Clinical impact of influenza – lessons learnt from the pandemic influenza A (H1N1) 2009



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Influenza is generally an acute, self-limiting, febrile illness without further complications in the majority of people. However, it can be associated with severe morbidity and mortality and the burden of the disease on society is likely to be underestimated. In 2009 an outbreak of H1N1 influenza A virus infection was detected in Mexico with further cases soon observed worldwide. Subsequently, in June 2009, the first influenza pandemic of the 21st century due to influenza A (H1N1) was declared by the World Health Organization (WHO). There were many uncertainties regarding the virulence, clinical symptoms and epidemiological features of this newly evolved influenza A strain. Over time, many similarities, but also some differences between the pandemic H1N1 influenza A and seasonal influenza were identified. We recently performed a systematic review of the literature, looking at articles published between 1 April 2009 and 31 January 2010, to identify the epidemiological and clinical features of the pandemic H1N1 influenza. In this current article we compare our findings with others from the international literature. There was more severe impact on young and healthy adults, children, pregnant women and the obese. Clinical features in general were similar between seasonal and pandemic influenza; however, there were more gastrointestinal symptoms associated with pandemic H1N1 influenza. Shortness of breath was characteristic of more severe pH1N1 2009 infection with a higher possibility of being admitted to an intensive care unit (ICU).

Epidemiology

In Australia 85 deaths and 4250 hospitalisations from influenza are notified on average each year[1]; excess mortality and hospitalisation from influenza is undoubtedly greater due to the lack of reporting of influenza as a cause of death. Extrapolation from US estimates suggests 2000 deaths and 10,000 hospitalisations annually in Australia[1]. Estimates from the Australian model used by Newall *et al*. suggest that influenza is responsible for 3,000 deaths and over 13,500 hospitalisations in individuals aged ≥ 50 years in Australia each year[2].

The mortality due to influenza infection shows substantial variability due to the unpredictability of circulating strains. The estimated annual number of influenza-associated deaths from respiratory and circulatory causes in the USA has ranged from ~3000 to ~49,000 deaths (1976–2007)[3]. Influenza is seen as the most common vaccine-preventable cause of death in Australia and elsewhere[4,5].

By July 2010, 491,382 cases of pH1N1 were laboratory-confirmed worldwide[6] with more than 18,449 associated deaths[7]. These numbers represent a major underestimate as regular testing for pandemic H1N1 was not done for all cases, even in hospital, and many deaths were never tested or recognised as influenza-related. Data from Australia reveal that by the end of 2009 37,636 cases including 191 associated deaths[8] were recorded.

A number of studies have been published reporting the epidemiological and clinical features of the pH1N1 influenza A strain. In order to obtain a comprehensive overview of the information available, we performed a systematic review of the literature published between 1 April 2009 and 31 January 2010. Our search (Medline, Embase, plus hand searching) identified 811 studies of possible relevance; after reviewing them, the number of relevant papers was reduced to 44 studies describing clinical and epidemiological features of pH1N1 2009 from different settings (hospital, community, school)[9]. In total 33,369 laboratory confirmed pH1N1 cases were reported from 23 countries worldwide, with seven studies from the southern hemisphere and 37 studies from the northern hemisphere.

Age

The weighted mean age of cases was 18.1 years (excluding school outbreaks) with a range from 0 to 93 years. Sixty-four per cent were aged between 10 and 29 years and only 1.1% aged over 60 years. Australian data[10] on confirmed pandemic H1N1 2009 cases are comparable, with a median age of 21 years in 2009.

A key finding in our review, in stark comparison to previous influenza seasons (where mainly very young or very old people were seen in hospital or out-patient departments) was that the clinical attack rate was highest in adolescents and young adults; and this was confirmed in other studies[11-16]. A large US survey reported that almost half of the hospitalisations involved persons under the age of 18 years; only 5% were 65 years and older[17].

Though many people thought this to be a new phenomenon, Kelly *et al*. were able to present data that revealed a tendency for a younger median age of infection with seasonal influenza A (H1N1) and influenza B virus compared with seasonal influenza A(H3N2)[18-20].

The relative sparing of adults older than 60 years of age is most likely due to the exposure of these persons to antigenically related influenza viruses much earlier in life, resulting in the development of cross-protective antibodies[21,22].

A study by Booy *et al*. looking at pre-pandemic sera from individuals aged 60 and above found a high proportion of individuals with cross-reacting antibody titres ≥ 1: 40 (37.8%) with a significant trend to have higher antibody levels the older the subject[23] such that those aged at least 85 years (born before 1925) had the highest levels.

