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Spotlight on measles 2010: Update on the ongoing measles outbreak in France, 2008-2010

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Since early 2008, France has been experiencing a measles outbreak with almost 5,000 notified cases as of 30 June 2010, including three measles-related deaths. The proportion of cases 20 years or older reached 38% during the first half of 2010. This situation is the consequence of insufficient vaccine coverage (90% at age 24 months in 2007) that led to the accumulation of susceptibles over the last years. It underlines the need for additional measures targeting susceptible children and young adults.

The current measles outbreak in France was first noticed in early 2008 [1] when a preliminary number of 579 notified measles cases contrasted sharply with the low number of notified cases in 2006 and 2007 (44 and 40 cases, respectively). The outbreak intensified and continued to spread throughout the country during 2009 and 2010 with a total number of notified cases that has reached almost 5,000 by 30 June 2010.

In France, a combined measles-mumps-rubella (MMR) vaccine has been recommended since 1986. The first dose is currently recommended at the age of 12 months and the second dose during the second year of life. A catch-up measles vaccination programme with two doses is recommended for children born in 1992 or later. For those born between 1980 and 1991, a single MMR vaccine dose is recommended [2].

Measles has been a mandatory notifiable disease in France since mid-2005. Clinicians and microbiologists are requested to report suspected measles cases immediately to the regional public health authorities. Notifications are collected and analysed at national level by the French Institute for Public Health Surveillance (InVS).

We included in our analysis the notified clinical and confirmed cases with a date of rash onset between January 2008 and June 2010 (preliminary data). A confirmed case can be i) laboratory-confirmed, by detecting either measles IgM antibodies or measles virus nucleic acid using RT-PCR in serum or oral fluid, or ii) epidemiologically confirmed, when a link with a laboratory-confirmed case is proven. Case definitions for measles are detailed on the InVS website [3].

Outbreak description

The outbreak started during early spring 2008 among students attending traditionalist catholic private schools for whom a low immunisation coverage was identified retrospectively [1]. It then spread first into other schools including public ones, and by the end of 2008 into the general population. The outbreak also affected socially vulnerable communities such as France's nomadic minorities ('gens du voyage') and Roma communities.

A total of 4,753 cases were notified as of 30 June 2010: 604 cases in 2008, 1,544 in 2009 and 2,605 in the first half of 2010 (Figure 1).

After excluding 99 cases (2%) who had returned from abroad within 7–18 days before the rash onset, the incidence of indigenous measles was highest, four cases per 100,000 population, in the first half of 2010, compared with 2.3 in 2009 and 0.9 in 2008 ($p<0.0001$). In 2010, the crude incidence was higher than 5.0 per 100,000 population in seven of the 22 regions in mainland France (Figure 2). Only three cases were reported from the French overseas regions but for two of these cases, the transmission has most likely occurred in mainland France.

The proportion of laboratory-confirmed cases increased from 50% (n=306) in 2008, to 54% (n=832) in 2009 and to 56% (n=1,410) in the first half of 2010.

The National Reference Centre for Measles in France identified the main measles virus genotypes in 2009 as D4 and D5. They accounted for 75% and 20% respectively of 284 genotyped cases. Genotypes D8, H2 and B3 accounted for the remaining 5%. Genotype D4 became predominant in 2010 (99% of the 467

genotyped cases). A great majority of the strains are linked to the last D4 variant identified in the United Kingdom in 2007, MVs/Enfield.GBR/14/07 (Genebank accession number EF600554).

Among the 4,753 cases, the sex ratio M/F was equal to 1.08. In 2010, the age distribution of measles cases has changed significantly compared with 2009 and 2008. The proportion of cases under one year of age has increased significantly from 4% (n=25) in 2008 to 8% (n=126) in 2009 ($p<0.001$) and 9% (n=243) in 2010 ($p<0.001$). The proportion of cases aged 20 years or older increased from 17% (n=100) in 2008 to 23% (n=360) in 2009 ($p=0.002$) and 38% (n=992) in 2010 ($p<0.001$). In the first half of 2010, the highest age-specific incidence rate was found in children under the age of two years (Figure 3). Over this six-month period, 56% (n=135) of the cases under one year of age were younger than nine months.

In 2010, 82% of the 2,123 cases with a known vaccination status were unvaccinated, 13% had received one dose, 3% two doses and 2% had been vaccinated with an unspecified number of doses. A high proportion of unvaccinated cases (86%) was observed among the cases aged between 5 and 19 years, who should have been vaccinated with two MMR doses. The highest proportion of cases vaccinated with at least one dose of MMR was 32% (156/487) in 20-29-year-old adults (Figure 4).

Figure 1

Notified measles cases by month of rash onset, France, January 2008 – June 2010 (n=4,753)

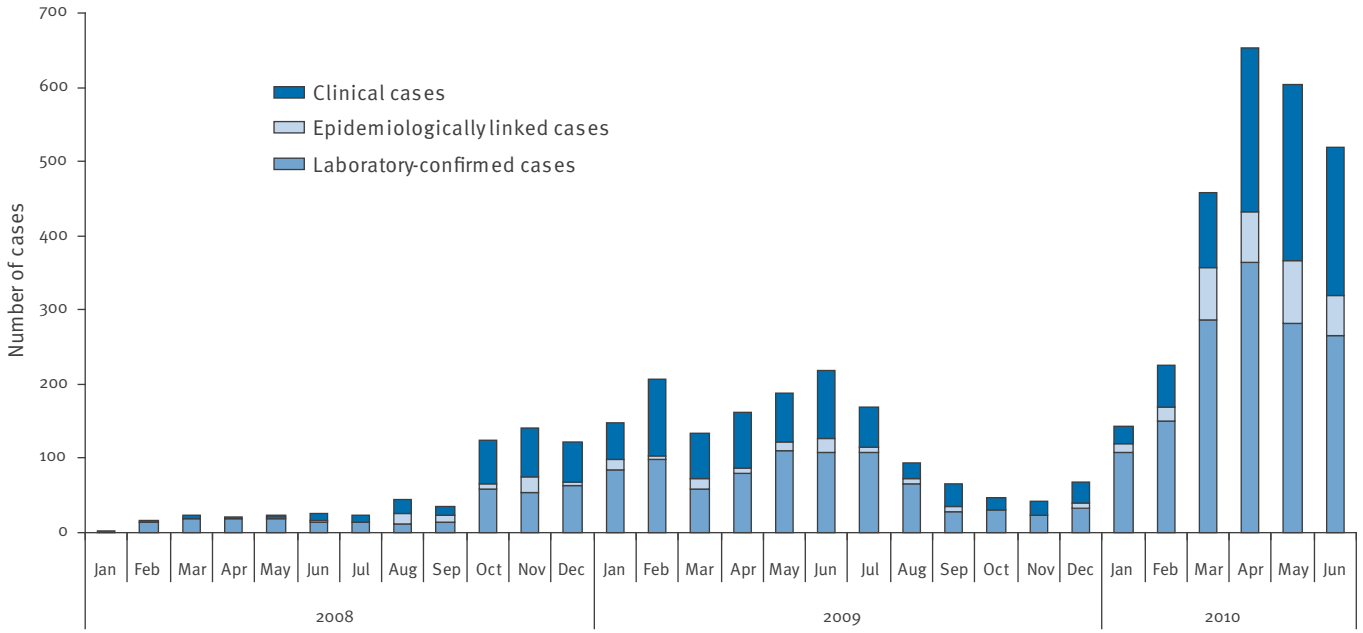
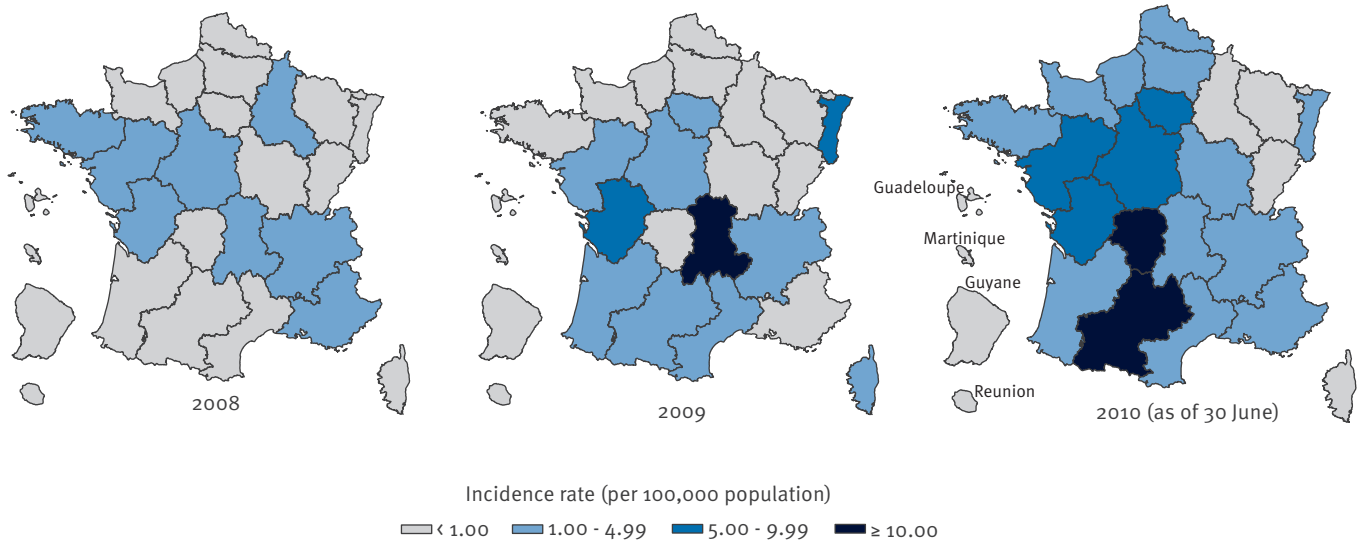


Figure 2

Incidence of notified measles cases, by regions, France, January 2008 – June 2010



Complications and deaths

Throughout the study period, 35% (n=137) of the cases under the age of one year, 18% (n=549) of the cases in the age group of 1-19-year-olds and 50% (n=725) of the cases aged 20 years or older were hospitalised. The percentage of hospitalised cases increased from 18% (n=110) in 2008 to 27% (n=422) in 2009 and to 34% (n=879) in 2010 (p<0.0001) reflecting the change in age distribution. In fact, the proportion of complications reported for the hospitalised cases was significantly higher among the cases aged 30 years or older (40%) than in the younger age groups (25%, p<0,001), whereas it remained stable over time (25%, 26% and 29% in 2008, 2009 and 2010 respectively). Among the hospitalised cases, three cases of acute measles encephalitis and 253 cases of measles-related pneumonia were reported.

