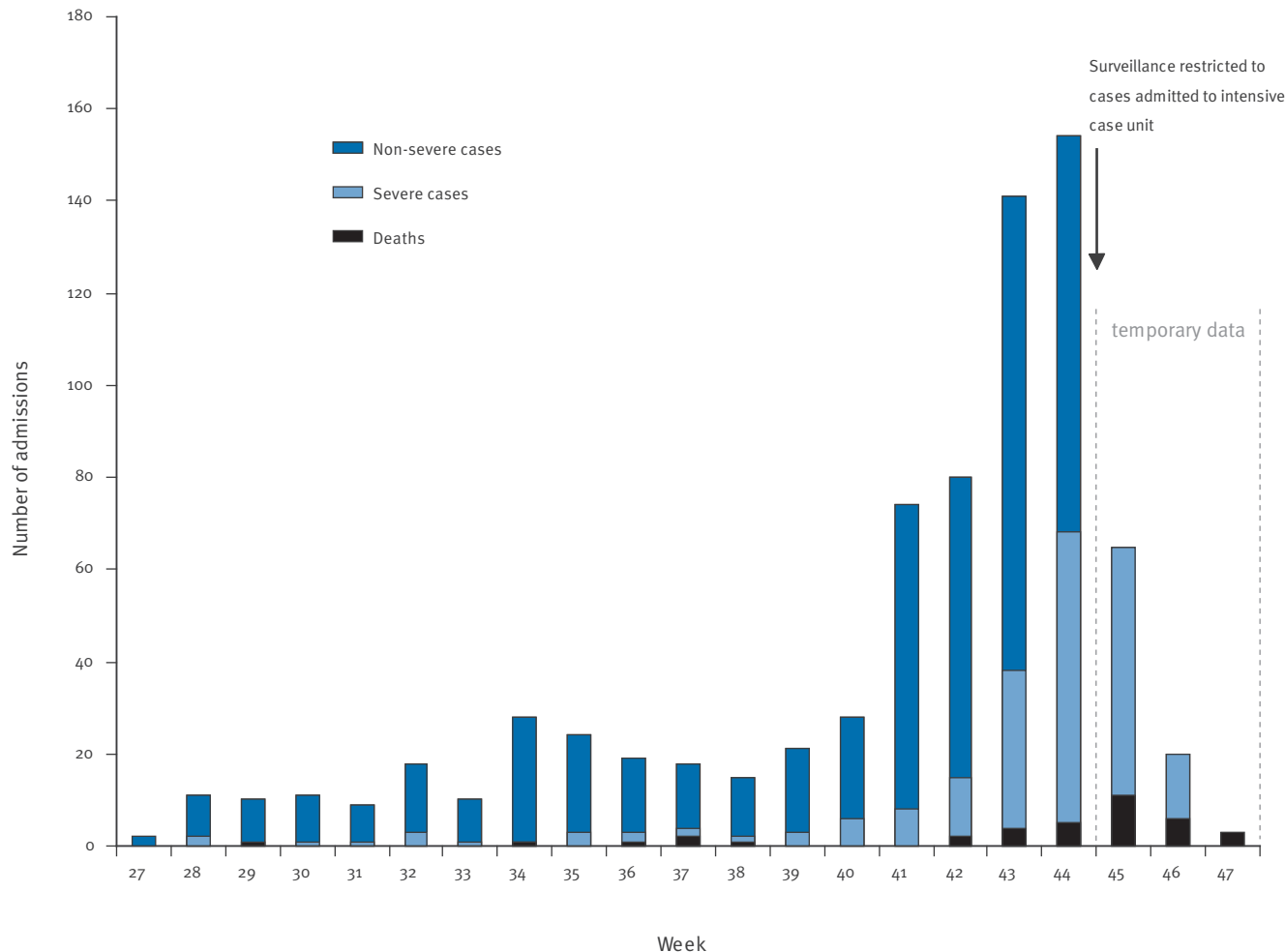
Compared with non-severe hospitalised paediatric cases, the risk of severe disease was significantly higher for children with an underlying condition (age-adjusted OR: 3.3); the excess risk associated with younger age (<1 year) however, did not reach statistical significance (Table 2).

