

EPIDEMIOLOGY OF FATAL CASES ASSOCIATED WITH PANDEMIC H1N1 INFLUENZA 2009

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This article was published on 20 August 2009.

Citation style for this article: Vaillant L, La Ruche G, Tarantola A, Barboza P, for the epidemic intelligence team at InVS. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. Euro Surveill. 2009;14(33):pii=19309. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19309>

This article describes the characteristics of 574 deaths associated with pandemic H1N1 influenza up to 16 July 2009. Data (except from Canada and Australia) suggest that the elderly may to some extent be protected from infection. There was underlying disease in at least half of the fatal cases. Two risk factors seem of particular importance: pregnancy and metabolic condition (including obesity which has not been considered as risk factor in previous pandemics or seasonal influenza).

Introduction

To date, there are few data on risk factors, severe cases and deaths associated with pandemic H1N1 influenza 2009. Estimating and interpreting case fatality ratios (CFR) is difficult, mainly due to the challenge of accurately estimating the numerator (N deaths) and the denominator (N cases) [1], especially during a pandemic that is still evolving. Furthermore, many countries have abandoned individual case counts and systematic screening of all suspect cases. This article aims to describe the characteristics of reported deaths, to assess the CFR and high-risk profiles linked with underlying disease, while assessing possible bias.

Methods

The study is based on an analysis of available data until 16 July 2009, as compiled by the epidemic intelligence team at the French institute for public health surveillance (Institut de Veille Sanitaire, InVS), using a well-defined methodology [2]. The individual or aggregated data originated from validated official sources (Ministries of Health, local or national public health authorities, European Centre for Disease Prevention and Control, United States Centers for Disease Control and Prevention, World Health Organization), completed by informal sources when needed.

Results

The first (retrospectively) confirmed death occurred in Oaxaca State, Mexico, (onset of symptoms on 4 April 2009). As of 16 July 2009, InVS was aware of 684 confirmed deaths reported worldwide since the start of the pandemic (Figure 1) for a total of 126,168 reported cases (Figure 2). At this stage, no deaths had been reported and scarce data was available from African countries.

Data were available for 574 deaths associated with pandemic H1N1 influenza 2009: individual data for 449 cases in 26 countries (Table 1, Figure 2) and aggregated data for 125 cases in Mexico [3].

The quality and completeness of the data regarding age, sex, date of death and the notion of underlying disease varied greatly for each case. The overall 'computed CFR' (number of reported deaths per number of reported cases as of 16 July 2009) was 0.6% and varied from 0.1% to 5.1% depending on the country (and the accurate quantification of deaths and overall case counts) (Table 1).

Deaths by sex and age

Data on sex were available for 503 fatal cases worldwide (257 men and 246 women, sex ratio=1.04). Data on age were available for 468 fatal cases worldwide (343 with individual data and 125 with aggregated data). Data on both information (age and sex) were available for 448 fatal cases (Figure 3).

Although previous reports suggested that cases of pandemic H1N1 influenza 2009 occurred mainly in children [4], the mean and median age of the 343 fatal cases in our analysis were 37 years (range 0-85 years). Most deaths (51%) occurred in the age group of 20-49 year-olds, but there was considerable variation depending on country or continent (Table 2). Overall, 12% of deaths occurred in cases aged 60 years or more, but 36% of reported deaths in Canada (mainly female) and 28% in Australia occurred in this age group.

