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Fatal and mild primary dengue virus infections imported to Norway from Africa and south-east Asia, 2008-2010

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Between 2008 and 2010, eight cases of viraemic dengue fever in travellers were diagnosed in Norway. They had returned from Eritrea, Thailand and Indonesia. All cases were primary dengue infections, seven non-complicated dengue fever and one dengue shock syndrome with a fatal outcome. Four patients were infected with dengue virus serotype 1, one with type 2 and three with type 3. Two cases from Thailand, the fatal case and the two imported from Eritrea were infected with type 1.

Introduction

Global incidence of dengue fever has increased strongly in recent decades, and dengue infections are now endemic in more than 120 countries throughout the world [1-3]. South-east Asia is the most important region of origin for the import of dengue fever into Europe [4]. In recent years, dengue virus has become a more prevalent cause of imported fever in Norwegian patients than malaria. Due to this increase, the Norwegian Institute of Public Health (NIPH) has recently proposed to the health authorities to make dengue fever a notifiable disease. Most cases diagnosed in Norway have been mild, but there have also been several cases with complicated dengue infections, including one fatal case in 2005 [5].

Of all dengue cases confirmed at the NIPH, we describe here the eight viraemic cases imported to Norway between 2008 and 2010.

Case descriptions

The eight viraemic cases reported in Norway between 2008 (n=1), 2009 (n=1) and 2010 (n=6), were imported from Eritrea (n=2), Thailand (n=4) and Indonesia (n=2). The patient's ages ranged from 19 to 65 years, five females and three males. None of the cases had evidence of previous dengue virus infection based on their medical history and serological evidence. Seven of the cases had non-complicated dengue fever, but

one patient suffered from dengue shock syndrome with a fatal outcome.

The fatal case first presented to the local health centre with a febrile viral influenza-like illness four days after returning from Thailand [6]. Nine days after returning, the patient visited the emergency centre as no relief was obtained from using paracetamol and ibuprofen, but returned home to continue ibuprofen treatment. Twelve hours later the patient was admitted to the intensive care unit, but was then suffering from circulatory collapse and died within a few hours. During the resuscitation attempts there was abnormal bleeding from the endotracheal tube and needle injection sites. Laboratory results showed a fall in haemoglobin from 15 to 7 g/dL and thrombocytopenia.

Another patient returning with dengue fever from Bali was examined for airway infections due to hoarseness and nasal congestion. *Mycoplasma pneumoniae* was detected by PCR in nasopharyngeal secretions and erythromycin tablets were prescribed. Clinical characteristics of all patients and their laboratory results are displayed in the Table.

Laboratory methods

Acute phase sera were obtained from the eight patients. Cases with no previous history of dengue virus infection and acute serum negative for anti-dengue IgG were defined as primary infections. Convalescent sera were available from only three patients and were taken 18-22 days after the acute sera. The acute samples were initially tested at the local laboratory and the positive samples were then referred to the virology laboratory at the NIPH for confirmation, except for one sample which was analysed directly at the NIPH. Infection with dengue virus was initially diagnosed in seven of the travellers by Panbio Dengue Duo IgM and IgG Rapid Strip Test (Inverness Medical Innovations, Australia) or SD Bioline Dengue NS1 Antigen and IgG/IgM tests (Standard Diagnostics, South Korea). All

Characteristics of the viraemic cases of dengue fever in Norway, 2008–2010 (n=8)

	Case 1 2008	Case 2 2009	Case 3 2010	Case 4 2010	Case 5 2010	Case 6 2010	Case 7 2010	Case 8 2010
Clinical symptoms	Fever, headache, vomiting, nuchal rigidity, dyspnoea, cyanosis, hypothermia, confusion, hypotension, cardiac arrest	Fever, headache, fatigue, muscle aches, non-petechial rash	Fever, shivering, hoarseness, nasal congestion, epistaxis, non-petechial rash	Fever, headache	Fever, cough, headache	Fever, shivering, headache, arthralgias	Fever, headache, muscle aches, arthralgias	Fever
Onset of symptoms after return (days)	4	Symptoms started before return	1	2	3	2	1	1
Travel destination	Thailand	Bali, Indonesia	Bali, Indonesia	Eritrea	Thailand	Eritrea	Thailand	Thailand
Initial laboratory findings	DENV IgM+[a]	Dengue IgM(+)[a]	*Mycoplasma pneumoniae* PCR+	DENV NS1 antigen+[b]	DENV NS1 antigen+[b]	DENV NS1 antigen+[b]	DENV NS1 antigen+[b]	DENV NS1 antigen+/IgM+[b]
DENV serology	IgG- / IgM+[c]	Acute sample: IgG- / IgM+[c] Convalescent sample: IgG+ / IgM+[c]	Acute sample: IgG- / IgM-[c] Convalescent sample: IgG+ / IgM+[c]	IgG- / IgM-[c]	IgG- / IgM-[c]	IgG- / IgM-[c]	IgG- / IgM+[c]	Acute sample: IgG- / IgM+[c] Convalescent sample: IgG+ / IgM+[c]
DENV PCR+ (day of sampling after symptom debut)	PCR+ (day 9)[d]	PCR+ (day of sampling after symptom debut unknown)[d]	PCR+ (day 1)[d]	PCR+ (day 3)[d]	PCR+ (day 4)[d]	PCR+ (day 5)[d]	PCR+ (day 4)[d]	PCR+ (day 6)[d]
DENV serotype	DENV-1	DENV-2	DENV-3	DENV-1	DENV-3	DENV-1	DENV-3	DENV-1

DENV-1: dengue virus serotype 1; DENV-2: dengue virus serotype 2; DENV-3: dengue virus serotype 3

[a] Detected by Panbio Dengue Duo IgM and IgG rapid test

[b] Detected by SD Bioline Dengue NS1 Antigen, IgG and IgM test

[c] Detected by Euroimmun Indirect Immunofluorescens anti-dengue virus IgM and IgG test

[d] Detected by RT-PCR assays [7,8]

samples were further analysed at the NIPH for the presence of dengue IgG and IgM antibodies using a commercial indirect immunofluorescence assay (IFA) (Euroimmun AG, Germany) and by a reverse transcription (RT) PCR detecting the four dengue serotypes [7,8]. The virus strains were characterised by direct sequencing of the PCR-products and a phylogenetic tree was obtained by comparing these strains with other dengue virus strains available in the NCBI GenBank sequence database.

Discussion and conclusion

We have described eight cases of viraemic dengue virus primary infection imported from endemic areas to Norway in 2008 to 2010, one of them with a fatal outcome. All patients developed fever within four days after returning to Norway, and the serological analyses demonstrated that they suffered from primary dengue infections. Anti-dengue IgM antibodies were detected in acute samples from the fatal case, in addition to the dengue virus serotype 2-positive case from 2009 and two cases from 2010. During primary infection, IgM and IgG antibodies are usually detectable from respectively five and 14 days after onset of symptoms