In the multivariate analysis, increasing age and obesity were significantly associated with severe disease when compared with non-severe hospitalised adult cases (adjusted OR 2.2; 95% CI 1.1 to 4.8) for age 65 years or more and 9.1 (95% CI 4.4 to 18.7) for obesity) (Table 2).

Pregnancy was more prevalent among female cases aged 15-45 years admitted to medical wards than among those in this age group admitted to ICU (50% and 31% respectively, $p=0.02$). Among pregnant women, having

FIGURE

2009 pandemic influenza A(H1N1) cases admitted to hospitals by week of admission and severity, France, 1 July–15 November 2009 (n=758)



an underlying condition was significantly associated with severe disease (age-adjusted OR: 8.4; 95% CI 2.5 to 28.6).

Interval from symptom to admission and treatment

The interval from onset of symptoms to admission was available for 216 severe cases and 427 non-severe cases. The median interval was 2.0 days (range 0-31)

TABLE 1

Characteristics of hospitalised severe cases of 2009 pandemic influenza A(H1N1), France, 1 July–15 November 2009 (n=244)

		All		Died	
		n=244		n=37	
Age (years)	<1	16	(7%)	2	(5 %)
	1-14	32	(13%)	3	(8 %)
	15-64	178	(73%)	29	(78 %)
	65 or more	18	(7%)	3	(8 %)
Sex (% men)		127	(52%)	21	(57%)
Risk factors					
None		47	(20%)	2	(5%)
At least one		188	(80%)	35	(95%)
Data not available		9		0	
Main risk factors ^a					
Chronic respiratory disease		76	(31%)	10	(27%)
Pregnancy		18		1	
1st trimester		2	(7%)	0	(3%)
2nd trimester		5		0	
3rd trimester or post-partum		11		1	
Diabetes		27	(11%)	9	(27%)
Obesity		51	(21%)	11	(30%)
Obesity with BMI ≥ 40 Kg/m ²		24	(10%)	6	(16%)
Immunosuppression		21	(9%)	8	(21%)
HIV infection		2	(1%)	0	
Chronic cardiac disease		16	(7%)	9	(24%)

BMI: body mass index.

^a Multiple entries per patient possible.

TABLE 2

Factors associated with severe disease in hospitalised 2009 pandemic influenza A(H1N1) cases (multivariate analysis), France, 1 July–15 November 2009 (n=758)

		Severity of disease							
		Non-severe ^a			Severe				
		n	%		n	%	AOR	95% CI	
Children									
Age (years)	<1 1-14	64 162	28% 72%		16 32	33% 67%	2.1 1	[0.9-4.5]	
Risk factors	None At least one Data not available	114 96 16	 54% 46%		15 31 2	 33% 67%	1 3.3	[1.5-7.0]	
Adults									
Age (years)	15-64 65 or more	274 14	95% 5%		178 18	91% 9%	1 2.2	[1.1-4.8]	
Main risk factors ^b									
Chronic respiratory disease		77	28%		65	33%	1.2	[0.8 -1.9]	
Pregnancy		67	23%		18	9%	0.5	[0.2-0.8]	
Diabetes		22	8%		26	13%	1.5	[0.8 -2.8]	
Obesity		10	3%		50	26%	9.1	[4.4-18.7]	
Immunosuppression		26	9%		19	10%	1.1	[0.6 - 2.2]	

AOR: Adjusted odds ratio for age and underlying condition; CI: Confidence interval.

^a Admitted for at least 24h in a medical ward.