Underlying risks

Pregnancy

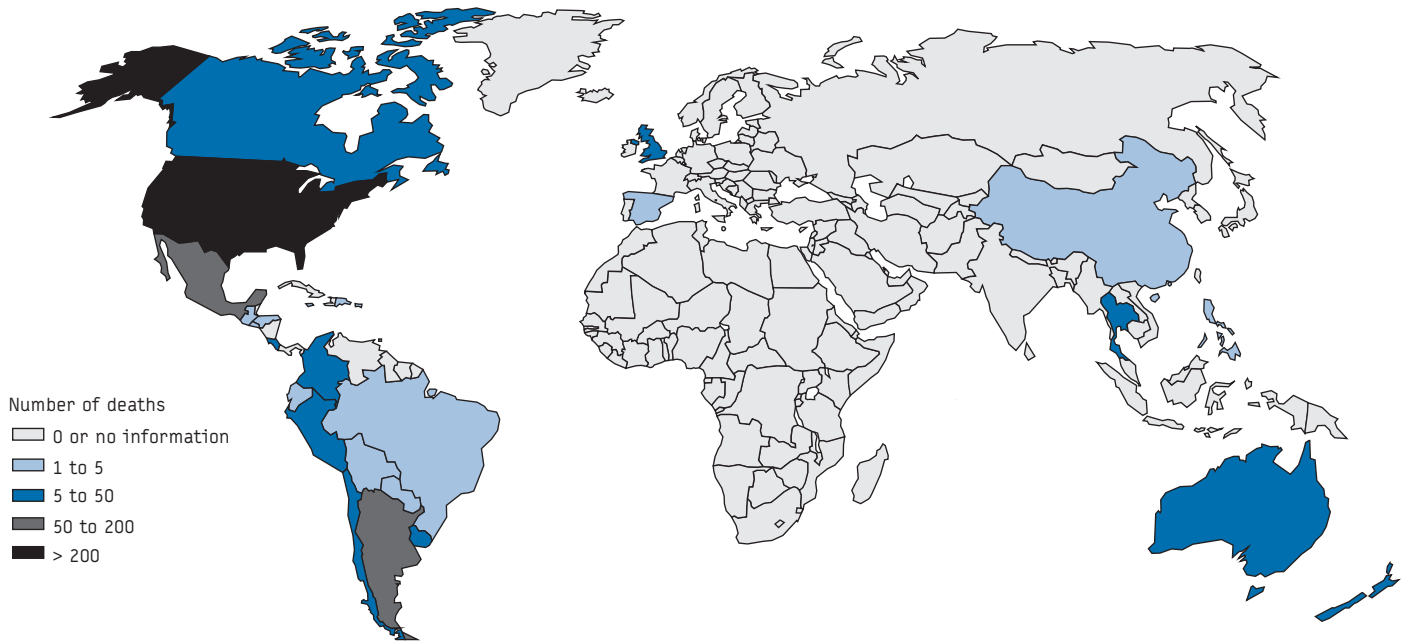
As of 16 July 2009, 16 women (10% of all individually documented female cases who died and 30% of the 20-39 year-old women who died) were pregnant or had delivered at the time of their death. Among these 16 women, at least eight had documented underlying health risks (obesity, heart disease or a respiratory disease such as asthma or tuberculosis). No information was available as to the underlying health status of the eight remaining women who died.

Underlying disease

A sub-analysis examined the 354 cases (241 cases with individual data and 113 with aggregated data) who died and were also documented for underlying disease and for sex and/or age (Figure 2). Presence or absence of underlying disease was documented for 241 of 449 (53% of the 449 cases with individual data) of deaths with individual data. Of these, 218 (90%) had documented underlying disease and 23 (10%) had documented absence of underlying disease. A further sub-analysis was conducted