Three measles-related deaths occurred during the study period: two in 2009 and one in 2010, all among unvaccinated cases. One death was linked to acute encephalitis in a 12-year-old girl and the other two occurred in young men, aged 23 and 18 years, with underlying immunodeficiency disorders (Crohn and Hodgkin).

Figure 3

Age-specific incidence rates of measles cases, France, January 2008 – June 2010

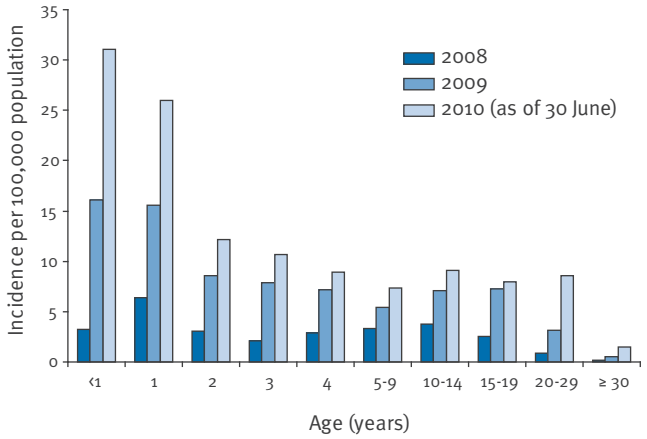
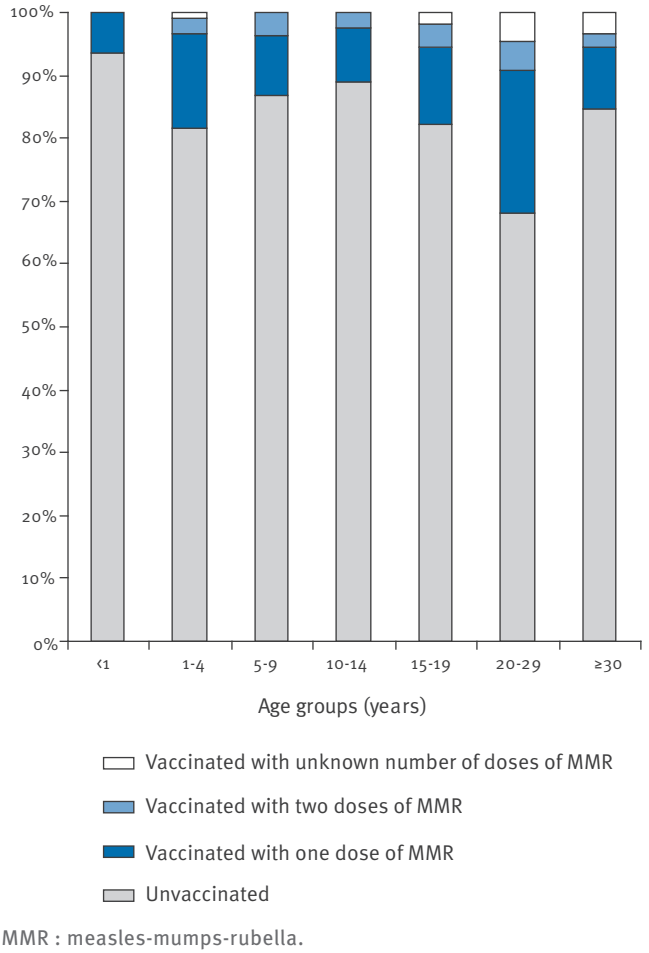


Figure 4

Vaccination status of measles cases by age groups, France, January–June 2010 (n=2,123)



MMR : measles-mumps-rubella.

Control measures

Specific control measures including catch-up and post-exposure vaccinations were recommended by local health authorities, targeting affected populations according to national guidelines within the National Plan for Elimination of Measles [4]. In case of localised outbreaks or clusters, the catch-up recommendation is to reach two doses of MMR vaccine for the susceptible individuals (not vaccinated or without history of measles) aged between 12 months and 45 years in the affected area or community.

Communication to the general public (e.g. leaflets, newspapers) and health professionals (e.g. medical journals) has been strengthened with also specific emphasis to the religious community concerned and to the national 'gens du voyage' associations (a meeting between representatives from the Ministry of Health and from the affected groups). Advantage was taken of the European Immunisation Weeks (EIW) in April 2009 and 2010 to reinforce this communication, with a special focus on the vaccination recommendations [5].

Discussion

Our data show that France has emerged as another among several European countries (e.g. Bulgaria, Switzerland, Ireland) with more than one measles case per 100,000 population (i.e. having a high incidence according to the criteria set by the World Health Organization (WHO) for the elimination of measles), together with countries like Greece, and Germany which have recently experienced measles outbreaks [6-11].

Measles reporting rate has probably increased since early 2008 in France. However, several factors still argue for an underestimation of the current incidence of the disease. The high proportion of hospitalised cases probably reflects a higher compliance of hospital health professionals than of general practitioners with regard to the notification of measles cases. In some local outbreak investigations less than 50% of cases were notified, and once a case was diagnosed in a household, the secondary cases were less likely

to seek medical advice. The number of patients with measles-positive results in the data collected from the main laboratories testing for measles IgM in France was 1.5 higher than the number of positive cases that were notified. The spread of the disease among socially vulnerable communities is even more difficult to assess because the notification forms do not contain information on social conditions.

It had already been predicted in 1998 that countries like France or England and Wales, where vaccine coverage had remained around 80% to 85% for many years with insufficient catch-up programmes, have built up large cohorts of susceptible people, becoming prone to large outbreaks with an increase of the average age of cases [12] .

Despite the current French recommendations, immunisation coverage for measles remains insufficient. At the age of two years, the vaccination coverage with one dose of MMR vaccine was estimated at 90% in 2007. Information on vaccination coverage in France is to be found on InVS website [3].

The vaccination coverage survey conducted in the school year 2005-6 among six-year-old school children, has shown a vaccination coverage of 93% for the first dose of an MMR containing vaccine and 44% for the second dose, and the one conducted in 2004-5 among 11-year-olds has shown a vaccination coverage of 96% and 74% respectively [13] .

The proportions of vaccinated cases in different age groups have to be interpreted with caution. It is possible that cases being more severe in the age group of 20-29-year-olds are more likely to be hospitalised and notified. The proportion of vaccinated cases in this population born after MMR introduction could therefore reflect a more accurate picture of the virus circulation in a population with suboptimal vaccination coverage.

Both awareness of the disease and a commitment by the French health authorities and health professionals are essential to strengthen the vaccination programme. The current measles situation in France underlines the need for additional urgent measures, both in terms of communication and vaccination, targeting susceptible children and young adults.

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Dengue virus infections in travellers returning from Benin to France, July-August 2010

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In July and August 2010, two cases of dengue fever were diagnosed in travellers returning from Benin to France. These two cases exemplify that dengue fever should be considered in febrile travellers, even those returning from areas where the infection is not usual.

Dengue virus infections are increasingly reported in travellers returning from West Africa [1,2]. Dengue cases detected in sentinel travellers may inform the international community of the onset of epidemic activity in specific areas. We report two cases of dengue fever identified by a EurotravNet site in Marseille, France, in two travellers returning from Benin. Up to 7 September 2010, no other dengue fever cases were reported in the EuroTravNet network from this area.

The first case was a French expatriate in his 40s, who had been resident in Cotonou, Benin for more than a year. When returning to France in July 2010, he suffered from fever, headaches and myalgias on the plane and took an anti-malaria drug, coartem, as a self-treatment, with no significant effect. Five days later he presented to the emergency ward in a hospital near Marseille and was transferred to the Tropical and Infectious Disease ward in Hôpital Nord, Marseille. On admission, the body temperature was 38 °C, the patient reported having dysphagia and the clinical examination revealed a diffuse non-petechial rash. Blood cultures were negative for bacteria and malaria was ruled out by microscopic blood examination. Serology was positive for IgM and IgG against dengue virus (ELISA, Euroimmun). In order to exclude possible cross-reaction with other flaviviruses, the presence of antibodies specific for West Nile virus and tick-borne encephalitis virus was tested by an ELISA test (Euroimmun), and that for yellow fever virus (YFV) was tested by in-house immunofluorescence using a previously reported method [3]. Only IgG against YFV were detected. The patient had previously been vaccinated against yellow fever. PCRs for dengue and chickungunya virus infections were negative, using published protocols [4,5].