FIGURE

Phylogenetic tree comparing published dengue viruses sequences with those from viruses isolated in Norway, 2008-2010 (n=8)
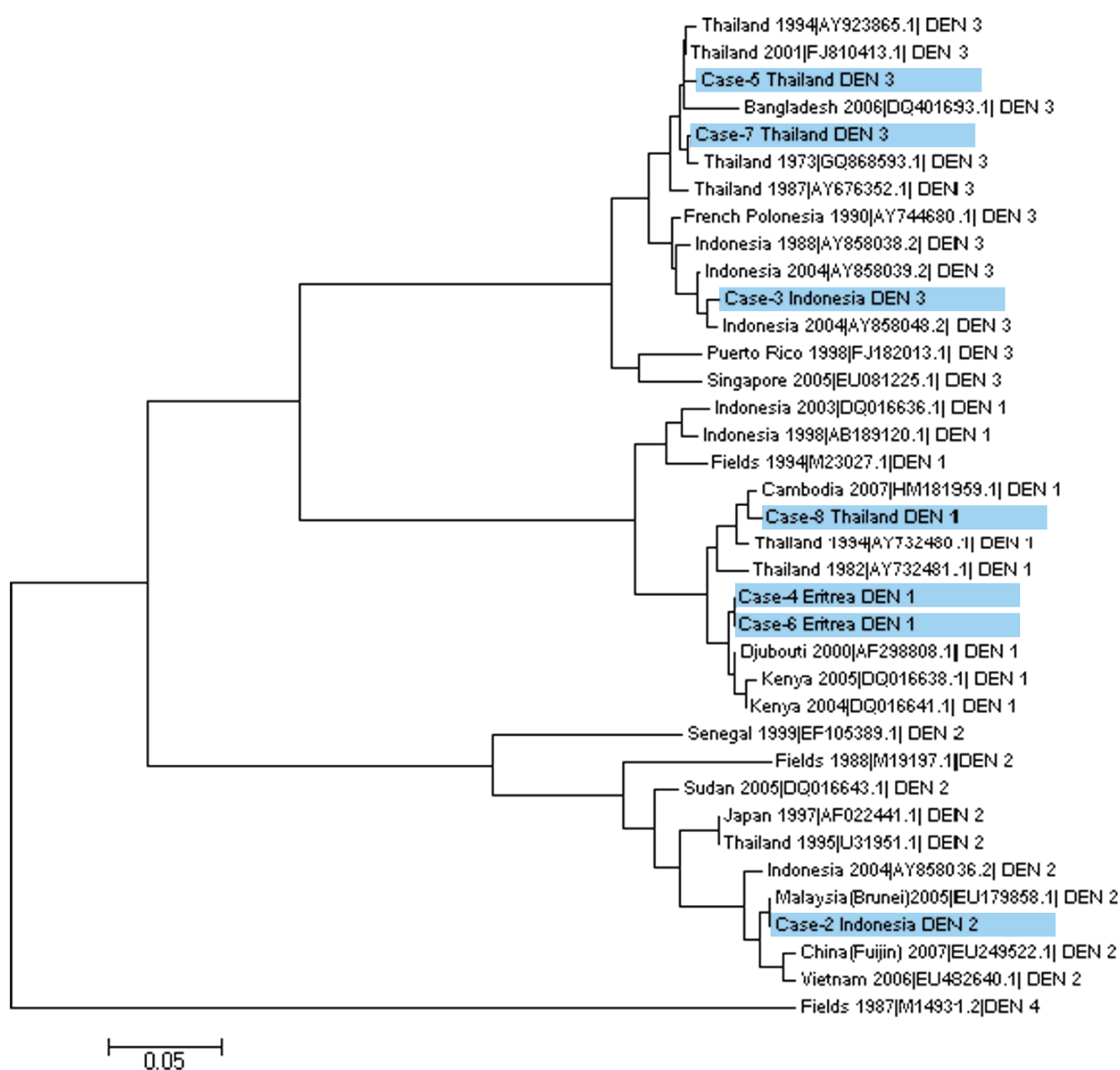
The tree is based on an approximately 300 nt fragment of the E glycoprotein gene. Sequence identification of selected dengue virus sequences is as follows: country of origin, year of isolation and NCBI GenBank accession number. The sequences determined in our study are identified by case number and country of origin. Phylogenetic analysis was conducted using MEGA 4 [12], and the tree was constructed using neighbour-joining method.

[3,9]. The fatal case highlights that fatal or severe dengue fever can also be caused by a primary infection. Severe or fatal dengue fever cases are more frequent in secondary than primary infections, but fatal primary dengue virus infection has been described in earlier reports [3,5,9].

For the reported cases, the rapid NS1 antigen tests were helpful for the initial diagnosis of dengue fever in the early phase of the disease. Our results show that dengue virus can be detected by NS1 antigen tests in patients who are negative for anti-dengue IgG and IgM.

This report shows the importance of performing dengue virus diagnostics in febrile patients returning from endemic areas even if other pathogens have been detected. Awareness of the different causes of travel-related infections and early inclusion of these in the differential diagnosis is particularly important in the context of destinations with a risk of such transmission.

Other studies have shown that most dengue virus infections diagnosed in European countries have been imported from Asia or the Americas, and in these regions all four dengue virus types have been shown to circulate [9,10]. Six of our study cases had returned from south-east Asia with dengue virus infection caused by virus serotype 1, 2 or 3. Import of dengue virus serotype 4 into Norway has so far not been reported.

Two of the cases in this study were imported from Eritrea, where only one dengue virus serotype 3 isolate has been reported earlier [10]. This country is not a specifically popular destination for Norwegian travellers and we are not aware of a concurrent outbreak in Eritrea. To date, there have been few reports of viraemic dengue fever cases imported into Europe from Africa. This may be due to underreporting in some African countries, as well as lack of adequate diagnostic tools [11]. Dengue surveillance is poorly implemented in Africa and surveillance of febrile travellers returning to Europe will add new knowledge on dengue virus distribution throughout Africa.

A comparison of sequences obtained in this study and from studies published elsewhere, are shown in the phylogenetic tree (Figure). In general, the sequence similarity between isolates of one dengue serovirus type was greater than 95%. The dengue virus serotype 1 isolates from Eritrea were closely related to dengue virus serotype 1 isolated in Kenya in 2004-5. Similarly, the dengue virus serotypes 1, 2 and 3 imported from south-east Asia in our study clustered together with the respective serotypes reported from this area earlier. To our knowledge, only few reports of dengue virus serotype 1 isolates from East Africa have been published [10], and this study provides evidence that this serotype 1 is circulating in this area.

Our report confirms that returning travellers may serve as sentinels for local outbreaks of dengue fever in endemic areas. The worldwide surveillance of dengue virus requires simple and accurate methods for the identification of virus types and is especially important since air travellers move quickly between endemic and non-endemic regions, allowing introductions of dengue virus to new areas that already are populated with *Aedes* mosquitoes.

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Public health advice based on routine mumps surveillance in England and Wales

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In view of the increase in the number of mumps cases in 2009 and of the reports of mumps outbreaks in 2010, we report on the most recently available mumps surveillance data in England and Wales.

Background

Most industrialised countries have had long-standing mumps immunisation programmes. Despite achieving relatively high coverage with one or even two doses of vaccine, several countries, including the United Kingdom (UK), have reported outbreaks of mumps, usually amongst older teenagers in settings such as universities and schools, in recent years [1]. In some outbreaks, populations have been highly vaccinated [2-7].