FIGURE 1

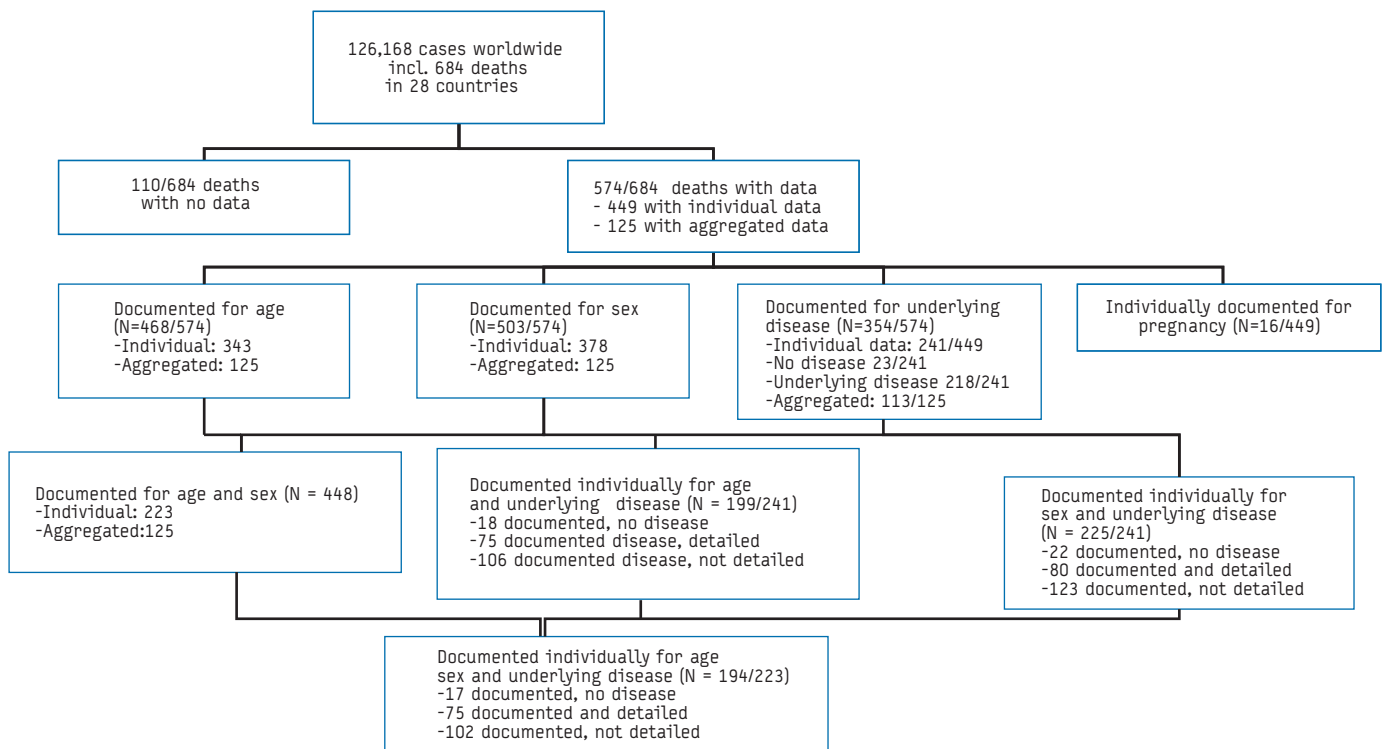
Deaths associated with pandemic H1N1 influenza 2009 reported officially worldwide as of 16 July 2009



Source: Ministries of Health, local or national public health authorities, European Centre for Disease Prevention and Control, United States Centers for Disease Control and Prevention, World Health Organization.
Map drawn with Philcarto (free software available from: <http://philcarto.free.fr/>)

FIGURE 2

Breakdown of fatal case counts used in our analysis



on 102 cases of known sex (80 with detailed underlying disease and 22 without disease) and 93 cases of known age (75 with detailed underlying disease and 18 without disease) (Figure 2). Underlying disease (or its absence) was equally distributed between the sexes, but understandably not among age groups (Figure 4). A high proportion of young children (27% of the 0-9 year-olds) and young adults (22% of the 20-29 year-olds) had no documented underlying disease, while 60% of people over the age of 60 years had heart or respiratory disease. Diabetes and obesity were the most frequently identified underlying conditions (Figure 5) and were found in fatal cases over the age of 20 years (the World Health organization defines "obesity" as a body mass index equal to or more than 30, but as the reporting format differed between sources and no standard definition of childhood obesity is applied worldwide, we cannot be sure the same definition has been applied for all cases). In the 13 fatal cases with individual detailed data on metabolic conditions, seven cases had obesity, five cases had diabetes, and one case had both. The available data for the other cases did not specify whether the metabolic condition included obesity only, diabetes only, or both.

Discussion and conclusions

Most cases described during the three pandemics of the 20th century and during seasonal influenza involve transient illness not requiring hospitalisation. Most deaths are described in the very young or the elderly or those with underlying disease. The 1918-1919 pandemic, however, was characterised by a high mortality rate in healthy young adults and an estimated CFR of 2-3% [5]. Even with a low CFR, seasonal influenza epidemics cause significant morbidity and mortality with an estimated three to five million cases of severe illness and about 250,000 to 500,000 deaths worldwide [6].

To date, the CFR attributable to the current H1N1 pandemic has been estimated at around 0.4%, based on surveillance data from Mexico and mathematical modelling [7]. This CFR is higher than that of average seasonal influenza but remains of the same order of magnitude. Whether this will change before the expected epidemic peak in the northern hemisphere in the autumn is unknown.