^b Risk factors were available for 463 cases. Multiple entries per patient possible.

for severe cases and significantly longer than for cases without severity criteria: 1.2 days (range 0-13) ($p<0.001$). Data about antiviral therapy were available for 153 severe and 306 non-severe cases; 93% of severe cases had received antiviral therapy (oseltamivir) versus 81% of non-severe cases. Information for the interval from onset of symptoms to antiviral treatment initiation was available for 322 patients (207 non-severe and 115 severe). This interval was ≤ 2 days for 153 (74%) non-severe cases and for 45 (39%) cases patients ($p<0.001$). Similar results were obtained when the analysis was restricted to cases with underlying disease: 100 (72%) of the non-severe cases and 38 (41%) of severe cases had received early antiviral therapy ($p<0.001$).

Outcome

Of the 244 severe cases, 147 (60%) required ventilator support, 60 (25%) had an acute respiratory distress syndrome (ARDS) and 21 (9%) required extracorporeal membrane oxygenation (ECMO). At the time of analysis, 143 patients had been discharged from the ICU, and 37 (15%) had died. The median length of stay in the ICU was five days (IQR 3-8). The median age of patients who died was 42 years (range 8 months-71 years) and the median time from hospital admission to death was four days (range 0-74). Among the five children who died, three were one year old or under, one was six and one was 14 years old and all of them had at least one underlying condition. Among the 32 adults who died, 30 (94%) had at least one underlying condition (Table 1). A pregnant woman with underlying condition died.

Chronic cardiac disease and immunosuppression were associated with fatal outcome but this was not the case for chronic respiratory diseases. Obesity had an OR point estimate of 2.6 but was not statistically significant (Table 3).

Discussion

This series of hospitalised patients with 2009 pandemic influenza confirms that the 2009 pandemic virus can induce severe illness among children and adults, even for those with no underlying medical conditions. The epidemic started almost two months before the usual influenza season in France. No co-circulation of other influenza viruses was identified through the enhanced virological surveillance during the period of data collection.

In our series, the highest ICU admission rate was found in infants and the lowest in the elderly. Being 65 years old or more seems, to be a risk factor for severe disease when hospitalised, but not for death, after adjustment for the presence of co-morbidities. Our results are coherent with other reports on 2009 pandemic influenza. In Australia and New Zealand, the rate of admission to ICU was low in the elderly but the risk of death increased with age [2]. In the analysis of Mexican data, confirmed cases aged 70 years or more, had the lowest mortality rate but the highest death to hospital admission ratio [3]. We did not identify an association for cases between death and being more than 65 years old. This could be explained by the fact that our analysis was adjusted to the presence of co-morbidity. It may also be due to the limited sample size of our series.

The underlying conditions leading to more severe illness we found are those reported in the literature. Chronic respiratory illness is the most prevalent in our case series, as described also by Jain *et al.* [4], but it is not associated with a higher risk of more severe disease or death among hospitalised cases. In contrast, obesity is clearly a risk factor for severe disease and probably for death as was reported in the literature [2,4,5]. Obesity is a risk factor for severe viral pneumonia [6] while severity connected to chronic respiratory disease is related to the exacerbation of the disease, and is usually responsive to bronchodilator

TABLE 3

Risk factors for death, among hospitalised severe adult cases of 2009 pandemic influenza A(H1N1) (multivariate analysis), France, 1 July–15 November 2009 (n=140)

	Alive and discharged from ICU		Dead		OR aj	95% CI
	n	%	n	%		
Adults	108		32			
Age (years)					1.00	[0.97 – 1.03]
Main risk factors ^a						
Chronic respiratory disease	46	43%	10	31%	0.7	[0.3 – 1.9]
Diabetes	12	11%	9	28%	2.3	[0.8 – 7.0]
Obesity	19	16%	11	34%	2.6	[0.97 -7.0]
Chronic cardiac disease	5	5%	7	22%	6.6	[1.7-26.0]
Immunosuppression	9	8%	7	22%	3.5	[1.02-11.9]
Pregnancy	14	13%	1	3%	0.3	[0.04 – 3.0]

ICU: intensive care unit; OR aj: adjusted odds ratio; CI: confidence interval.

a Multiple entries per patient possible.

treatment [7]. Pregnancy, especially at the end of the gestation, is overrepresented among the patients hospitalised and accounts for 7% of admissions to ICU whereas pregnancy (estimated from the number of live birth in 2008 and the number of abortions in France) represents around 1% of the general population. Our finding confirms that pregnancy should be considered as a risk factor for complications from 2009 pandemic influenza [8]. A similar conclusion stands for infants, also accounting for 7% of admissions to ICU.