The second case was a migrant from Benin in her 30s, established in France for over five years, who visited friends and relatives in Cotonou in July and August 2010. During her stay, she suffered from fever (39 °C), headaches, arthralgias, myalgias, nausea, anorexia and fatigue. On day 4, she consulted in a clinic in Benin, where she was given quinine despite negative blood examination for malaria. She remained febrile until day 7. On returning to the south of France (on day 17), she was seen by her general practitioner for asthenia. Dengue serology was positive for IgM and IgG (ELISA, Biotrin). Serology for human immunodeficiency virus (HIV) infection (MEIA Abbot Axsym, HIV Ag/Ab Combo), acute hepatitis A, B and C (CMIA Abbot Axsym), amoebiasis (ELISA, Ridascreen, IFI bioMérieux), schistosomiasis (ELISA, Bordier) and falciparum malaria (indirect immunofluorescence, bioMérieux) were negative. No PCR was attempted because the patient had no chance to be been viraemic 17 days following the onset of fever, nor any other flavivirus serology.

The detailed laboratory findings for both cases are shown in the Table. Both had non-complicated dengue

Table

Laboratory findings for two cases of dengue fever in travellers returning from Benin, France, July-August 2010

	Case 1	Case 2
Time between onset and blood sampling	5 days	18 days
Leukocyte count/µL	3,200	5,100
Platelet count/µL	99,000	520,000
SGOT (U/L)	240 (5N)	41 (1.2N)
SGPT (U/L)	264 (4N)	85 (1.5N)
GGT (U/L)	176 (3N)	28 (1N)
Serology	IgM + IgG[a]	IgM + IgG[b]

N: normal upper value; GGT: gamma-glutamyl transferase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

[a] Dengue virus ELISA IgG and IgM (EuroImmun, Biodavance France.

[b] Dengue virus ELISA IgG and Ig M (Biotrin France).

fever, according to the new classification of the World Health Organization [6].

Dengue fever is not a common diagnosis in travellers returning from Benin (in addition to the presented cases we are aware of three published cases since 2006 [7,8]). Nevertheless, it was decided to test for dengue virus in the first patient because of the typical clinical presentation and because dengue virus had been detected in our unit shortly before, in travellers returning from West Africa [1] and from islands in the Indian Ocean [9]. For the second patient, the general practitioner decided to test for dengue virus infection for retrospective diagnosis because, working part-time in the tropical and infectious disease ward, he was aware of the diagnosis in the first patient.

The first serological evidence of transmission of dengue virus in Benin was provided by a seroprevalence study conducted in asymptomatic Germans working overseas for the German Aid Agency 'Deutscher Entwicklungsdienst' from 1987 to 1993 [10]. Two cases of dengue virus infection were also reported in 2006 in travellers returning from Benin to France [2,7]. Because a confirmed case of dengue 3 virus infection (positive PCR for detection and typing using published protocols [4,5]) in a traveller returning from Togo to Marseille was evidenced this summer (data not shown), and because a confirmed case of dengue 3 virus infection was reported in a Japanese travellers returning from Benin in July [8], we suspect our two cases to be type 3 dengue virus infections too. Dengue virus serotype 3 was also recently identified in European travellers returning from Côte d'Ivoire [1,11], from Eritrea and Senegal [2], and from the Comoros islands and Zanzibar [9], and in an outbreak in Cape Verde [2], which suggests that this serotype has emerged in different parts of Africa.

So far there have been no reports about a current outbreak of dengue virus in Benin. However, local investigations are of interest to identify a possible outbreak in Benin, and surveillance should be reinforced among febrile travellers returning from Benin and neighbouring countries to detect additional cases. In conclusion, these two cases exemplify that dengue fever should be considered in febrile returned travellers, even in areas where the infection is not usual.

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Practical usage of computer-supported outbreak detection in five European countries

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This paper discusses computer-supported outbreak detection using routine surveillance data, as implemented at six institutes for infectious disease control in five European countries. We give an overview of the systems used at the Statens Serum Institut (Denmark), Health Protection Agency (England, Wales and Northern Ireland), Robert Koch Institute (Germany), Governmental Institute of Public Health of Lower Saxony (Germany), National Institute for Public Health and the Environment (the Netherlands) and Swedish Institute for Infectious Disease Control (Sweden). Despite the usefulness of the algorithms or the outbreak detection procedure itself, all institutes have experienced certain limitations of the systems. The paper therefore concludes with a list of recommendations for institutes planning to introduce computer-supported outbreak detection, based on experiences on the practical usage of the systems. This list – which concerns usability, standard operating procedures and evaluation – might also inspire improvements of systems in use today.

Introduction

Over the past decade, a number of institutes for infectious disease control throughout Europe have gained experience of systems for computer-supported outbreak detection. There are several reasons for introducing such systems to complement the daily surveillance already performed, mainly: (i) to detect outbreaks earlier, (ii) to detect outbreaks that would probably not have been detected otherwise, and (iii) to highlight potential problematic increases in incidence of a disease in the pre-outbreak phase.

Outbreak detection starts with the detection of an aberrant number of reported cases (suspected or confirmed) of a particular disease in a given time and space. Computer programs are used to compare the observed number of cases with expected values. When an increase is detected, the computer program raises an alert (the signal). Next, an expert (for example, an epidemiologist) assesses the public health relevance of the aberration, to determine if further investigation is warranted. Such investigations – which may involve a number of people at international, national and local level – are aimed at confirming whether there is an outbreak or not. If an outbreak is confirmed, further investigations will follow, where, for example, the magnitude of the outbreak is assessed, the source is traced and control measures are suggested. The task of the system is thus to warn of possible outbreaks. The process is outlined in the Figure.

Many algorithms can be used to detect deviations in infectious disease data, ranging from simple fixed thresholds to the application of complex statistical methods taking, for example, historical data into account (for reviews, see, for example, [1] or [2]). These algorithms can be applied to both laboratory data and clinical diagnoses as well as to syndromic surveillance data. Algorithms can be used for both geospatial and time series data. Considerable research has been carried out to improve these algorithms, that is, to increase specificity while reducing noise. To our knowledge, there are, however, no documented best practices on how to deal with the detected signals.

As part of a Swedish national project on computer-supported outbreak detection, the Swedish Institute for Infectious Disease Control contacted all focal points in the 27 countries that had participated in the former Basic Surveillance Network (BSN), in September 2006. (BSN was a European network for sharing national case-based reports on infectious diseases [3], which constitutes the basis for the current European surveillance system (TESSy) [4] maintained by the European Centre for Disease Prevention and Control (ECDC).) The country contacts were asked if their institute was using any form of electronic outbreak detection or had any information on the issue. A total of 19 replies were

received. National institutes in the following countries had experience to share with the Swedish institute: Denmark; England, Wales and Northern Ireland; Germany; the Netherlands; and Norway. These countries were subsequently sent a more detailed questionnaire and a dialogue was initiated. One result of this dialogue was a workshop on presenting and interpreting automatic outbreak detection signals, held at the Robert Koch Institute in Berlin, Germany, in May 2007, with participants from the six countries, along with representatives from the World Health Organization and ECDC. In November 2008, a second workshop was held, at which it was agreed that the institutes with computer-supported systems in place and represented at the meeting should share their experiences with institutes planning to introduce such systems.

In this paper, we describe how six surveillance institutes in five European countries have implemented computer-supported outbreak detection in their routine surveillance, giving an overview of how they are currently used, along with the lessons learnt. We also provide some recommendations for institutes that plan to introduce similar systems. The paper does not describe infectious disease control in the contributing countries, nor is the description of the implemented computer-supported systems exhaustive.

Country experiences

The countries that describe their experiences of computer-supported outbreak detection in this article vary in population size, ranging from a small country such as Denmark, with about 5.5 million people, to a large country such as Germany, with more than 82 million. Although infectious disease control is structured differently in each of the five countries, there are a number of common experiences in using the systems in daily work.

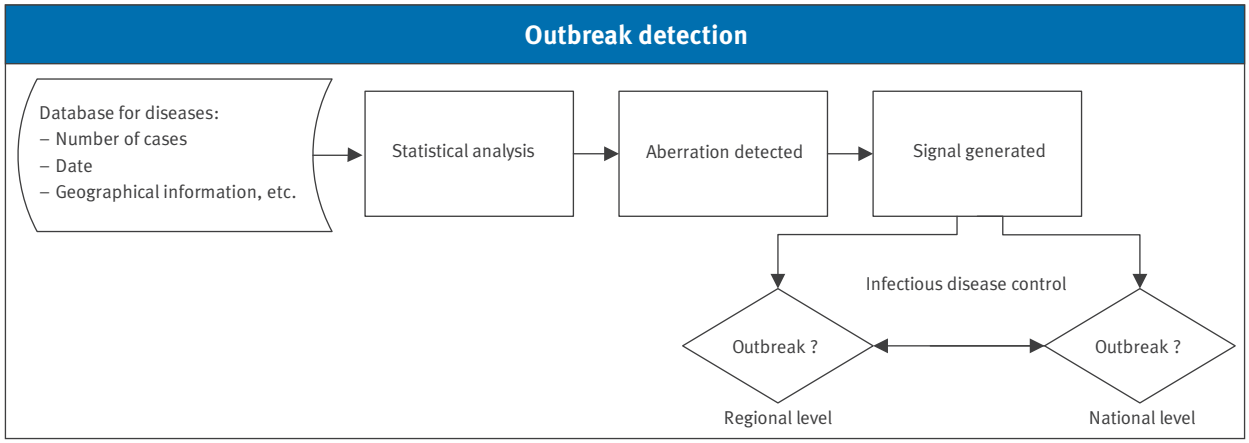
The authors describe the computer-supported outbreak detection system of their institution either as person in charge of the system, as the main user, or in collaboration with the users of the system. The perspective is that of the user of the system: it does not focus on the performance of the underlying algorithms. Although figures showing, for example, the sensitivity and positive predictive value of a particular algorithm applied to data collected in a particular country for a particular disease will reveal some information about its performance, there are many other aspects that are even more important, which are addressed in this paper.