Evaluating CFR during a pandemic is a hazardous exercise. Aside from the issue of whether or not a death has been caused by

TABLE 1

Available individual and aggregated data on cases of pandemic H1N1 influenza 2009 and associated deaths worldwide, by country, as of 16 July 2009

Country	Data reported in official bulletins* to 16 July 2009				N deaths with individual data available**
	N deaths**	N confirmed cases	Computed CFR	Mortality per million inhabitants	
United States	211	37,246	0.6%	0.66	242
Argentina	137	3,056	4.5%	3.37	13
Mexico	124	12,645	1.0%	1.12	0
Canada	39	9,855	0.4%	1.15	41
Chile	33	10,491	0.3%	1.93	10
Thailand	24	4,057	0.6%	0.35	23
Australia	21	10,389	0.2%	0.98	31
United Kingdom	17	9,739	0.2%	0.27	17
Uruguay	15	550	2.7%	4.45	8
Costa Rica	10	428	2.3%	2.16	6
New Zealand	9	1,984	0.5%	2.09	10
Colombia	7	185	3.8%	0.15	4
Peru	6	2,082	0.3%	0.20	4
Brazil	4	1,027	0.4%	0.02	13
Paraguay	3	125	2.4%	0.46	4
Philippines	3	2,668	0.1%	0.03	4
Ecuador	3	277	1.1%	0.22	3
Salvador	3	404	0.7%	0.48	3
Bolivia	2	585	0.3%	0.20	2
Spain	2	1,099	0.2%	0.04	2
Guatemala	2	339	0.6%	0.14	2
Dominican Republic	2	108	1.9%	0.20	2
Jamaica	2	39	5.1%	0.73	1
Puerto Rico	1	20	5.0%	0.25	1
Brunei	1	334	0.3%	2.46	1
China	1	1,362	0.1%	0.00	1
Honduras	1	123	0.8%	0.13	1
Hong Kong (China)	1	1,389	0.1%	0.14	0
Total	684	112,606	0.6%	0.27	449

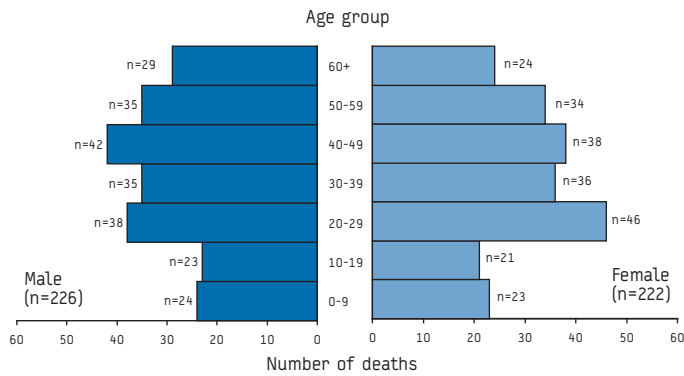
CFR: case fatality ratio.

* As per national bulletins, ECDC and WHO.

** For some countries, the N value in the first column is higher than in the third column due to a time lag for official reports.

FIGURE 3

Deaths associated with pandemic H1N1 influenza worldwide by age and sex, as of 16 July 2009* (n=448)



* Individual data, except from Mexico where aggregated data originate from the Ministry of Health.

the influenza infection, cases tend to be detected initially among severely ill patients with a higher probability of dying. This leads to an overestimation of the computed CFR at the beginning of an outbreak. The computed CFR subsequently evolves as the case reporting strategy is adapted to the situation. When the situation no longer requires exhaustive reporting of cases, the computed CFR will inevitably increase and grossly overestimate the true CFR.

Specific investigations or modelling allow for a more accurate estimation of the number of cases. As of 27 May 2009, there had been 820 confirmed cases in New York City, of whom two had died, resulting in a computed CFR of 0.2%. A telephone survey estimated that in fact 250,000 cases had occurred in that city of 8.3 million inhabitants, resulting in an estimated CFR of 0.0008% [8,9]. In the United Kingdom (UK), there were 28 deaths reported for a documented 10,649 cases as of 16 July 2009 and a computed CFR of 0.26%. However, health authorities estimated that the cumulative number in the UK on that date was 65,649 cases and 28 deaths, which corresponds to an estimated CFR of 0.04% [10].

The pandemic, however, is far from over, and deaths will unfortunately continue to occur. As in previous pandemics, available

TABLE 2

Deaths associated with pandemic H1N1 influenza 2009*, percentage and mortality rate (per million inhabitants), by age group and by country or continent, as of 16 July 2009 (n=468)**