Several mumps outbreaks have been reported in the UK during 2009–2010. The UK introduced a mumps vaccine with the start of the single-dose

measles-mumps-rubella (MMR) programme in 1988. There was, however, a large outbreak of mumps in 2005 in England and Wales mainly affecting individuals aged between 18 and 24 years who were not eligible for routine MMR vaccination, but who had also had minimal exposure to mumps during childhood due to the reduction in number of cases following the introduction of the MMR vaccine programme [2]. There were 43,378 confirmed mumps cases in 2005. Although there was a subsequent decline in case numbers for a couple of years, the number of confirmed mumps cases started to increase again in 2008 and a further increase was observed in 2009, with cases again mainly occurring in school or college settings where there is high potential for transmission due to close contact . This alone is, however, unlikely to be the sole reason for the current increase in mumps cases. Increasingly, mumps outbreaks in populations with high vaccination coverage are being reported [3-6]. Waning immunity leading

FIGURE 1

Age-specific clinical notifications of mumps cases (five-week moving averages), England and Wales, week 1 1995 – week 33 2010
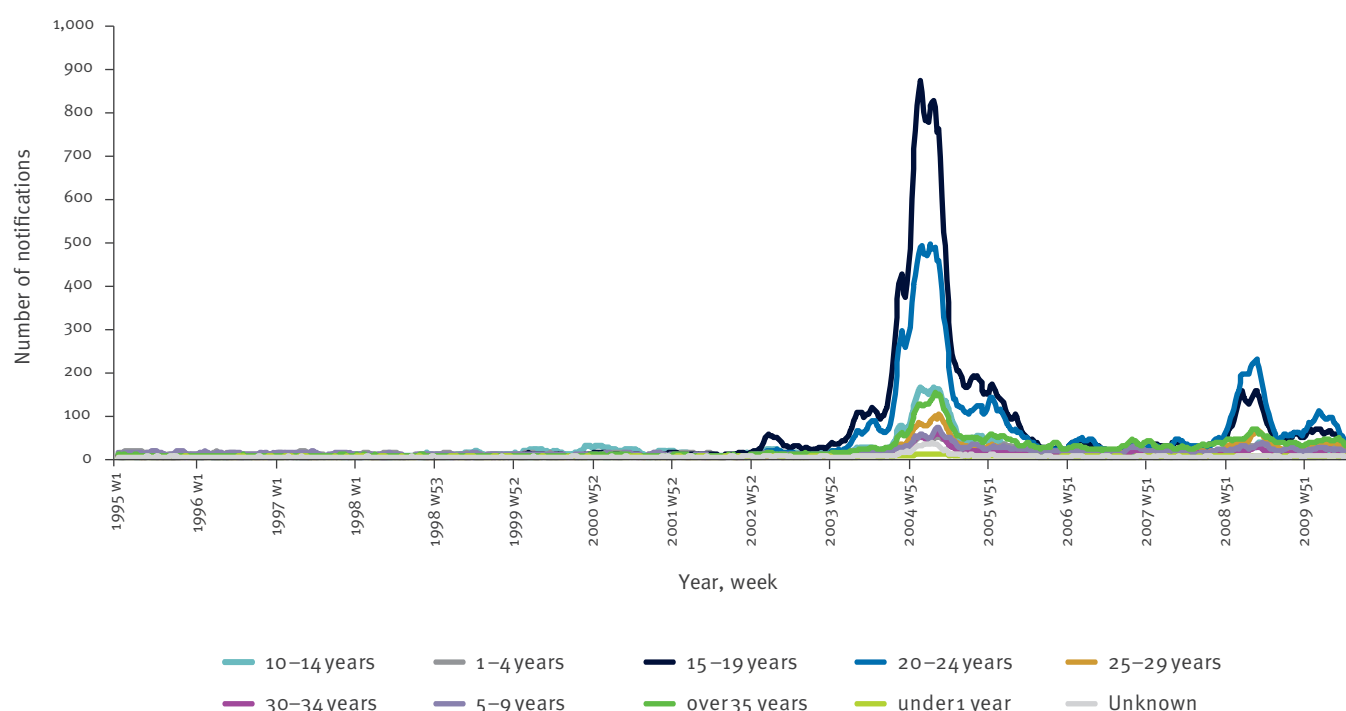
to secondary vaccine failure is likely to contribute to these outbreaks [7,8].

Methods

In England and Wales, mumps is a notifiable disease and hence must be reported to the appropriate officer (an official working in the local health authority). Following notification of a suspected case, a confirmatory oral fluid testing kit is sent out to the patient's general practitioner. Vaccination status is requested on the sample form. All oral fluid samples are tested in the Immunisation and Diagnosis Unit, Virus Reference Laboratory, Centre for Infections, Health Protection Agency (HPA), London. Once cases are laboratory confirmed, an enhanced surveillance form is sent out to request further epidemiological data, including confirmation of vaccination status and number of doses administered. The system is based on a voluntary return of surveillance forms, with a return rate greater than 50%.

Mumps vaccination status combines information from both the sample request form and the enhanced surveillance of laboratory-confirmed cases. A case with no documented evidence from either source as being vaccinated is assumed to be unvaccinated (27% of cases had unknown mumps vaccination status).

Results

Following a large outbreak in 2004 and 2005, there has been a further increase in mumps cases in 2008 and 2009 (Figure 1). During the first quarter of 2010, there was a small increase in notifications of mumps by clinicians compared with the previous quarter in 2009 (3,786 versus 3,009 cases). There is now a downward trend in the second quarter of 2010 (Figure 1 and 2).

FIGURE 2

Age and MMR vaccination status of laboratory-confirmed mumps cases, England and Wales, Quarter 1 and Quarter 2, 2010 (n=2,680)
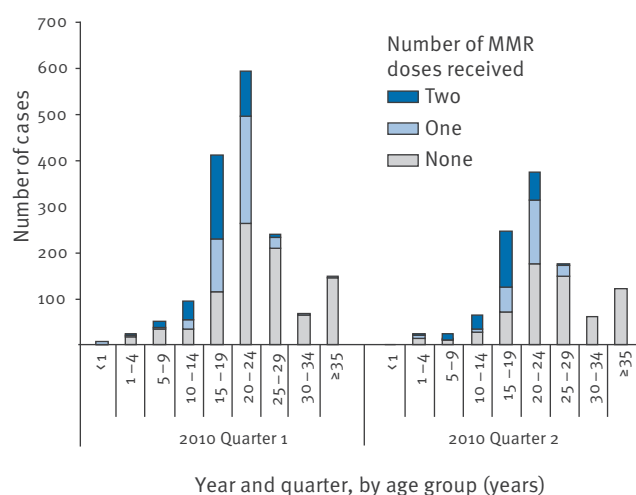
MMR: measles-mumps-rubella.

Laboratory data also show a similar downward trend, with 1,074 cases in the second quarter of 2010 compared with 1,606 cases in the first. This compares with 1,691 and 3,271 laboratory-confirmed cases in the first and second quarters of 2009 respectively.

Analysis of confirmed mumps cases in the first half of 2010 shows that the 20–24-year age group is most affected (35.9%; 962 of 2,680 cases) followed by the 15–19-year-olds (24.4%; 654 of 2,680 cases) (Figure 2). There were slightly more male (51.5%) than female cases (47.6%).

In both age groups with the highest number of cases (cases aged 15–24 years), only 28.8% (n=466) of 1,616 cases had received two doses of MMR vaccine. In total, the majority of all confirmed cases being reported were still either unvaccinated (55.3%; 1,481 of 2,680) or had received only one dose of MMR vaccine (23.3%; 625 of 2,680).

Discussion

There was an increase in the number of mumps cases in the first quarter of 2010 compared with the final quarter in 2009, but this increase did not continue into the second quarter. The number of confirmed mumps cases for the first six months of 2010 (2,680 cases) was much lower than in the same period of last year, when there had been a steep increase (4,962 cases). The observed increase in the number of confirmed cases of mumps in 2009 and 2010 had not been seen in the three preceding years.