Deaths

The systematic review revealed an adjusted case fatality rate (CFR) of 0.02%, which is consistent with another study[24], but we also acknowledge that variations between countries in CFR were reported. For instance, data from New Zealand showed only 0.005% CFR[13], whereas in a study from Brazil[25] 11.2% CFR was reported. In general, the CFR was significantly lower in high-income countries compared to lower income countries.

In Mexico, more than 80% of the 100 reported deaths occurred in patients between the ages of 15 and 59 years[26], but this is likely to be biased by reporting severe and newsworthy cases more commonly. Although the absolute number of cases in the elderly was not high, the CFR was high[24] and age-specific CFR followed a U-shaped pattern as seen in the 1957 and 1968 pandemics[27].

Clinical features

The clinical symptoms of pandemic H1N1 influenza were similar to those known to occur during seasonal influenza periods and were manifold but generally mild, ranging from afebrile upper respiratory illness to fulminant viral pneumonia[10]. The most commonly reported symptoms identified in the systematic review (Table 1), including in- and out-patients were cough (84.9%) and fever (84.7%) with no significant differences between community and hospitalised cases. A study done in Australia found similar results[28]. Runny nose was seen more often in out-patients than in hospitalised patients (59% compared with 25.7%). Shortness of breath as a presenting symptom was more commonly associated with being hospitalised and/or being admitted to ICU, occurring in 51.6% of hospitalised patients and 61.5% of patients treated in ICUs, compared to only 14.8% of community cases being short of breath (Table 1).

Gastrointestinal symptoms seem to occur more commonly in patients with pandemic H1N1 2009 influenza than in seasonal influenza[14,21,29], with 39% in a large US survey[17] compared to <5% of adults during the peak period of seasonal influenza[30]. In the systematic review, diarrhoea and vomiting were presenting symptoms in 19.9% and 13.0% of all patients respectively

Table 1. Common clinical symptoms of confirmed cases of pandemic influenza A (H1N1) 2009 (systematic review).

Symptoms	All cases in-patient & out-patients (N=33,369)* %	Community cases (N=22,692)* %	Hospitalised cases (N=2,309)* %	ICU cases (N=233)* %
Cough	84.9	83.0	81.2	76.9
Fever	84.7	81.8	85.8	93.3
Headache	66.5	65.8	18.7	48.2‡
Runny nose	60.1	59.0	25.7	†
Muscle pain	58.1	59.5	23.6‡	43.1‡
Sore throat	49.5	51.4	29.9	†
Shortness of breath	31.2	14.8	51.6	61.5§
Vomiting	19.9	22.2	11.3	23.1
Diarrhoea	13.0	11.2	14.5	†

* Individual denominators for each symptom vary
† No data were available or reported on these symptoms.
‡ P=0.0001
§ P=0.0002

with confirmed pandemic H1N1 infection. The pathogenic mechanism of the gastrointestinal symptoms is not understood completely, but results of an *in vitro* study[31] showed a higher viral load in intestinal cells with the pandemic H1N1 influenza infection compared to seasonal influenza and, therefore, a higher number of gastrointestinal symptoms might be expected.

Intriguingly, vomiting appeared to be much more a presenting symptom of influenza, especially in children, than a complication of antiviral treatment[32].

Children

It is important to note that the burden on health care services from influenza infections in young children is large. In addition, children have in general the highest morbidity, but not mortality, during an influenza outbreak and are the main disseminators of the virus[33]. The rates of children infected by influenza per year vary according to the literature, ranging from 8% to 15% (out-patient visits due to influenza)[34] to 20.3%–45% (clinical attack rate)[35,36]. For example, in Australia during 2008, notifications of influenza in the 0–4 year age group were 98 per 100,000 population and in the 5–9 year age group 54 per 100,000[37]. During the pandemic a surveillance system called PAEDS (Paediatric Active Enhanced Disease Surveillance) was running in six major Australian Children's Hospitals and managed by APSU (Australian Paediatric Surveillance Unit) in association with the National Centre for Immunisation Research and Surveillance. The aim was to identify and document data on children <15 years of age hospitalised with laboratory-proven influenza. Between 1 June and 30 September 2009, 601 cases were identified. Influenza A infection was most commonly detected (99.2%) with 84.3% of these subclassified as pandemic H1N1, while 6.7% were found to be influenza A but not further subtyped, so might have been due to the pandemic virus. Median age at presentation of PAEDS cases was 3.4 years and 59.9% were male. As seen in Figure 1, the majority of admitted children were under the age of one year and this age group also had the most PICU admissions. However, there were also a considerable number of admissions in five-year-olds, perhaps related to onset of school attendance. Of all admitted children, 35% had influenza-related complications, of which the most common were pneumonia (20.8%), seizure (8.3%) and bacterial co-infection (6.8%)(Elliot, E.J. *et al.*, personal communication).