Denmark

In Denmark, each week all clinical laboratories are required to report to a national database person-identifiable information on cases found positive for pathogenic gastrointestinal bacteria. Since 2001, an automated outbreak detection system based on these data has been in use at the Statens Serum Institut, generally running once a week. The system is an implementation, made in the statistical software SAS, of the algorithm described by Farrington *et al.* [5]. This algorithm uses Poisson regression on weekly counts of cases positive for each bacterial agent. Both national data and data from each laboratory's uptake area are analysed and the possibility of an outbreak is expressed on a scale from one to 10 by the system. Results are evaluated by an epidemiologist and signals deemed relevant are communicated by email to the appropriate investigators or discussed at weekly national inter-institutional outbreak meetings. In addition, surveillance and outbreak algorithm results for the most frequent bacterial agents have been published as maps, graphs and tables on a designated public website (http://www.germ.dk) on a weekly basis. Molecular subtyping data are not part of the algorithm. The algorithm has proven to be a useful surveillance tool, particularly for salmonella infections [6]. It has helped detect several outbreaks that might otherwise not have been noted at the time, both non-point source (diffuse) outbreaks of disease due to rare serotypes and local outbreaks resulting from frequent serotypes.

Figure

Process of computer-supported outbreak detection, involving both computerised and manual elements



England, Wales and Northern Ireland

In England, Wales and Northern Ireland all clinical laboratories are asked to electronically submit details of all organisms isolated to a laboratory database at the Centre for Infections of the Health Protection Agency (HPA). The information sent by the clinical laboratories will have come from patients within hospital departments or those attending general practices. Since 1993 an automated algorithm, developed by Farrington *et al*. [5], has been used weekly to detect possible outbreaks by comparing the current week's total reports for each organism with a threshold calculated using Poisson regression on the past five years' data. Analyses are run using all regions combined and also within each of 11 regions, producing lists of all organisms, ranked according to the level of exceedance above the threshold. For organisms with an exceedance (typically five to 20 organisms per week), plots are also produced showing the time series and the distribution of cases by age group and region or district along with an indication if this differs significantly from the past age group or regional distribution of cases. Results are posted on the HPA intranet and are also emailed to national and regional epidemiologists who further investigate the exceedances where necessary and initiate an outbreak investigation if appropriate. A weekly teleconference, based in the Centre for Infections, is held with national and regional epidemiologists to discuss any signals. The algorithm is currently being updated to allow data to be aggregated according to the date the clinical specimen was taken rather than date of receipt of the case report at the Centre for Infections. This may enable more rapid detection of outbreaks and reduce false signals, but it does require allowance for reporting delays in the model. The algorithm has enabled detection of outbreaks (particular salmonella) not otherwise identified, but the number of false signals and delays in reporting have limited its usefulness.

Germany – national level

In Germany, approximately 60 pathogens and health issues are reported by laboratories, general practitioners or other entities to the local health authorities [7,8]. Detailed information about cases is entered into a decentralised database, anonymised and transferred via the state health department at the regional level to the national level – the Robert Koch Institute (RKI). The RKI runs automated outbreak detection on the case reports [9], using a slightly modified version of the algorithm described by Stroup *et al*. [10]. By applying the algorithm to subsets of the data, such as certain regions (Bundesland, county), age groups, sex, countries of infection, etc. it is possible to detect outbreaks in a population group even if the excess cases would be undetectable when looking at the whole population. Cases can be linked to electronic outbreak reports at the different administrative levels [8].

The automated outbreak detection runs weekly. The detected aberrations are recorded on Microsoft Excel spreadsheets, including information on the particular subset of the data that led to the signal. A trained administrative clerk screens these signals and notifies the epidemiologist in charge when a signal subjectively seems to require further action. This decision is based on, for example, the disease, strength of signal and whether or not it is related to an outbreak that has already been detected at the local or regional level.

In 2002, the RKI tried to visualise the alerts, with a graphical output. A system presented the cases and incidence for each disease at each administrative level in charts and maps, including the possibility of showing the place of residence of the affected cases [11]. The main advantage of that system was that the user could label a signal as handled, avoiding repeated presentation of the same signal when running the algorithms daily. Unfortunately, the implementation of the surveillance system's front end did not easily allow for such an extension and this tool was therefore developed as an independent application. This lack of integration negatively influenced the usability and the tool was never incorporated into the regular surveillance.

Germany – Lower Saxony

At the governmental institute of public health in the German Land of Lower Saxony (NLGA), a system for automated outbreak detection has been developed with freeware tools. The starting point is case counts aggregated by disease (for salmonellosis, also by serotype of the causative agent), week of notification and 46 administrative districts. The data are exported weekly from the case database at the NLGA [7]. The following statistical methods (and corresponding software) are applied: detection of clusters in time by the method of Stroup *et al*. [10] and the method developed by Farrington *et al*. [5], as implemented in the R package surveillance [12], as well as detection of spatial clusters by SaTScan spatial scan statistics [13]. Data are also visualised on a website through time series charts using R software and maps (EpiMap) [14]. Validation of the signals since 2002 suggests that attention should be focused on highly significant signals ($p<0.01$). The results vary widely between diseases due to their different epidemiological characteristics. Spatial cluster-signals are frequently caused by diagnostic effects, for instance, by a tuberculosis screening programme in an immigration centre [15] or by specific awareness for *Cryptosporidium parvum* in a regional laboratory [16]. The methods are primarily valuable for noticing case clusters at an early stage. However, the initial suspicion or even detection of the clusters has often already occurred elsewhere – for example, at a local public health department or in a laboratory. Besides cluster identification, the statistically justified cluster signals have been proven to be helpful for communication purposes and decision support.

The Netherlands

In the Netherlands, for notifiable diseases (except salmonella and campylobacter infections) the simple model of Stroup *et al*. [10] has been used at the National Institute for Public Health and the Environment (RIVM)

since 1998. Laboratory surveillance, however, is voluntary and based on a sentinel of clinical laboratories that has been difficult to sustain. At RIVM, the algorithm developed by Farrington *et al.* [5] was implemented and in use from 2002 to 2006 for 34 pathogens [17], and from 1996 to date for more than 700 salmonella serotypes and phagetypes on a weekly basis. Observed, expected and tolerance levels are presented as time series that can be visually inspected retrospectively; observed frequencies are flagged if above the defined level of tolerance. A one- and a four-week window is used and a weekly window is run day by day, to improve sensitivity [17]. For salmonellosis, a website is available on the RIVM intranet, showing the period above tolerance levels and if cases are significantly clustered in space or demographically deviating from expected results. Maps are automatically generated each week for significant clusters. Out of hundreds of pathogens and serotypes analysed, the system draws attention to those signals that need further investigation and aids in the first steps of signal verification. Results are evaluated by an epidemiologist and signals deemed relevant are communicated by email and discussed weekly together with other signals, to decide upon further action [18]. Attention has been drawn to numerous small and large outbreaks in the past 10 years of using this system of algorithms and presentation of underlying information [19].

Sweden

The Swedish Institute for Infectious Disease Control has implemented a framework for computer-supported outbreak detection, called Computer Assisted Search for Epidemics (CASE) [20]. The source code for the framework is available as open source, licensed under the General Public License GPLv3 [21]. There is no limit set to the number of statistical algorithms that the CASE framework can support, and one or more algorithms can be applied to each disease. In addition, the parameter settings for each algorithm can be different for different diseases, even for different types if required. When an aberration is detected, an email is sent to the people listed for the particular disease, such as the epidemiologist in charge of that disease. The database behind CASE is populated with disease, disease agent type (when available) and regional information (county code), and the date when a case was first entered in the database. Two SaTScan algorithms [13,22] are fully integrated in the system, as are the algorithm described by Farrington *et al.* [5], as implemented in [12], and OutbreakP, which is used to investigate if an increase in the number of cases is more than expected, thus implying a potential outbreak [23]. In addition, a simple threshold can be set, where the number of reported cases is not to exceed a manually predefined value. Specified parts of the output generated by the algorithms are automatically extracted and processed further – for example, a signal is conveyed to the person responsible for the surveillance of the disease in question only if it occurred during the two preceding weeks. The system is implemented for all 62 notifiable diseases in Sweden. The algorithms are still being fine-tuned to suit the diseases, in order to find a reasonable balance between false alarms and not missing true outbreaks.

Recommendations

Drawing on everyday experience with computer-supported outbreak detection from all the institutes represented in this paper, we present a number of recommendations. These recommendations, summarised in the checklist (Box), should be valuable not only to countries wishing to implement their own system, but also to those that already have such a system in place. On the basis of practical experience, we consider that complying with these recommendations is a prerequisite for an optimally functioning computer-supported outbreak detection system.