Country or continent	Age group [years]								Total	Missing data
	0-4	5-9	10-19	20-29	30-39	40-49	50-59	60+		
Canada	0	3	2	1	2	6	4	10	28	13
%	0%	11%	7%	4%	7%	21%	14%	36%	100%	32%
Mortality rate	0.00	1.67	0.48	0.22	0.43	1.15	0.81	1.48	0.83	
USA	5	8	22	29	22	34	34	24	178	64
%	3%	4%	12%	16%	12%	19%	19%	13%	100%	26%
Mortality rate	0.23	0.38	0.51	0.65	0.52	0.76	0.81	0.42	0.56	
Mexico	11	8	5	30	25	22	17	7	125	0
%	9%	6%	4%	24%	20%	18%	14%	6%	100%	0%
Mortality rate	1.10	0.77	0.24	1.65	1.39	1.64	1.81	0.68	1.13	
Latin America	6	6	7	18	14	3	6	4	64	13
%	9%	9%	11%	28%	22%	5%	9%	6%	100%	17%
Mortality rate	0.17	0.16	0.09	0.25	0.23	0.06	0.16	0.10	0.16	
Europe	1	4	3	0	2	2	0	2	14	5
%	7%	29%	21%	0%	14%	14%	0%	14%	100%	26%
Mortality rate	0.17	0.70	0.25	0.00	0.13	0.12	0.00	0.08	0.13	
Asia	0	2	5	2	2	9	3	3	26	3
%	0%	8%	19%	8%	8%	35%	12%	12%	100%	10%
Mortality rate	0.00	0.13	0.17	0.07	0.08	0.44	0.20	0.21	0.16	
Oceania	1	1	1	4	5	6	7	8	33	8
%	3%	3%	3%	12%	15%	18%	21%	24%	100%	20%
Mortality rate	0.61	0.62	0.29	1.13	1.41	1.62	2.10	1.61	1.28	
Total	24	32	45	84	72	82	71	58	468	106
%	5%	7%	10%	18%	15%	18%	15%	12%	100%	18%
Mortality rate	0.26	0.34	0.24	0.46	0.43	0.54	0.57	0.36	0.40	

* Individual data, except from Mexico where aggregated data originate from the Ministry of Health.

** Latin America: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Paraguay, Peru, Dominican Republic, Salvador and Uruguay; Europe: Spain and United Kingdom; Asia: Philippines and Thailand; China is not included; Oceania: Australia and New Zealand.

data show that age groups are not equally affected. Compared to younger age groups, the elderly seem to be protected from infection to some extent, perhaps due to previous exposure to strains akin to influenza A(H1N1)v virus [11-13]. When infection does occur, however, the percentage of deaths in elderly cases seems to be higher than in others. Initial estimates available from Mexico for the period until 16 July 2009 showed that the risk of death in aged cases (over 50 years) was higher (6% deaths among cases) than in children (0-1% deaths among cases aged 0-19 years) and young adults (2-4% deaths among cases aged 20-49 years) [3].

There was documented underlying disease in at least 49% of documented fatal cases worldwide to date. Diseases most frequently associated with death were the same as those identified for death from seasonal influenza. Nevertheless, two risk factors are noticeable: pregnancy and obesity. Pregnancy is a well-documented risk factor for severe infection and death in seasonal influenza and in previous pandemics [14-16]. The role of obesity, however, remains to be further analysed in order to ascertain whether

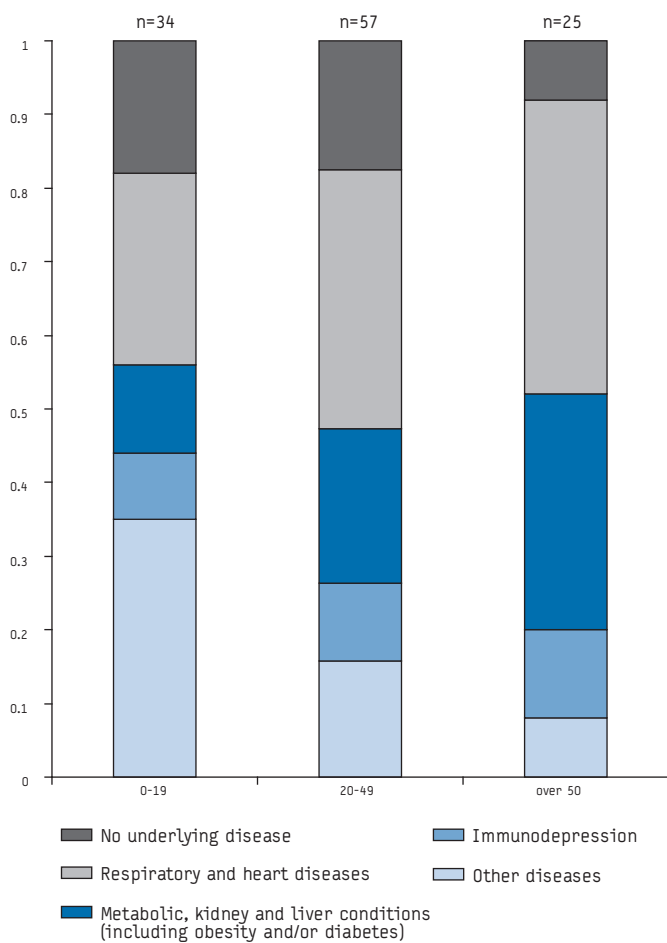
the risk is linked with complications of obesity during intensive care [17,18] or with a severe course of disease due to diabetes frequently associated with obesity [19], or whether obesity plays a specific role in the pathogenesis of severe influenza A(H1N1)v infection, for example by interfering with the host's immune responses, as has been shown in rodents [20].