The main limitation of analysing confirmed cases in a timely manner is that delays in receipt of samples or testing could result in underestimation of cases. However, clinical notifications, which though less specific, do reveal a trend in a timely manner, which can help in the interpretation of confirmed cases. The fall in clinical notifications of mumps cases in the second quarter of 2010 suggests that the similarly lower number of confirmed cases in this period is a real effect and is not due to the inherent reporting delays. The other possible limitation is the assumption that cases with missing vaccination status are unvaccinated, which could potentially overestimate the proportion of cases that are unvaccinated. However, we think this is unlikely, as the proportion of cases with missing vaccination status is not different by either age or region compared with those with known vaccination status.

It is clear from the data presented that the surge in mumps cases following clusters in educational settings in the early half of 2009 did not occur in 2010. As we now move from the third quarter and school summer holidays, we are not expecting this situation to change.

The majority of mumps cases are from the 15-24-year age group: the majority of cases in this age cohort had received either no MMR vaccine or only one dose. Most of the 15-19-year age group would have been eligible

to receive two doses MMR vaccine. The 20-24-year age group was eligible for one dose of MMR but is unlikely to have received the second dose of MMR, which was only introduced in the UK in 1996. The recommended schedule to ensure optimum protection against mumps is two doses of MMR vaccine. It thus remains important to ensure that all individuals, in particular school leavers and those at highest risk aged between 15 and 24 years, have two documented doses of MMR vaccine. Any opportunity to check this should be undertaken to reduce the likelihood of another increase in mumps cases in the future – in particular this can be done at school leaving and also entry into college, university or other higher education institutions. The same rationale should be applied in other European settings.

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Risk factors for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April – December 2009

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We describe the clinical and epidemiological characteristics of patients hospitalised with confirmed 2009 pandemic influenza A(H1N1) in Spain from April to December 2009 and the risk factors associated with a worse outcome (admission to an intensive care unit or death) in adults. Case-based epidemiological information was collected as part of the national strategy for the surveillance of severe cases. Of 3,025 patients, 852 were admitted to an intensive care unit and overall, 200 died. The median patient age was 38 years (range: 0–94). A total of 662 (26%) patients had no underlying risk conditions. Antiviral therapy was initiated within 48 hours after symptom onset in only 35.2% (n=711); the median length of time before treatment was four days. In a multivariate analysis, the start of antiviral therapy more than 48 hours after symptom onset (odds ratio (OR) 2.39; 95% confidence interval (CI): 1.79 to 3.2), morbid obesity (OR: 2.01; 95% CI 1.38 to 2.94), cardiovascular disease (OR: 1.79; 95% CI: 1.2 to 2.67) and chronic obstructive pulmonary disease (OR: 1.51; 95% CI: 1.03 to 2.2) were significantly associated with a worse outcome in adults.

Introduction

On 25 April 2009, the World Health Organization (WHO) declared the outbreak of the new influenza A(H1N1) viral infection, previously reported by the United States [1] and Mexico [2], a public health emergency of international concern under the International Health Regulations (2005) [3]. On 11 June 2009, WHO raised the pandemic alert level to phase 6 [4]. At the end of 2009, human infection with the pandemic virus had been reported in almost the whole world [5].

Following a previous alert issued by WHO on 24 April 2009 [6], Spain issued a national epidemiological alert and, on 27 April, reported the first laboratory-confirmed case of the 2009 pandemic influenza A(H1N1) in Europe [7]. On 26 June, in view of the evolving situation, the transition in Spain from containment to mitigation strategies, and under the new pandemic phase, a new national surveillance strategy was approved by the Public Health Commission of the Spanish Ministry of Health. One of the objectives of this surveillance was to detect severe influenza cases, identify their clinical, epidemiological and virological characteristics and assess their impact on the healthcare system. This *ad hoc* surveillance strategy was built on top of the existing Spanish National Surveillance Network, which covers all Spanish territory and has been in place since 1995. In addition to this surveillance strategy, the evolution of the pandemic was monitored through the influenza sentinel surveillance system and the investigation and follow-up of influenza outbreaks by regional health authorities.

The overwhelming majority of people infected worldwide with the 2009 pandemic virus have experienced uncomplicated influenza-like illness, with full recovery even without medical treatment [8]. However, it is still necessary to improve our knowledge of the epidemiological characteristics of small subsets of patients with very severe pulmonary complications [9-11]. Furthermore, while people with certain underlying medical conditions are known to be at increased risk for seasonal influenza complications, new risk factors, such as morbid obesity, have been suggested to be associated with pandemic influenza severity [12-14].

In this report, we describe the demographic characteristics, presence of risk factors, clinical findings and treatment of the first 3,025 patients who were hospitalised in Spain for severe pandemic influenza and notified to the Spanish Ministry of Health and Social Policy by the National Surveillance Network from 24 April 2009 to 15 December 2009. We also analyse the risk factors associated with a worse outcome (admission to an intensive care unit (ICU) or death) in adults.

Methods
Inclusion criteria
Eligible patients included all adults and children admitted to any hospital in Spain with laboratory confirmation of 2009 pandemic influenza A(H1N1) infection from 24 April to 15 December 2009. The national health system defines paediatric patients as those under the age of 15 years. The initial case definition for severe 2009 pandemic influenza A(H1N1) disease included, among other criteria, severe respiratory infection or death by acute respiratory disease of unknown aetiology. Since June 2009, a specific case definition for severe cases has been adopted as part of the strategy for the surveillance of severe cases and has been applied to the whole country by the National Surveillance Network. Suspected severe cases were those:

- with clinical features compatible with influenza requiring hospitalisation for clinical severity;

- who developed these clinical features during hospitalisation for another reason; or
- with severe pneumonia admitted to ICUs in the absence of a known cause.

Diagnostic testing was clinically driven. All cases were confirmed by a specific reverse transcription-polymerase chain reaction (RT-PCR) for 2009 pandemic influenza A(H1N1) virus at either the national or regional reference laboratories. These laboratories were accredited by the national reference laboratory (the National Centre for Microbiology).

Data collection
This study was conducted as part of the routine activities in the institutions concerned, both at national and regional level. Data were collected by either

TABLE 1

Characteristics and underlying conditions of reported hospitalised patients with 2009 pandemic influenza A(H1N1) infection by outcome, Spain, 24 April – 15 December 2009 (n=3,025)

Patient details	Patients not admitted to an ICU and who survived n=2,134	Patients admitted to an ICU or who died n=891	p value[c]
	Percentage (Number/Total)[a,b]	Percentage (Number/Total)[a,b]	
General characteristics			
Median age	37 years (range: 0–94)	41 years (range: 0–92)	<0.001
Female	45.6 (970/2,129)	45.2 (402/890)	0.873
Current smoker[d]	32.1 (313/974)	34.5 (183/531)	0.012
Underlying conditions[e]			
Any chronic pulmonary disease	35.5 (687/1,933)	34.8 (281/807)	0.726
Asthma	22.7 (362/1,594)	14.5 (101/698)	<0.001
COPD	11.5 (183/1,588)	16.9 (122/722)	<0.001
Morbid obesity[d,f]	11.1 (120/1,080)	19.3 (119/616)	<0.001
Diabetes	9.4 (157/1,676)	13.8 (108/780)	<0.001
Other metabolic disease	8.8 (116/1,313)	11.5 (74/644)	0.001
Pregnancy[g]	15.0 (61/407)	15.8 (29/184)	0.806
Cancer	7.4 (123/1,653)	8.5 (66/779)	0.373
Immunodeficiency	10.2 (168/1,644)	12.4 (97/783)	0.110
Cardiovascular disease[h]	9.6 (159/1,657)	16.1 (125/778)	<0.001
Chronic hepatic disease	6.1 (81/1,322)	9.0 (59/657)	0.025
Haemoglobinopathy or anaemia	4.6 (59/1,276)	5.7 (36/632)	0.316
Cognitive dysfunction	6.3 (80/1,273)	8.9 (57/640)	0.039
Seizures	3.4 (53/1,573)	6.5 (49/751)	0.001
Chronic renal insufficiency	4.1 (52/1,283)	7.3 (47/644)	0.003
Asplenia	0.7 (9/1,269)	0.3 (2/627)	0.357
Neuromuscular disease	4.1 (52/1,260)	4.9 (31/627)	0.407
Treatment with aspirin	2.5 (31/1,242)	3.9 (24/613)	0.109

COPD: chronic obstructive pulmonary disease; ICU: intensive care unit.