Box

Checklist for a computer-supported outbreak detection system

- Signals and alerts are presented in a way that works well for the receivers.
- The output is user friendly, preferably in a graphical format (maps, epidemic curves etc.).
- People in charge of the surveillance of a particular disease can obtain signals for only that disease.
- The system is tightly integrated with the database, giving easy access to the case reports that contributed to the signals.
- Feedback from the receivers of the alerts is continuously incorporated into the system.
- Feedback to the public health workers at the local level, laboratories, etc. is part of the process.
- Outbreak algorithms can be scheduled as needed, e.g. daily or at least weekly, as well as run on an *ad hoc* basis.
- Algorithms can be fine-tuned easily and can also be applied to subsets of the data.
- Routines are in place for assessing if follow-up of a signal is needed.
- Routines are well documented, including vacation replacement strategies.
- Evaluation strategy is defined and regular evaluations are scheduled.
- The system supports logging of judgements of the detected signals to allow for future analysis and improvement of the algorithms.
- System-generated alerts can be linked to reported outbreaks.
- Signals presented once can be suppressed by the user until a second threshold is crossed.
- Sufficient support and maintenance of the hardware and software is provided. Also routines for user support and maintenance of software and hardware are documented.

Usability

Well-functioning computerised outbreak detection should be able to detect outbreaks of infectious diseases, to notify the people in charge of the surveillance and possibly also to reduce the workload of those working in outbreak detection. It is therefore crucial to not only improve the algorithms but to give the users the tools they need – that is, to find a suitable way to present the signals, which works for the receiver (for example, showing an epidemic curve of the cases contributing to the signal, visualising the expected maximum number or threshold, and showing a map that displays the regional distribution of the cases). The outbreak alert system should be tightly integrated with the surveillance database and allow the user easy access to the case reports that contributed to the signal. In addition, system-generated alerts can be linked to reported outbreaks. When the system is run frequently – which is critical for timely outbreak detection – users might receive the same signal several times. It is therefore important to allow the users to suppress signals presented until a second threshold is crossed. Acceptance of the system can increase if the signals can be filtered according to disease, so that those in charge of a particular disease receive signals for that disease only. Signals generated on other diseases are then not visible to them. It should be possible to schedule the algorithms as needed, for example, daily or at least weekly, as well as to run them on an *ad hoc* basis.

Some outbreaks affect only a certain risk group, meaning that the number of cases is so low that the excess cases cannot be detected automatically. It is therefore recommended to look at subsets of the data, such as regions, age groups and sex. Regional clustering together with time is extremely useful. In particular this may compensate for the lack of typing detail for frequently reported pathogens such as campylobacter. Changes in the system, such as new reporting laboratories, new test methods, etc., can significantly affect the performance of the algorithms and have to be carefully taken into account.

Standard operating procedures

The value of computerised outbreak detection is low if it is used only occasionally and if it is not embedded in standard operating procedures (SOPs) that clearly state the procedures for both the assessment of the signals and the actions to be taken if a detected outbreak is considered to pose a risk to the public. These SOPs should include feedback to the local level, the laboratories, etc. They should also handle more technical aspects, such as user support and maintenance of software and hardware.

Evaluation

We strongly recommend regular evaluation of the computerised outbreak detection system. This evaluation should include, for example, the system's usefulness and acceptance and should not be restricted to the performance of the algorithms used. To assess specificity, it would be helpful to log the experts' judgements of the detected signals, whether the signal indicates a real outbreak or it should be considered a false alarm. Information on outbreaks detected by more traditional means, such as by people in laboratories or at local health authorities, can be used to assess the sensitivity and timeliness of the algorithms.

Other aspects of a computerised system, such as report generation and presentation and visualisation of the data related to an outbreak, should also be evaluated.

Discussion

The different algorithms described in this paper have shown their ability to detect outbreaks that without their application would have been detected later or maybe even remained unnoticed. However, despite the obvious usefulness of the algorithms or the outbreak detection procedure itself, all countries have experienced certain limitations of the systems.

At all six institutes, the electronic systems are a central part of the outbreak detection process. The output is used in several complementary ways, and signals can often raise awareness among the people in charge of disease surveillance. The signals are either sent automatically from the system directly to a wider audience, or may already be filtered by a trained administrative clerk or an epidemiologist before being disseminated for further assessment. Tables, charts and maps, as well as results of statistical analyses by the outbreak detection algorithms are used to aid the assessment of the relevance of a signal. In addition, contextual information might be needed from other departments, for example, agricultural and census data. In several of the countries, the output of the system is also published on internal or public websites, allowing information to be shared with a broader audience as well as feedback to be given to the information provider.

By using a computerised system, it is possible to analyse data at various aggregation levels (e.g. different administrative levels) as well as data on different subsets of the population (e.g. by sex and age group). In addition, hundreds of pathogens can be analysed in a short period of time. The use of different outbreak detection methods, ranging from simple thresholds to complex statistical algorithms, in combination with the possibility of fine-tuning the system over time means that the system can be adapted according to different disease patterns. Running the algorithms on hundreds of pathogens and on different population subsets is, however, likely to pose a problem of many false alerts, which can reduce the usefulness of a computerised system. Although fine-tuning the system over time might reduce the problem, sufficient human resources are needed to deal with the generated alerts.

It has been noted by the users of the systems described that automatically detected disease clusters frequently have been observed at the same time or even earlier by

someone else, for example, by a laboratory. In such a case, the role of the system is rather that of providing further evidence and acting as a complement to the traditional surveillance. However, several countries also report that outbreaks that would otherwise have been missed have been detected by the computerised systems (for references, see for example [9]).

We consider that following the recommendations presented in this paper is a prerequisite for an optimally functioning computer-supported outbreak detection system. In so doing, a system that is user-friendly and supports a complex epidemiological reality may be obtained.

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Characteristics of paediatric patients with 2009 pandemic influenza A(H1N1) and severe, oxygen-requiring pneumonia in the Tokyo region, 1 September–31 October 2009

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Few reports describe the features of 2009 pandemic influenza A(H1N1) pneumonia in children. We retrospectively reviewed 21 consecutive children admitted to hospital from September to October 2009 in the Tokyo region. The diagnosis of 2009 pandemic influenza A(H1N1) virus infection was based on positive results of real-time RT-PCR or rapid influenza antigen test. All patients were hospitalised for pneumonia with respiratory failure and severe hypoxia. The median interval from onset of influenza symptoms to admission was 14 hours (range: 5–72 hours) and the median interval from the onset of fever (≥38ºC) to hospitalisation was 8.5 hours (range: 0–36 hours). All patients required oxygen inhalation. Four patients required mechanical ventilation. Chest radiography revealed patchy infiltration or atelectasis in all patients. Antiviral agents and antibiotics were administrated to all patients. Antiviral agents were administered to 20 patients within 48 hours of influenza symptom onset. No deaths occurred during the study period. Paediatric patients with this pneumonia showed rapid aggravation of dyspnoea and hypoxia after the onset of influenza symptoms.

Introduction

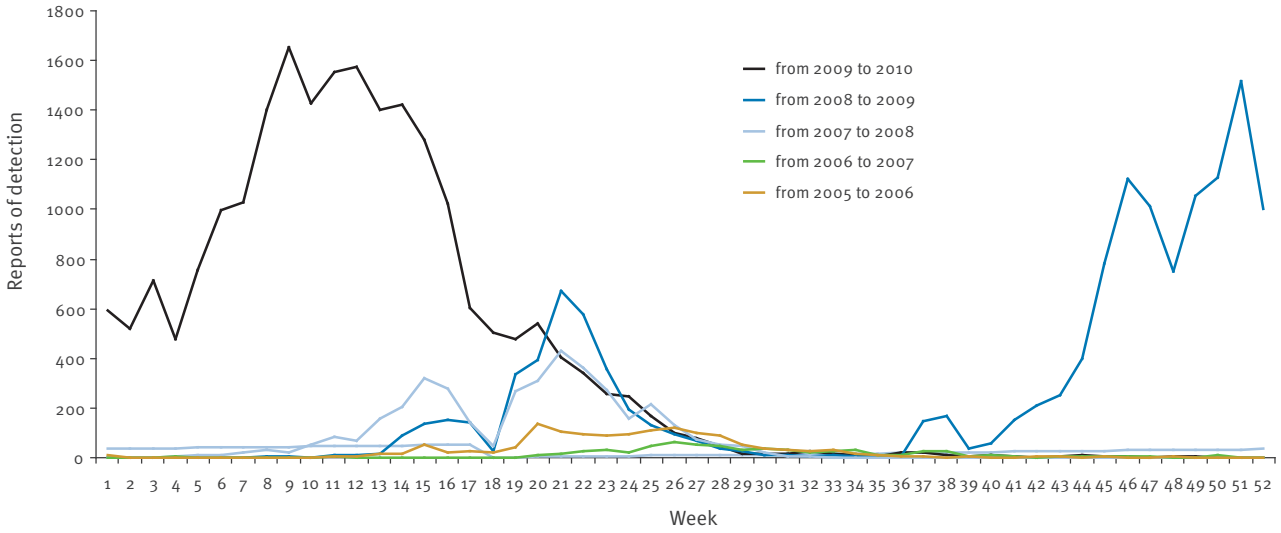
The 2009 pandemic influenza A(H1N1) infection has already been seen across most of the world. At least 18,449 deaths have been confirmed through 1 August, 2010 [1]. The mortality rate was 7% among 272 hospital patients in the United States (US). Of these, 122 were children and 100 of the 272 had pneumonia. The mortality rate was 17.3% for 168 critically ill patients in Canada, 50 of whom were children, and 119 of whom had pneumonia [3]. The median interval between onset of influenza symptoms and admission to the hospital was three days for US patients and four days for Canadian patients.