All the data presented here were from official sources and were carefully documented. Yet they are to be interpreted cautiously due to the variable quality of data regarding underlying disease (especially for pre-existing respiratory disease), small numbers, incomplete reporting using different formats, a mixture of individual and aggregated data, epidemic dynamics within the population (epidemics initially affecting school children or travellers) and population structure. For instance, we found that deaths in Canada seem to have been especially frequent in elderly women. Finally, the difficulty in determining whether the cause of death is attributable to influenza A(H1N1)v infection or to associated factors remains a major limitation.

The proportion of deaths with documented underlying disease must be interpreted with care due to a significant amount of missing data. There may be an information bias which overestimates the proportion of underlying disease since its presence may be reported more readily than its absence.

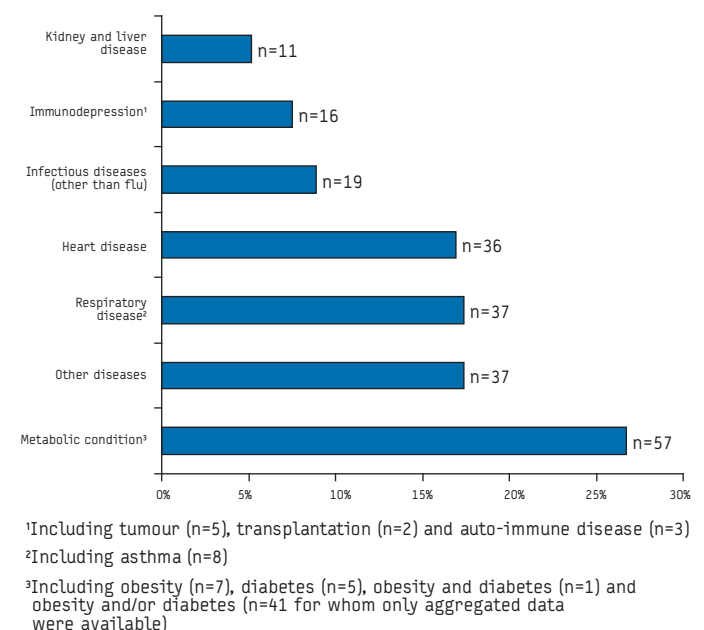
The analysis in this article is based on data collected only 10 weeks after the first international alert, and the pandemic is still in its very early phase. All evidence acquired so far remains to be completed and confirmed in the coming months, especially in view of the influenza epidemics currently ongoing in the southern

FIGURE 4
Distribution of underlying diseases in pandemic H1N1 influenza 2009-associated deaths by age, worldwide* as of 16 July 2009 (116 disorders documented in 93 fatal cases)



* Individual data, except from Mexico where aggregated data originate from the Ministry of Health.

FIGURE 5
Underlying diseases in pandemic H1N1 influenza 2009-associated deaths worldwide* as of 16 July 2009 (213 diseases documented in 193 fatal cases)



¹Including tumour (n=5), transplantation (n=2) and auto-immune disease (n=3)

²Including asthma (n=8)

³Including obesity (n=7), diabetes (n=5), obesity and diabetes (n=1) and obesity and/or diabetes (n=41 for whom only aggregated data were available)

* Individual data, except from Mexico where aggregated data originated from the Ministry of Health.

hemisphere. Surveillance of the progression of the pandemic H1N1 influenza 2009 will focus more and more on severe cases. A more reliable CFR could be estimated through specific surveys, mathematical modelling, syndromic surveillance of influenza-like illness and of reported deaths in the population. Encouraging reporting in a common international format would also be useful.

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