[a] Unless otherwise indicated.

[b] The number is the number of patients with a particular condition. The total is the total number of patients for whom the condition was recorded.

[c] Comparison of patients not admitted to an ICU and who survived with patients admitted to an ICU or who died.

[d] Children under 15 years (n=605) were excluded from the analysis of this variable.

[e] Conditions listed are not mutually exclusive: some patients had multiple underlying conditions.

[f] Defined as body mass index of or greater than 40. Body mass index was calculated as weight in kilograms divided by the square of the height in metres.

[g] Data calculated using the number of female cases of reproductive age (15–44 years) as denominator. One pregnant case was not included because she was under 15 years.
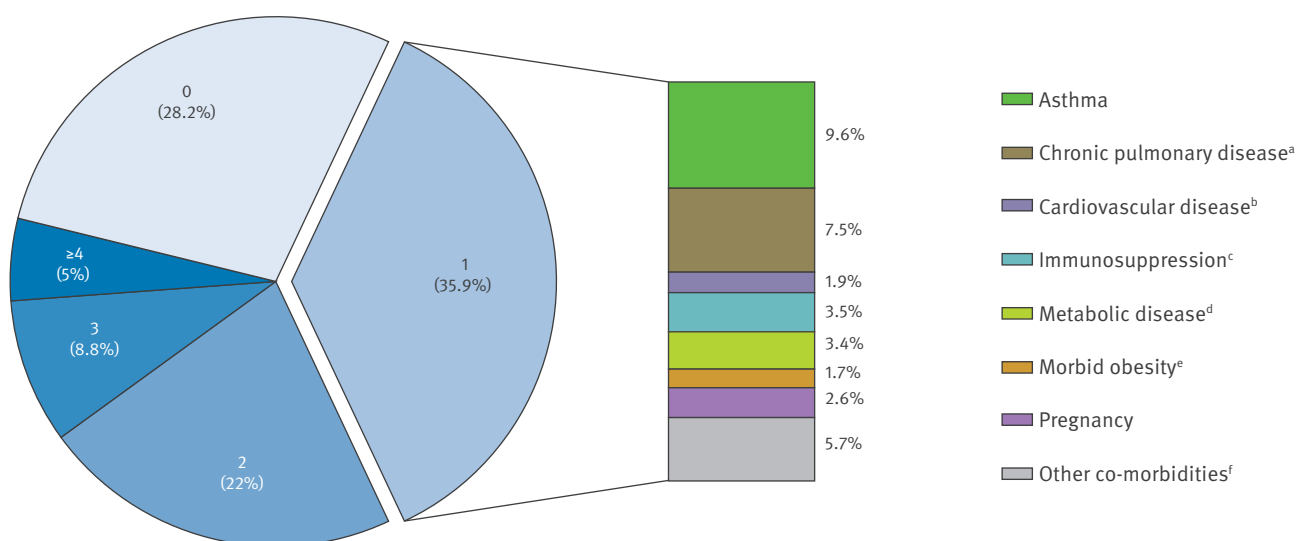
[h] Excludes hypertension.

infection-control physicians at hospitals or medical epidemiologists at local public health departments, as recommended by the national surveillance strategy for severe cases. Case-based information was gathered at the Coordinating Centre for Health Alerts and Emergencies at the Ministry of Health and Social Policy,
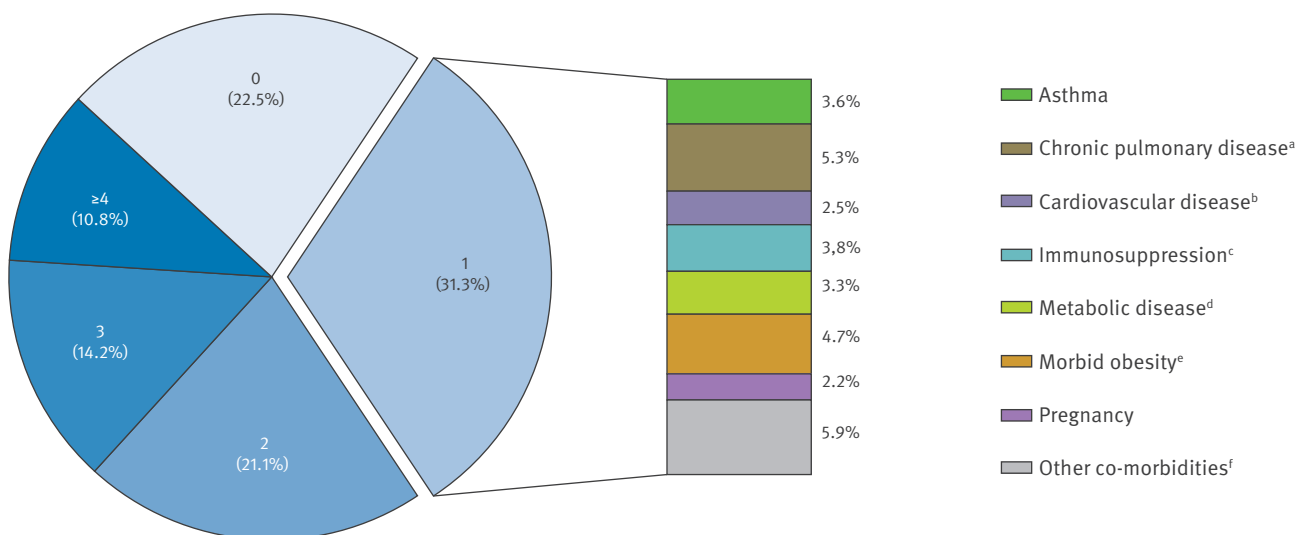
Number of co-morbidities of reported hospitalised patients with 2009 pandemic influenza A(H1N1) infection by outcome, Spain, 24 April – 15 December 2009 (n=2,058)

Number of co-morbidities (percentage of patients) in patients not admitted to an ICU and who survived (n=1,722)

Segment	Percentage
Asthma	9.6%
Chronic pulmonary disease[a]	7.5%
Cardiovascular disease[b]	1.9%
Immunosuppression[c]	3.5%
Metabolic disease[d]	3.4%
Morbid obesity[e]	1.7%
Pregnancy	2.6%
Other co-morbidities[f]	5.7%

Number of co-morbidities (percentage of patients) in patients admitted to an ICU or who died (n=786)

Segment	Percentage
Asthma	3.6%
Chronic pulmonary disease[a]	5.3%
Cardiovascular disease[b]	2.5%
Immunosuppression[c]	3,8%
Metabolic disease[d]	3.3%
Morbid obesity[e]	4.7%
Pregnancy	2.2%
Other co-morbidities[f]	5.9%

ICU: intensive care unit.

[a] Includes chronic obstructive pulmonary disease.

[b] Excludes hypertension.

[c] Includes cancer, asplenia and immunodeficiency.

[d] Includes diabetes.