In Japan, the total number of patients hospitalised for 2009 pandemic influenza A(H1N1) between 8 May 2009 (the first reported case [4]) and 31 March 2010 was 17,646 [5]. The Japanese population was 127,510,000 as of 1 October 2009 [6]. Therefore, the calculated hospitalisation rate was 0.014%. A survey of influenza virus A(H1) in Japan revealed that the epidemic peak of the season 2009-10 was earlier than that of previous years. In a normal year in Japan, the epidemic season of influenza is from week 47 to week 12 of next year [7] (Figure 1). An overwhelming number of patients were reported this season compared with the previous year. As a result, this year's influenza infection was unique both temporally and quantitatively. In detail, the number of patients started increasing in week 26, surged in week 39, and peaked in week 49 of this season. Our study period was from week 36 to week 44 of 2009, the early phase of the epidemic in Japan.

Of all patients in Japan hospitalised with 2009 pandemic influenza A(H1N1), 79.2% (13,981 patients) were children (under 15 years of age) [5]; this number was higher than those reported in other countries [2,3,8]. A total of 198 deaths were caused by this influenza infection [9], including 38 paediatric cases. The hospital mortality rate for all age groups was 1.1%, which was markedly lower than 7% that reported in the US [2]. The hospital mortality rate for children was 0.27%, which was lower than that of adult cases. The Japanese Ministry of Health, Labour and Welfare reported that 1,002 cases with severe symptoms were admitted to the intensive care unit (ICU) and 763 cases required mechanical ventilation [5]. Although children are considered to be more vulnerable to pandemic influenza pneumonia, few reports describe the characteristics of this pneumonia in paediatric patients [10,11].

Figure 1

Weekly reports of influenza virus A(H1), Japan, 2005-6–2009-10



This season's epidemic peak occurred earlier than in previous years.

Table 1 - Part 1

Characteristics of children hospitalised with 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September-31 October 2009 (n=21)

Patients	Age	Sex	Previous significant medical history	Time from onset of illness to admission (hours)	Time from onset of fever up to admission (hours)	Body temperature upon admission (oC)	Duration of hospital stay (number of days)	In need of intensive care yes/no (number of days)	In need of oxygen yes/no (number of days)	In need of mechanical ventilation yes/no (number of days)	Time from onset of illness to intubation (hours)
1	4	M	-	5	5	38	7	Yes (5 days)	Yes (5 days)	Yes (4 days)	7
2	5	F	-	12	12	37.3	12	Yes (8 days)	Yes (8 days)	Yes (7 days)	12
3	7	M	F.C.	5	5	38.1	15	Yes (3 days)	Yes (11 days)	Yes (8 days)	3
4	9	M	K.D.	24	2	39.8	17	Yes (7 days)	Yes (9 days)	Yes (7 days)	0.5
5	5	M	-	14	6	37.3	6	No	Yes (4 days)	No	-
6	5	M	F.C.	8	2	38.6	6	No	Yes (5 days)	No	-
7	5	F	Asthma	12	9	38.5	9	No	Yes (7 days)	No	-
8	5	M	A.B.	24	16	39	7	No	Yes (3 days)	No	-
9	6	M	-	72	1	39	8	No	Yes (5 days)	No	-
10	6	F	Asthma	48	36	40.4	6	No	Yes (3 days)	No	-
11	6	M	Asthma	31	22	39.2	6	No	Yes (3 days)	No	-
12	7	F	A.D.	12	2	38	7	No	Yes (5 days)	No	-
13	7	F	-	24	24	38	9	No	Yes (6 days)	No	-
14	7	F	Asthma	20	5	39.4	6	No	Yes (3 days)	No	-
15	9	F	-	12	22	38.5	9	No	Yes (4 days)	No	-
16	9	M	H.D.	6	7	37.4	7	No	Yes (3 days)	No	-
17	9	M	Asthma	10	10	38	5	No	Yes (2 days)	No	-

18	9	M	Asthma	11	11	39.6	5	No	Yes (3 days)	No	-
19	11	M	Asthma	22	2	39.5	7	No	Yes (5 days)	No	-
20	12	M	A.B.	20	8	39	7	No	Yes (4 days)	No	-
21	15	M	-	24	24	40.1	3	No	Yes (1 days)	No	-
Median (range)				14 (5-72)	8.5 (0-36)	38.8 (37.3-40.4)	7 (3-17)		4 (1-9)		

Table 1 - Part 2

Characteristics of children hospitalised with 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September-31 October 2009 (n=21)

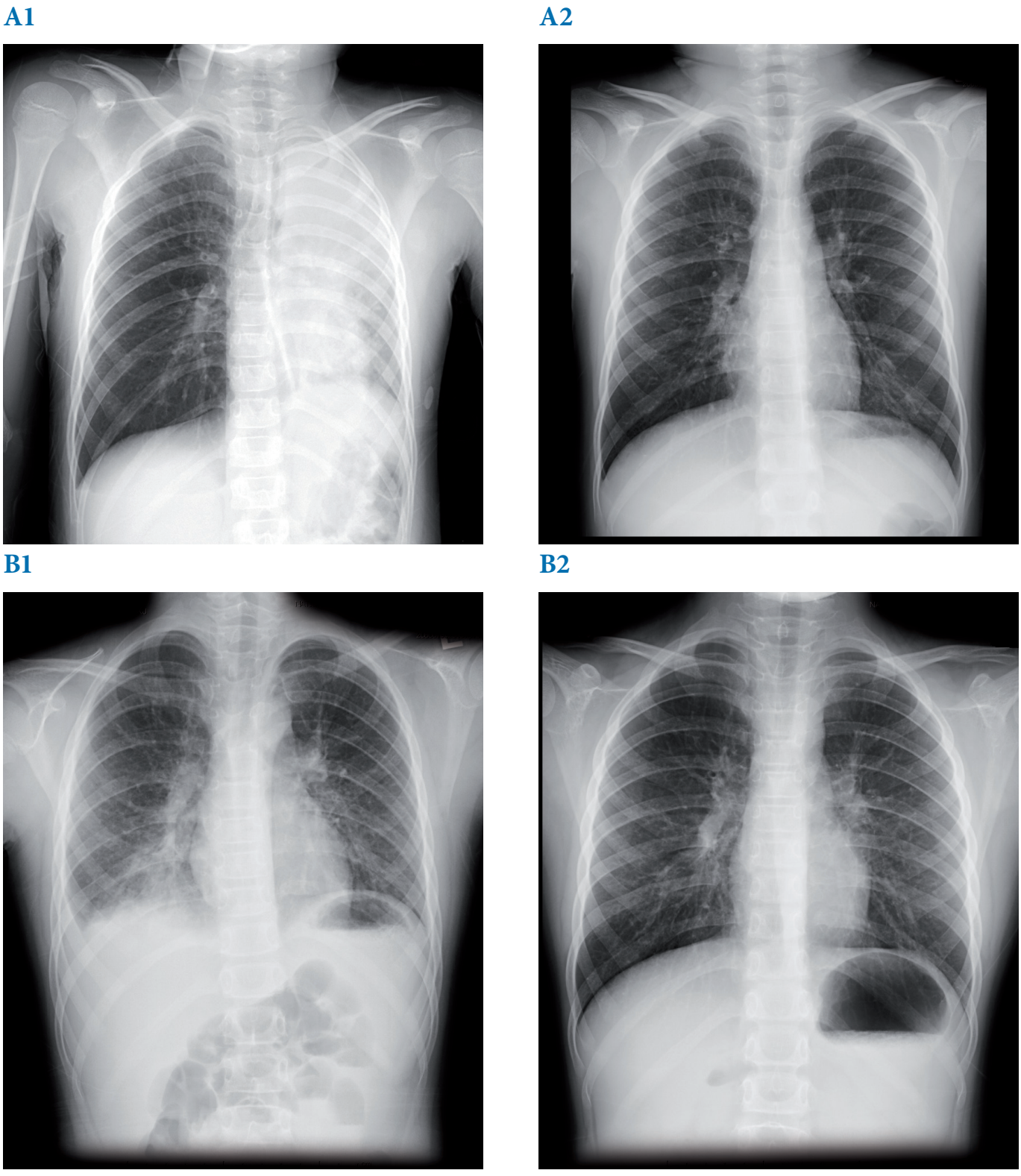
Patients	Antibiotics	Antibiotics (macrolids)	Steroid treatment	White blood cell count (/μ1) 4000-8000	Lymphocyte count (/μ1) 1500-4000	C-reactive protein (mg/d 1)<0.3	Creatine kinase (IU/L) 0-160	Lactate dehydrogenase (IU/L) 100-225	p H 7.380-7.460	p CO_2 32.0-46.0	PaO_2/FiO_2
1	ABPC/SBT	AZM	2mg/kg/day	22,300	892	5.9	543	408	7.17	84	X
2	ABPC/SBT	AZM	pulse therapy	5,400	66	7.9	872	346	7.35	43.9	X
3	ABPC/SBT	CAM	2mg/kg/day	12,100	370	2.13	76	270	7.404	35.2	X
4	PAPM/BP	AZM	pulse therapy	400	8	0.9	97	299	7.38	36.8	57.9
5	ABPC/SBT	AZM	2mg/kg/day	13,700	1,370	2.6	123	418	7.313	51	237.8
6	ABPC/SBT	AZM	2mg/kg/day	19,400	1,552	0.7	81	303	7.408	34.6	104.4
7	ABPC/SBT	AZM	2mg/kg/day	10,000	160	3.8	75	233	7.418	36.6	183.6
8	ABPC/SBT	AZM	2mg/kg/day	4,500	873	2.8	131	298	7.438	33.9	262.9
9	ABPC/SBT	AZM	2mg/kg/day	13,200	528	5.4	172	261	7.36	46.6	219.0
10	CLDM	AZM	2mg/kg/day	6,400	780	6.2	126	281	7.497	28.7	375.0
11	ABPC/SBT	AZM	2mg/kg/day	12,300	233	2.3	173	335	7.388	34	104.6
12	ABPC/SBT	AZM	2mg/kg/day	17,500	350	0..3	102	286	7.391	37.5	134.4
13	ABPC	AZM	2mg/kg/day	11,600	904	4.8	215	284	7.427	34.1	X
14	ABPC/SBT	AZM	2mg/kg/day	9,600	691	3.3	194	121	7.356	27.1	346.0
15	ABPC/SBT	AZM	not used	14,170	130	2.9	125	273	X	X	X
16	CTX	AZM	2mg/kg/day	13,100	1,440	0.4	X	197	7.4	37.7	X
17	not used	AZM	2mg/kg/day	17,400	175	2.8	285	240	7.35	41.2	X
18	ABPC/SBT	AZM	2mg/kg/day	6,900	414	0.7	111	245	7.441	34.7	159.0
19	not used	AZM	2mg/kg/day	9,600	X	5.4	62	233	7.41	37.7	X
20	ABPC/SBT	AZM	2mg/kg/day	8,800	431	3.6	90	281	7.279	37.4	240.8
21	ABPC/SBT	AZM	2mg/kg/day	9,900	495	3.9	156	237	7.482	30.7	353.3
Median (range)				11,600	463	2.9	125.5	281	7.4	36.7	219.0
				(400-22,300)	(8-1,152)	(0.3-7.9)	(62-872)	(121-418)	(7.17-7.50)	(27.1-84)	(57.9-375.0)