The interval from the onset of symptoms to admission was longer for severe cases than for non-severe cases. Furthermore, antiviral treatment was initiated less than 48 hours after the onset of symptoms for 74% of non-severe hospitalised cases and 39% for severe cases. As already suggested by data from the United States, it is possible that delayed initiation of antiviral therapy may have contributed to increased severity of illness [4,9]. Communication to patients and physicians should be strengthened on the need for rapid initiation of treatment, whenever indicated.

Of the 244 patients with severe disease, 60% required ventilator support, 25% had an acute respiratory distress syndrome (ARDS) and 9% required extracorporeal membrane oxygenation (ECMO). These results are also consistent with previously published reports [2,4]. Our study has several limitations. Although our surveillance was implemented in the context of public health emergency some cases may have not been reported to InVS. However, several factors are in favour of only few cases having been missed. Firstly, only a few additional cases were identified after cross-checking with data from laboratories. Secondly, cases considered by clinicians as likely to be due to 2009 pandemic influenza, even in the absence of laboratory confirmation, were included in the definition of cases to be notified. Thirdly, regular phone calls with physicians of ICU wards were made by InVS staff in order to complete missing information on received forms and ask for cases not notified. Last but not least, the hospital surveillance is strongly supported by various ICU medical practitioners' societies.

To assess risk factors for severe clinical presentation we used 2009 pandemic influenza cases admitted to medical wards as a control group. This choice of controls may have lead to an underestimation of odds ratios because for some specific population groups potentially more prone to complications such as pregnant women and children, individuals may have been hospitalised as a precautionary measure even in the absence of severe disease. This could explain our finding of a higher proportion of non-severely ill pregnant women hospitalised in medical wards compared to those admitted to ICU.

Our study confirms the role of the underlying conditions as risk factors for severe disease and strengthens the need for a rapid start of antiviral therapy,

especially for patients with underlying conditions. Furthermore, it confirms the French national strategy which recommends priority vaccination of pregnant women, close contacts of infants and patients of any age with co-morbidities known to increase the risk of severe influenza.

Our analysis will be renewed when a larger series of cases will be available: as of 2 December, 511 severe cases have been identified with 74 deaths and the epidemic does not seem to have reached its peak yet.

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References

1. Vaux S, Bonmarin I, Enouf V, Valette M, Van Der Werf S, Lina B, et al. Cas d'infection par le nouveau virus de la grippe A(H1N1) v en France, situation au 5 juin 2009. BEH 2009. French. Available from: http://www.invs.sante.fr/beh/actualite_epidemiologique/r-4.html
2. Webb SA, Pettit V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med*. 2009;361(20):1925-34.
3. Echevarria-Zuno S, Mejia-Arangure JM, Mar-Obeso AJ, Grajales-Muniz C, Robles-Perez E, Gonzalez-Leon M, et al. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. *Lancet* 2009 Nov 11. [Epub ahead of print]
4. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20):1925-44.
5. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA*. 2009;302(17):1896-902.
6. Rello J, Rodríguez A, Ibanez P, Socias L, Cebrian J, Marques A, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care*. 2009;13(5):R148.
7. Gordon E, Lazarus SC. Management of chronic obstructive pulmonary disease: Moving beyond the asthma algorithm. *J Allergy Clin. Immunol*. 2009;124(5):873-80.
8. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009;374(9688):451-8.
9. Trémolières F. Les antiviraux de la grippe servent-ils à quelque chose ? *Med Mal Infect*. 2009;39:667-73. French.