[e] Defined as body mass index of or greater than 40. Body mass index was calculated as weight in kilograms divided by the square of the height in metres (adults only).

[f] Other co-morbidities include chronic hepatic disease, haemoglobinopathy and anaemia, cognitive dysfunction, seizures, chronic renal insufficiency, neuromuscular disease and treatment with aspirin.

where it was reviewed and analysed. All cases were identified through the National Surveillance Network.

A standardised clinical form was used to collect demographic data (age and sex), underlying risk conditions for severe influenza, clinical characteristics, disease outcome and complications, treatment course and time course of illness.

Underlying risk conditions included all chronic diseases and conditions that constitute an indication for seasonal influenza vaccination in Spain, including pregnancy [15]. Current smoking status, cognitive dysfunction and body mass index (BMI) were also recorded. The last two were included based on data from other studies [12,16,17]. In this study, we report information on morbidly obese adults (with a BMI≥40).

Disease outcome included three possible options: patients who were not admitted to an ICU and who survived; patients who were admitted to an ICU and patients who died. The last two categories were joined (admitted to an ICU or death) and were considered as the worst outcome for this analysis.

Data analysis
Information on each underlying risk condition was analysed and described independently. All percentages were calculated using the number of patients with available data as denominator. For pregnancy, proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (15–44 years). An additional variable, the number of co-morbidities, was created, taking into account the number of underlying risk conditions associated with severe influenza reported for each patient. For this analysis, morbid obesity and cognitive dysfunction were

TABLE 2

Characteristics and underlying conditions of reported hospitalised patients with 2009 pandemic influenza A(H1N1) infection by age group, Spain, 24 April – 15 December 2009 (n=3,022)[a]

Patient details	Patients aged <15 years n=605	Patients aged 15–64 years n=2,092	Patients aged >64 years n=325	p value[c]
	Percentage (Number/Total)[b]	Percentage (Number/Total)[b]	Percentage (Number/Total)[b]	
General characteristics				
Female sex	41.7 (252/604)	46.5 (970/2,087)	46.2 (150/325)	0.114
Current smoker[d]	NA	37.6 (510/1,355)	15.3 (32/209)	<0.001
No co-morbidities	39.4 (180/457)	26.6 (465/1,747)	5.3 (16/300)	<0.001
At least two co-morbidities	23.6 (108/457)	38.2 (668/1,747)	67.7 (203/300)	<0.001
Underlying conditions[e]				
Any chronic pulmonary disease	33.6 (182/542)	33.5 (633/1,892)	50.5 (153/303)	<0.001
Asthma	24.7 (113/458)	20.2 (320/1,585)	12.1 (30/247)	<0.001
COPD	0 (0/450)	13.0 (208/1,595)	36.9 (97/263)	<0.001
Morbid obesity[d,f]	NA	14.1 (207/1,471)	14.2 (32/225)	0.918
Metabolic disease	3.3 (17/515)	14.6 (272/1,857)	39.6 (118/298)	<0.001
Diabetes	0.8 (4/472)	9.9 (169/1,707)	33.5 (92/275)	<0.001
Immunosuppression[g]	8.0 (29/364)	19.6 (272/1,385)	28.6 (66/231)	<0.001
Cardiovascular disease[h]	3.9 (18/462)	8.6 (146/1,699)	44.0 (120/273)	<0.001
Neuromuscular disease	7.7 (28/364)	3.7 (48/1,315)	3.4 (7/207)	0.003
Cognitive dysfunction	9.8 (35/358)	6.3 (84/1,341)	8.5 (18/213)	0.054
Seizures	9.0 (40/446)	3.5 (57/1,627)	2.0 (5/250)	<0.001
Chronic hepatic disease	1.9 (7/376)	8.9 (122/1,377)	4.9 (11/225)	<0.001
Haemoglobinopathy or anaemia	2.7 (10/366)	5.0 (67/1,327)	8.4 (18/214)	0.010
Chronic renal insufficiency	0.8 (3/366)	4.5 (61/1,342)	16.1 (35/218)	<0.001
Treatment with aspirin	1.7 (6/355)	2.1 (27/1,289)	10.5 (22/210)	<0.001

COPD: chronic obstructive pulmonary disease; NA: not applicable.

[a] Data on age were missing for three patients.

[b] The number is the number of patients with a particular condition. The total is the total number of patients for whom the condition was recorded.

[c] Comparison of patients by age group.

[d] Children under 15 years (n=605) were excluded from the analysis of this variable.

[e] Conditions listed are not mutually exclusive: some patients had multiple underlying conditions.

[f] Defined as body mass index of or greater than 40. Body mass index was calculated as weight in kilograms divided by the square of the height in metres.

[g] Includes cancer, asplenia and immunodeficiency.

[h] Excludes hypertension.

considered as risk conditions whereas status as a current smoker was not. Co-morbidities were considered to be absent in patients for whom information on all underlying risk conditions was complete and reported as absent. If one or more underlying risk conditions were reported present, the number of co-morbidities would be the sum of these underlying conditions.

For time calculations, the day of admission was considered to be hospital day 0. Length of stay was calculated as the time from day 0 to day of discharge or death; cases still in hospital when data were extracted for analysis (15 December 2009) were classified as missing for this variable.

We performed a bivariate analysis to compare the risk factors among patients who were not admitted to an ICU and who survived with those among patients who either were admitted to an ICU or who died. The Mantel–Haenszel chi-square test (or Fisher's exact test when appropriate) was used to compare discrete variables and the Wilcoxon rank-sum test to compare continuous variables. The statistical tests were two-sided. We used multivariate logistic regression models to further investigate associations with a worse outcome using those variables that were significant ($p<0.05$) in the bivariate analysis of data from adults. The multivariate logistic regression analysis was only performed for adults because of the different type and distribution of underlying conditions in children.

Ethical aspects
Both the surveillance protocol and standardised clinical form were approved by the Public Health Board of the Spanish Ministry of Health and Social Policy. Our study was determined to be part of the public health response to the 2009 influenza pandemic and therefore no explicit ethical evaluation was necessary.

Results
From 24 April to 15 December 2009, a total of 3,025 severe cases of 2009 pandemic influenza A(H1N1) were notified to the Coordinating Centre for Health Alerts and Emergencies from the whole country. The first severe case reported was admitted to hospital on 12 June 2009 and the last on 5 December 2009. Of the 3,025 patients we studied, 852 required admission to an ICU. Overall 200 patients died, of whom two died before being admitted to hospital.

Demographic characteristics
The median age of the patients was 38 years (range: 0–94 years). There was a significant difference ($p<0.001$) between the median age of those who were not admitted to an ICU and who survived (37 years) and the median age of those who were either admitted to an ICU or who died (41 years). Overall, 605 (20%) of the patients were children under 15 years and 325 (10.7%) were aged 65 years or older. Patients aged under two years represented 5.5% of all severe cases and 27.3% of paediatric cases. Of the patients requiring admission to an ICU (n=852), 15.4% (n=131) were children and 11.2% (n=95) were over 64 years.