A.B. Asthmatic bronchitis, ABPC: Ampicillin, ABPC/SBT:Ampicillin/Sulbactam, A.D. Atopic dermatitis, AZM:Azithromycin, CAM:Clarithromycin, CLDM: Clindamycin, CTX: Cefotaxime, F: female, F.C. Febrile convulsion, H.D. Hodgkin's disease, K.D. Kawasaki disease, M: male, PAPM/BP:Panipenem/betamipron, X: not measured

In our institution, we have seen 14 paediatric patients hospitalised for this viral pneumonia since the first case was admitted on 12 September 2009. The period from onset to admission is remarkably shorter than in previous reports [2,3,8,12]. Despite some serious cases requiring ventilation, no deaths occurred. In this report, we investigated clinical findings, laboratory data including chest radiography and computed

Figure 2

Typical chest radiography findings seen in two cases of 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September-31 October 2009



A1 (upper left panel): At the time of admission, patient A's left lung field volume was decreased and left upper lobe showed atelectasis. The patient's right lung had compensatory hyperinflation and the right upper lobe showed interstitial shadow enhancement. B1 (lower left panel): At the time of admission, all of patient B's lung fields showed interstitial shadow enhancement. Atelectasis and infiltration were seen in the right lower lobe. A2, B2 (right panels): Chest radiographs of both patients one month after discharge were normal.

tomography (CT) findings, and medical treatments in paediatric patients with this pandemic influenza pneumonia.

Methods

Subjects consisted of 21 consecutive children (under 15 years of age) who were hospitalised between 1 September and 31 October 2009 with pneumonia caused by 2009 pandemic influenza A(H1N1). The reason for admission was respiratory failure with hypoxia requiring oxygen inhalation in all patients. The 21 cases investigated and included in the present study were hospitalised in three neighbouring institutions in the Tokyo region, the National Defense Medical College Hospital, the National Centre for Child Health and Development, and the Kawaguchi Municipal Medical Centre.

The diagnosis of 2009 pandemic influenza A(H1N1) was based on influenza-related symptoms, such as fever, cough, joint pain, muscle pain and general fatigue, and a positive result of either of a real-time RT-PCR or a rapid influenza antigen test. The former test was performed at regional public health centres using standard primers, and the protocol was provided by the National Institute of Technology and Evaluation and the National Institute of Infectious Diseases of Japan [13]. The latter test was performed using an immunochromatography kit, ESPLINE Influenza A&B-N (FUJI REBIO Inc. Tokyo). We did not test for the presence of any other viruses. We carried out blood culture for all cases. All patients had dyspnoea combined with hypoxia. The diagnosis of pneumonia was made by auscultation and by chest radiography and CT findings.

Data were collected by retrospective review of hospital records by each physician, including clinical course, laboratory data on admission, chest radiography findings, chest CT findings, treatment, and outcome. Radiologists of each hospital provided the chest radiography and CT findings.

On chest radiographs, interstitial shadow enhancement was defined as a ground glass-like pattern (increased lung field density with visible normal bronchial/pulmonary vascular structures), and atelectasis was defined as consolidation associated with decreased volume of the affected lung segment.

Results

Patients' characteristics

The median age of the children in our study was seven years (range: 4–15 years) and the median body weight was 22.5 kg (range: 17–65 kg). Fourteen of the 21 patients were male.

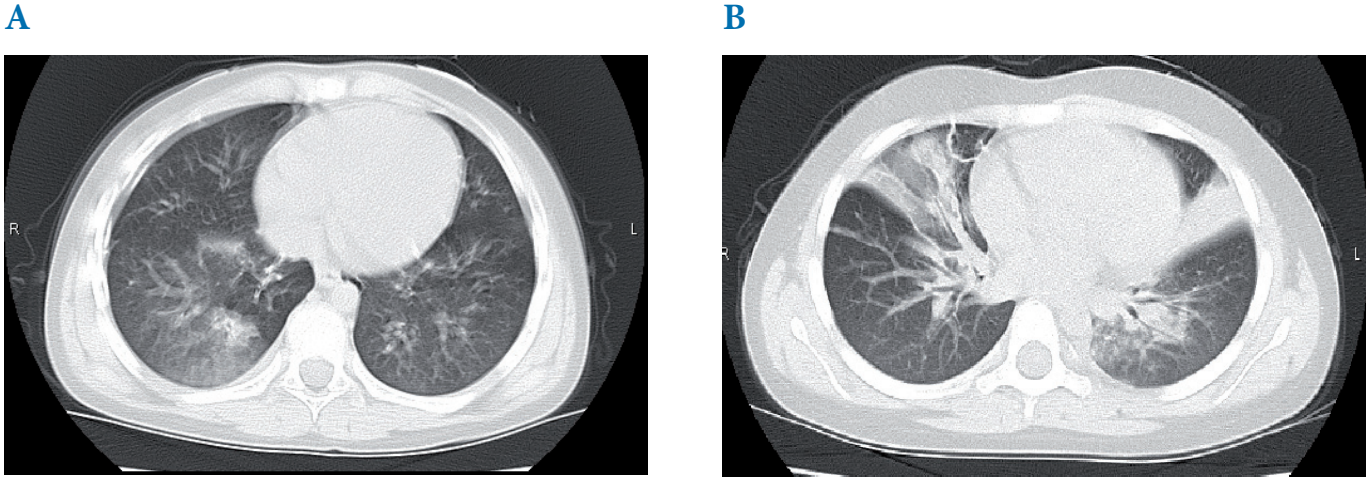
The median interval from the onset of influenza-related symptoms to admission to the hospital with respiratory failure was 14 hours (range: 5–72 hours) and the median interval from the onset of fever (≥38ºC) to hospitalisation was 8.5 hours (range: 0–36 hours). Nineteen patients were hospitalised within 24 hours of the onset of influenza symptoms, and no patient was hospitalised four or more days after onset.

At admission, all of the patients had marked dyspnoea and hypoxia. Seventeen of the 21 patients had already been given oxygen because of the hypoxia. Mechanical ventilation was required for four cases with severe respiratory failure and was initiated 0.5–12 hours after admission. The median body temperature was 38.8°C (range: 37.3–40.4°C) on admission.

The medical history included bronchial asthma in seven patients, asthmatic bronchitis in two patients, febrile convulsions in two patients, and Hodgkin's disease, Kawasaki disease, and atopic dermatitis in one patient each. Seven patients had no underlying diseases.

Figure 3

Typical chest computed tomography findings seen in two cases of 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September-31 October 2009



A (upper panel): Bilateral lung fields showed interstitial shadow enhancement. B (lower panel): Atelectasis and interstitial shadow enhancement are seen in the bilateral lung fields.

None had had previous severe influenza complications (Table 1).

Examination on admission

The rapid influenza antigen test was positive in 20 of the 21 patients. The remaining patient was proven to be positive for 2009 pandemic influenza A(H1N1) using the RT-PCR assay. All 15 patients examined by RT-PCR were positive for 2009 pandemic influenza A(H1N1). The blood cultures of all 21 patients were negative.

The median leukocyte count was 11,600/µl (range: 400–22,300/µl). The median lymphocyte count, however, was markedly decreased to 463/µl (range: 8–1,552/µl), with 17 patients having a count ‹1,000/µl. Lactate dehydrogenase (LDH) and creatine kinase (CK) levels were normal in most of the patients. The median C-reactive protein (CRP) level was 2.9 mg/dl (range: 0.3–7.9 mg/dl), showing a mild inflammatory reaction. The median arterial pH was 7.40 (range: 7.17–7.50). The median arterial partial pressure of carbon dioxide (pCO2) was 36.7 mm Hg (range: 27.1–84 mmHg), with 17 patients showing a normal value (≤45 mm Hg). The median ratio of arterial oxygen concentration to the fraction of inspired oxygen (P/F ratio), however, was decreased to 219.0 (range: 57.9–375.0), with 10 of 13 patients having lower than normal values (Table 1). In five cases, the P/F ratio was ≤200, which is one of the criteria of acute respiratory distress syndrome defined by the American-European Consensus Conference [14]. Blood cultures were negative in all patients. On chest radiographs and CT, interstitial shadow enhancements or patchy infiltrations/atelectasis were observed in all patients (Figures 2 and 3).