Of 3,019 patients, 1,372 (45.4%) were female and 91 were pregnant (15.2% of female patients of childbearing age). Information on gestational duration was available for 74 patients: 39 were in the third trimester

Patient details	Patients not admitted to an ICU and who survived n=2,134		Patients admitted to an ICU or who died n=891	
	Number of patients[a]	Median number of days (IQR)[b]	Number of patients[a]	Median number of days (IQR)[b]
Time course of illness				
Interval between symptom onset and hospital admission[c,d]	1,997	3 (1–5)	796	3 (2–6)
Interval between hospitalisation and ICU admission	NA	NA	811	0 (0–1)
Length of stay in hospital[c,d]	1,618	5 (3–7)	643	12 (7–21)
Length of stay in an ICU	NA	NA	608	6 (3–14)
Duration of clinical illness[d]	1,573	8 (6–11)	636	17 (11–25.75)
Antiviral treatment				
Patients receiving any antiviral treatment	1,961	90.1%	818	92.2%
Patients treated within 48 hours after symptom onset[d]	1,465	39.2%	555	24.5%
Interval between symptom onset and start of treatment[d]	1,465	3 (2–5)	555	5 (3–7)
Duration of antiviral treatment[d]	1,107	5 (4–5)	322	5 (4–9)

ICU: intensive care unit; IQR: interquartile range; NA: not applicable.

[a] Number of patients for whom this information was recorded.
[b] Unless otherwise indicated.
[c] Excludes 54 cases with symptom onset after hospital admission.
[d] There was a significant difference in the values for this variable in the bivariate analysis ($p<0.001$) when comparing patients not admitted to an ICU and who survived with patients admitted to an ICU or who died.

and 26 in the second. Of 90 pregnant patients of child-bearing age, 29 (32.2%) were admitted to an ICU. This percentage was similar in non-pregnant women of childbearing age (30.9%).

Underlying risk conditions

The distribution of underlying risk conditions by outcome is described in Table 1. The most frequently reported co-morbidities were any chronic pulmonary disease (35.3%) and morbid obesity (14.1%). While asthma was more frequently reported in less severe cases (22.7%), chronic obstructive pulmonary disease (COPD) was more frequent in those admitted to an ICU or who died (16.9%).

Information on the number of co-morbidities was analysed in 82.9% (n=2,508) of the patients. Overall, 26.4% had no underlying conditions while 73.6% had at least one underlying risk condition (60.8% of the children and 76.5% of adults); 39.1% had at least two such conditions. The number of co-morbidities reported in our cohort by outcome is summarised in the Figure. Details of the underlying conditions are presented for patients reporting only one co-morbidity. For patients with at least two underlying conditions, there was no frequent association of co-morbidities. In patients aged under 15 years, the likelihood of having a co-morbidity was significantly higher in those admitted to an ICU or who died compared with those not admitted to an ICU and who survived (73.2% versus 56.5% respectively; p<0.001).

Underlying disease was not equally distributed among age groups. More than a third of the children (39.4%) (Table 2) and young adults (33.6% of patients aged 15–44 years) had no co-morbidities. Among children with only one co-morbidity, 62.6% (n=109) had a chronic pulmonary disease, of which asthma accounted for 54.1% (n=59).

Among pregnant patients (n=91), 35 had no co-morbidities and 16 had one co-morbidity, with asthma being the most frequently reported (n=6).

Of the 1,696 adult patients with available information, 239 (14.1%) were morbidly obese. Among the 173 morbidly obese patients with other underlying risk conditions, the most frequent were asthma or COPD (n=80), diabetes (n=64) and cardiovascular disease (n=40). Of the 120 morbidly obese patients not admitted to an ICU and who survived, 24.2% did not have other established risk factors for severe influenza. This percentage was higher (31.1%) in the 119 of patients who were either admitted to an ICU or who died. Of the 44 morbidly obese patients who died, 12 (27.3%) had no other underlying condition.

Course of illness and antiviral treatment

The time course of illness and antiviral treatment are described in Table 3. The time from the onset of illness to hospital admission was slightly higher in patients who were either admitted to an ICU or who died

(median: three days; interquartile range (IQR): 2–6) when compared with patients who were not admitted to an ICU and who survived (median: three days; IQR: 1–5) (p<0.001).

Overall, 2,521 (90.7%) of the 2,779 patients with available information received treatment with antiviral drugs. Adults (2,090 of 2,234) were significantly more likely to be treated than children (431 of 544) (93.6% versus 79.2%; p<0.001). Of 2,020 patients, 711 (35.2 %) received treatment within 48 hours of symptom onset, including 507 (39.4%) of 1,288 patients with underlying risk conditions for severe influenza. Overall, the median time from symptom onset to treatment with antiviral drugs was 4 days (IQR: 2–6). The time between symptom onset and the start of antiviral therapy was significantly longer in patients admitted to an ICU or who died (median: five days), compared with the same interval in those who were not admitted to an ICU and who survived (median: three days) (p<0.001) (Table 3).

Outcomes

Of 2,739 patients with available information, 2,252 (82.2%) had radiological findings consistent with primary viral pneumonia and 1,585 (73.4%) had hypoxemia. A secondary bacterial infection was reported in 292 (30.5%) of the 957 patients with available information. Among patients admitted to an ICU or who died, the most frequent complications reported were acute respiratory distress syndrome (n=316, 51.1%), sepsis (n=209, 35.2%), shock (n=170, 29.4%), acute renal failure (n=120, 20.1%) or multi-organ failure (n=95, 19%).

Of the 702 critically ill patients with available information, 438 (62.4%) required mechanical ventilation for a median of five days (range: 1–35) and 37 (6.9%) required dialysis. The median length of ICU stay was six days (IQR: 3–14).

At the time of analysis, 200 patients had died; all but two had been hospitalised (they died before they could be hospitalised) and 161 (80.5%) had been admitted to an ICU, with a median length of stay of eight days (IQR: 3–14). The median age of the patients who died was 46 years (range: three months – 92 years): 36 (18%) were over 64 years and 21 (10.5%) were under 15 years.

While 13.9% (n=27) of patients who died had no risk factors, 60.8% (118 of 194) had two or more underlying conditions. In patients who died, the most frequent co-morbidities were pulmonary disease (in 72 of 180 patients; COPD in 34 of 168) and morbid obesity (44 of 162). The median time from the onset of illness to death was 13 days (IQR: 7–21). Of the patients who died, 28 of 131 with available information (21.4%) received antiviral therapy within 48 hours after the onset of symptoms.

Comparison of cases by outcome

We conducted a multivariate analysis on data from adult patients that included the patient's age and sex, underlying conditions (asthma, COPD, diabetes, morbid

obesity, chronic renal insufficiency and cardiovascular disease) and start of antiviral therapy within 48 hours after symptom onset. The variables that were significantly associated with a worse outcome (admission to an ICU or death) were the start of antiviral therapy more than 48 hours after the onset of illness (OR: 2.39; 95% confidence interval (CI): 1.79 to 3.2; p<0.001), morbid obesity (OR: 2.01; 95% CI: 1.38 to 2.94; p=0.001), cardiovascular disease (OR: 1.79; 95% CI: 1.2 to 2.67; p=0.005) and COPD (OR: 1.51; 95% CI: 1.03 to 2.2; p=0.002).

Discussion

We report on one of the largest series to date of hospitalised patients infected with the 2009 pandemic influenza A(H1N1) virus during the first seven months of the pandemic. It covers the spectrum of severe disease experienced in 3,025 hospitalised patients in Spain, including 852 patients admitted to an ICU during the study period. Overall 200 patients died.

The surveillance of pandemic influenza cases began in Spain in April 2009 following WHO's alert [6], but it was not until June 2009 that the first severe cases were detected, probably reflecting the beginning of community transmission in Spain.

In contrast to seasonal influenza, and as previously described for this pandemic [13,18-20], most of our hospitalised patients were young and middle-aged adults. However, if we take into account data from the Spanish influenza sentinel system on influenza rates in the community, the likelihood of having severe disease and dying from it appears to be higher in adults aged over 64 years. In our study, 11.2% of patients admitted to an ICU and 18% of those who died were aged over 64 years, although cases of influenza in the community in this age group represented only 2.5% of all estimated cases in Spain during the study period, based on data from the Spanish influenza sentinel system (personal communication, Amparo Larrauri-Cámara, 12 February 2010) and [21]. This is consistent with reports elsewhere [14,22,23] and is probably explained by the fact that in our hospitalised cases the likelihood of an underlying co-morbidity increased with age: 60% of the patients under 15 years were reported to have a co-morbidity, compared with 95% in those aged over 64 years.

As in seasonal influenza, most of our cases were people with underlying risk conditions: 71.8% of the patients not admitted to an ICU and who survived and 77.5% of those admitted to ICU or who died. The most common co-morbidities were COPD, asthma, morbid obesity and cardiovascular disease. These findings are in line with published reports from other countries [13,14,19,24,25]. The high prevalence of morbid obesity in our adult patients is striking (11% in those not admitted to an ICU and who survived and 19.3% in those admitted to an ICU or who died), when compared with the estimated 0.5% prevalence in the adult population in Spain [26]. The prevalence of all co-morbidities increased with disease severity, with the exception of asthma, which was more prevalent in patients not admitted to an ICU and who survived.

Another noteworthy finding in our study is the presence of neuromuscular disease (7.7%), seizures (9.0%) and cognitive dysfunction (9.8%) in the paediatric patients, as has been previously described for children with severe pandemic influenza in the United States [13,17]. In Spain, morbid obesity and cognitive dysfunction had not been previously considered as conditions that should prompt seasonal influenza vaccination. As a result of our findings, the Vaccine's Board, coordinated by the Spanish Ministry of Health, has considered inclusion of people with each condition in the target groups for influenza vaccination.

Pregnancy has been previously reported as a possible risk factor for complications from the pandemic influenza [27,28]. The prevalence of pregnancy in female patients in our study (15.2 %) is higher than the 5.2% prevalence in Spanish females of reproductive age (extrapolated from the number of births in 2009 in Spain) [29]. However, the need for intensive care was similar in hospitalised pregnant women (32%) and hospitalised non-pregnant women of childbearing age (31%).

Patients who died were significantly older and had a higher prevalence of co-morbidities (86%) than those who survived, suggesting that the presence of chronic illness may increase the likelihood of death. However, 13.9% of those who died were previously healthy people. Disease progression was rapid in patients who died, with a median time from symptom onset to death of 13 days.

In a multivariate analysis, we found that a delay in the start of antiviral therapy, morbid obesity, cardiovascular disease and COPD were independent risk factors for a worse outcome in adults. Cardiovascular disease and COPD had already been established as risk factors for seasonal influenza [30]. A possible link between obesity, especially morbid obesity, and disease severity in pandemic influenza patients has been pointed out by others [12-14]. However, this is one of the few studies [19] where obesity, specifically morbid obesity, has been found to be an independent risk factor for influenza severity (OR: 2.01; 95% CI 1: 38 to 2.94). Of note, 31.1% of the morbidly obese patients who were admitted to an ICU or who died did not have any other established risk factors for severe influenza.

The median interval from the onset of illness to hospital admission was three days, with complications appearing early in the illness course. Primary viral pneumonia and severe hypoxemia requiring mechanical ventilation were the most common complications in our hospitalised cases. Critically ill patients experienced a rapid worsening that required intensive care within 24

hours of hospital admission. Acute respiratory distress syndrome, sepsis and shock were the most frequent complications, each occurring in 30–50% of critically ill patients. These findings are consistent with reports from other countries [13,24,31].

Protocols that were current during the study period recommended antiviral treatment of individuals in at-risk groups and in all hospitalised cases. In our study, a high proportion (90.7%) of patients received antiviral treatment. However, only around a third received it within 48 hours of symptom onset, regardless of their status as a risk group. This may be due to the fact that patients generally do not seek medical care immediately (median of three days from symptom onset to hospital admission). Data from this pandemic suggest that the use of antiviral drugs can reduce disease severity and mortality from the pandemic influenza, especially when such therapy is started early [13,32]. Our results support these findings, as patients who were admitted to an ICU or who died were less likely to have received such therapy within 48 hours after symptom onset (OR: 2.39; 95% CI: 1.79–3.2). Antiviral treatment should be started as soon as possible in hospitalised patients with suspected infection with the pandemic virus, especially in patients at increased risk for complications, including those who are morbidly obese.

Our data are subject to a number of limitations. As the data were gathered during an evolving public health alert, some considerations need to be borne in mind. First, the data were collected for surveillance purposes and provide mainly epidemiological information on cases hospitalised for severe pandemic influenza. Although they also provide some clinical details, they are not exhaustive. Second, inherent to surveillance in epidemic outbreaks, some data are incomplete. This may have affected the analysis of the presence of underlying risk conditions as we have been conservative when considering co-morbidities as absent. It is therefore possible that the actual percentage of cases with no underlying risk conditions for severe influenza may be more than the reported 26%. Third, at the time of data extraction, case-based reporting of severe pandemic influenza to the central level had not been exhaustive in all regions, due either to delays in reporting or to differences in individual data collection. On the basis of individualised data from regions where reporting was complete and on aggregated data of severe hospitalised cases, we estimate that those analysed in this report represent more than 90% of the patients who died, 60% of those admitted to an ICU, and 35% of those not admitted to an ICU in Spain. The difference in these proportions may bias our results towards the null hypothesis, as non-reported hospitalised cases not admitted to an ICU may be less severe than those reported. However, when we analyse only data from regions with complete reporting, the results are consistent with those from the analysis of all reported cases. Finally, although this analysis does not cover the whole period of the pandemic, at the time of

data extraction, the epidemic in Spain had reached its peak and was declining towards baseline levels, with an incidence rate of 78 cases per 100,000 population (week 49) [21]. Therefore, we do not believe that the characteristics of future severe cases will be different from those described in this report.

Data on pandemic influenza vaccination were not recorded in our study. Despite the absence of these data, we do not think this introduces bias in our results. In Spain, pandemic influenza vaccination started on 16 November 2009 and the reported coverage for the pandemic vaccine among target groups in Spain at the end of the study period was 13.8% (unpublished data). Only 415 (13.7%) cases in our study had symptom onset after 15 November 2009.

In conclusion, our study confirms the role of cardiovascular disease and COPD as risk factors for severe influenza and highlights the importance of an early start of antiviral therapy, especially for patients with underlying risk conditions. Furthermore, it demonstrates that morbid obesity is an independent risk factor for influenza severity. Healthcare planners and providers should be aware of the potential for severe illness and death in morbidly obese influenza patients. These findings should be taken into account when planning, including vaccination strategies, for upcoming influenza seasons.

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European Medicines Agency updates on the review of Pandemrix and reports of narcolepsy

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The European Medicines Agency's Committee for Medicinal Products for Human Use today 23 September 2010 announced that it has reviewed all available data on the suspected link between narcolepsy and Pandemrix and concludes that the available evidence is insufficient to determine whether there is any link between the illness and the vaccine.

The Committee agrees that further studies are necessary to understand the issue fully and that while the review is still ongoing there is no need for Europe-wide restrictions on the use of Pandemrix. The ongoing review will take some three to six months to conclude and will require new epidemiological research to establish conclusions on the possibility of a link between Pandemrix and narcolepsy.

Until mid-September there were 81 reports from healthcare professionals which suggested narcolepsy. Of these the majority came from Sweden (34) and Finland (30), 10 from France, six from Norway and one from Portugal.

To read more about the issue, please visit the website of the European Medicines Agency: www.ema.europa.eu.