Treatment

All patients required oxygen. None of the patients had received the vaccination against 2009 seasonal influenza or pandemic influenza Antiviral drugs (oseltamivir) were administered to all 21 patients, 20 of whom received them within 48 hours of the onset of influenza symptoms. In addition, all patients received antibiotics and 19 received combination therapy of two antibiotics. The combination of antibiotics most frequently used, administered to 12 patients, was ampicillin/sulbactam (ABPC/SBT) and azithromycin (AZM). Furthermore, steroid therapy was given to 20 patients.

As mentioned above, four patients required mechanical ventilation; however, none of the patients received nitric oxide or extracorporeal membrane oxygenation.

Clinical course and outcome

No deaths occurred during the study period and no respiratory sequelae were observed. The median hospital stay was seven days (range: 3–17 days) and the median duration of oxygen therapy was four days (range: 1–9 days) (Table 1). Fourteen patients received physical examinations and chest radiographs at one month after discharge. No abnormal shadows were seen, nor was any deterioration of the patients' physical condition observed (Figure 2).

Discussion

We observed a large number of hospitalisations for 2009 pandemic influenza A(H1N1) pneumonia during the 2009-10 season in our hospital, while no seasonal influenza pneumonia had been observed in the previous year. There were differences to the previous sea-

Table 2

Comparison of 2009 pandemic influenza A(H1N1) virus infections in Japan in the period 1 September-31 October 2009 with reports from other countries

Patients	Australia / New Zealand	United States	Canada	Mexico	This study	Japan
Clinical setting	Intensive care	Hospitalised	Intensive care	Intensive care	Hospitalised	Surveillance hospitalised
Study period	1 June to 31 August 2009	1 May to 9 June 2009	16 April to 12 August 2009	24 March to 1 June 2009	1 September to 31 October 2009	Up to 31 March 2010
Number of total cases reported	722	272	168	58	21	17,646
Number of total cases with pneumonia	499	100	119	—	21	—
Number of paediatric cases reported	—	122 (‹18years-old)	50 (‹18 years-old)	2 (‹15 years-old)	21 (‹15 years-old)	13,981 (‹14 years-old)
Number of children with pneumonia	—	—	—	—	21	—
Time from onset of illness to admission (days, median)	4 days	3 days	4 days	6 days	0.54 days	—
Mortality rate (%)	14.30%	7%	17.30%	41.40%	0%	1.10%
Number of patients on oseltamivir treatment (%)	—	200 (75%)	152 (90%)	45 (78%)	21 (100%)	—
Number of patients provided oseltamivir 48 hours or earlier after onset of illness n (%)	—	75 (39%)	a	b	20 (95%)	—
Number of patients provided concomitant antibiotic treatment n (%)	—	206 (76%)	166 (99%)	52 (90%)	21 (100%)	—

a,b: These percentages were presumably low because median time from onset of symptoms to hospitalisation was four (a) and six (b) days.

—: not mentioned.

son not only in the number of hospitalised patients but also in the severity of their symptoms.

The pneumonia seen in this patient group was considered fulminant, because of the short interval between symptom onset and hospital admission with respiratory failure (several hours in most cases). At the present time, it is not known whether this is a new type of pneumonia or whether it is simply due to the physical characteristics of Japanese people in general, children specifically, or our medical system.

According to previous reports on 2009 pandemic influenza, the median interval between symptom onset and hospitalisation was four days (range: 2–7 days) for 722 ICU inpatients in Australia and New Zealand [12], three days (range: 0–18 days) for 272 inpatients in the US [2], four days (range: 2–7 days) for 168 critically ill patients in Canada [3], and six days (range: 4–8 days) for 58 critically ill patients in Mexico [8] (Table 2). The intervals in these reports were longer than that found of our study. A report of 13 children in the United Kingdom (UK) with serious pandemic influenza infection described that four patients were hospitalised within two days after influenza onset [10]. In seven of 36 fatal paediatric cases in the US [11], the interval between symptom onset and hospitalisation was within two days. Generally, this interval is shorter in children than in adults. According to a Japanese Paediatric Intensive Care Unit (PICU) network survey, seven of nine patients with 2009 pandemic influenza pneumonia showed dyspnoea within 24 hours from fever onset [15]. The Japan Pediatric Society reported that 15 of 19 cases of this serious pneumonia also showed respiratory failure within 24 hours from onset of fever according to a nationwide study [16]. These results suggest that a short interval from the onset of symptoms to hospitalisation may be one characteristic of paediatric patients, especially in Japan.

The 2009 pandemic influenza A(H1N1) virus shows a strong affinity for the lower respiratory tract, which is one potential reason why it takes a fulminant course [17,18]. A lack of specific antibodies to this virus, helps it to proliferate rapidly. It may be difficult for antiviral drugs to prevent proliferation of viruses in the lung if they are given after the symptoms have already progressed. However, in the late-onset type of pneumonia, early administration of antiviral agents may prevent further progression of symptoms.

Chest radiographs revealed not only diffuse interstitial changes that are usually observed in patients with viral pneumonia [19] but also patchy infiltration and atelectasis. Although patchy lesions usually suggest bacterial pneumonia [19], bacterial infection was not detected in any of our patients. Similar findings including patchy lesions of infiltration and atelectasis on chest radiography have been reported for pandemic influenza patients [20], and this feature may be a characteristic of this viral pneumonia in contrast to seasonal influenza pneumonia. The 2009 pandemic influenza virus has been reported to show a strong affinity for type 2 alveolar epithelial cells [21]. Consequently, it causes deficiency of pulmonary surfactant, a defect that may lead to chest lesions including atelectasis.

All of our patients had dyspnoea, and blood gas analysis revealed hypoxia without CO_2 retention. Similar findings have been reported elsewhere [20]. Severe lymphopenia was seen in this study (most of the lymphocyte counts were ‹1,000/µl), a finding that was already reported among serious paediatric cases in the UK [10]. There was a similar report from Mexico describing that the lymphocyte count was decreased in pneumonia patients, especially in serious cases [20]. Lymphopenia may also be characteristic of this disease. It has been reported that H5N1 influenza virus induces lymphopenia [22] and destroys lymphocytes [23], but the cause of lymphopenia associated with 2009 pandemic influenza A(H1N1) pneumonia has not been clarified.

Oseltamivir is considered ineffective if it is administered later than 48 hours after symptom onset [24]. Antiviral therapy was given to only 39% of hospitalised patients in the US within 48 hours of symptom onset [2]. This percentage was also low in critically ill Canadian and Mexican patients, with a median interval between symptom onset and hospitalisation of four days in Canada [3] and six days in Mexico [8] (Table 2). Of the 36 fatal paediatric cases in the US, only four received oseltamivir within two days of symptom onset [11]. In our study, 20 of 21patients received antiviral therapy within 48 hours of symptom onset. Since this percentage is much higher than those reported previously, early administration of antiviral agents might have improved the outcome of the pneumonia by inhibiting viral proliferation. Furthermore, none of the patients developed late-onset pneumonia that became aggravated beyond four days after influenza symptom onset. We think that our results could be due to early administration of antiviral agents (within 48 hours of onset), which is recommended in Japan [25] and is widely performed at outpatient clinics, although the seasonal influenza vaccination is optional. Therefore, late-onset type pneumonia might have been prevented, as has already been suggested elsewhere [2,3,8,12]. Early treatment with antiviral agents for outpatients and inpatients may lead to good prognoses.

Contrary to what has been reported previously [2,3,12,14,25-27], concomitant bacterial infection was not detected in our patients. We considered these cases as primary viral pneumonia, caused by a virus with high affinity for the lower respiratory tract for which the population did not have specific antibodies. These experiences might be useful information for a clinician encountering a new mutated respiratory virus infection.

None of our cases died and each had a good clinical outcome. According to other reports, the mortality rate was higher for US inpatients (7%) [2], critically ill Canadian patients (17.3%) [3] and critically ill Mexican patients (41.4%) [8] (Table 2). These differences may

be due to the fact that the other studies included both adult patients and those who were hospitalised with other complications of this virus. In addition, disease severity was not taken into consideration in these and our study As mentioned above, our good results might also be attributable to the inhibition of viral proliferation by early antiviral therapy and the prevention of secondary bacterial infection by antibiotic therapy that were applied in this study.

Conclusion

Contrary to previous reports, the Japanese children in this study had fulminant 2009 pandemic influenza A(H1N1) pneumonia. Each developed dyspnoea soon after influenza symptom onset and showed patchy infiltration and atelectasis on chest radiographs. They also had hypoxia without retention of CO2 and lymphopenia. Although four patients required mechanical ventilation, no deaths occurred. Early antiviral therapy may have caused these good results.

Limitations

The limitations of this study were as follows: it had a small numbers of subjects and participating institutions, all institutions were in close proximity and not widely distributed. Because three hospitals were referral central hospitals, it is unlikely that only mild cases of pandemic influenza pneumonia presented to these hospitals. Our experience may be not representative of Japan, but similar characteristics were showed at a clinical meeting in Japan. The follow-up period was short, and treatment efficacy was not assessed by a randomised control. We did not test for other viruses.

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