Interestingly, comparison with the previous peak influenza season of the 2000s showed little difference between the number of children admitted to the Children's Hospital at Westmead (in Sydney) during the predominantly H3N2 influenza season in 2003 and the pandemic H1N1 2009 season: 257 admissions compared to 226, with 22 PICU admissions in each year but three deaths in 2003, compared to none in 2009[32].

Influenza vaccination uptake in Australia is suboptimal even in those with underlying medical conditions for whom the vaccine is recommended in the *9th Australian Immunisation Handbook*. Regarding the PAEDS data, only 43 of 256 children with an underlying condition were vaccinated despite a recommendation.

For more than five years in the USA and three years in Western Australia, influenza vaccine has been recommended for all children between six months and five years of age and there is a growing call for routine immunisation[38-41].

ICU admissions

The WHO estimates that approximately 10–30% of hospitalised patients required admission to an ICU during the pandemic, and nearly one-third of patients with very severe illness admitted to ICU were previously healthy people[11]. In Australia 14% of all hospitalisations (13% of all confirmed pandemic H1N1 2009 cases) became ICU admissions, consistent with the WHO estimation[10].

Numbers from an inception-cohort study conducted in all Australian and New Zealand ICUs during the winter of 2009 revealed that the number of ICU admissions due to viral

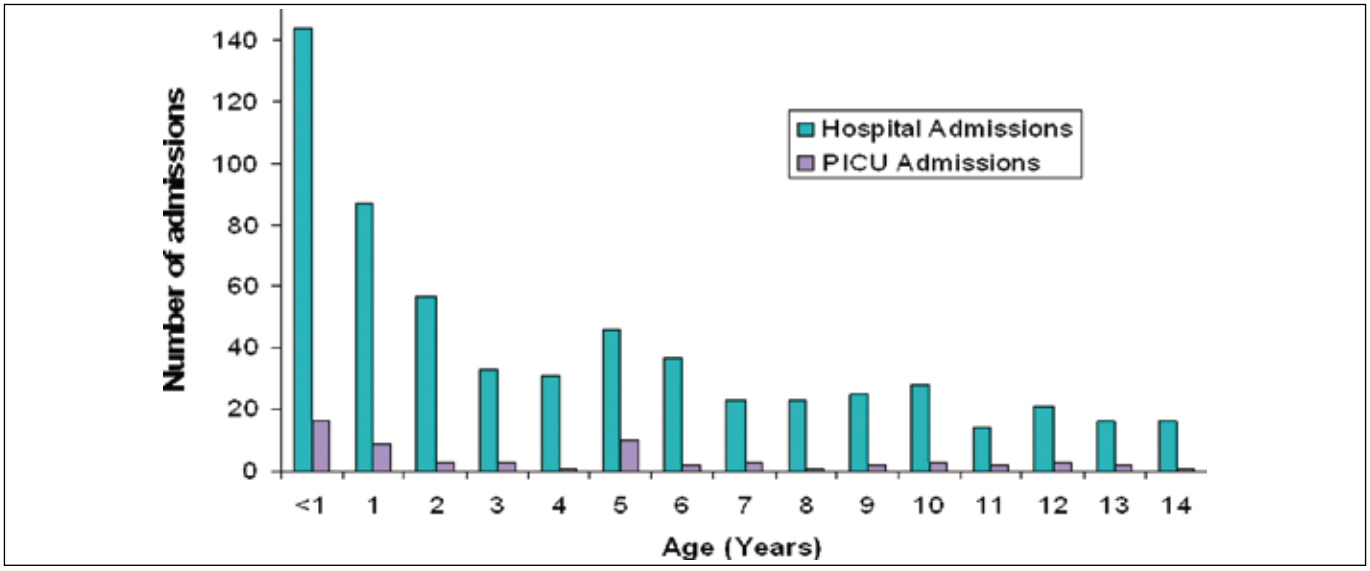

Figure 1. Admissions for influenza by age: June – September 2009, n=601 (Elliot, E.J. *et al.* personal communication).

pneumonitis caused by influenza A was 15 times higher than in any recent year. Age-specific incidence rates were highest among infants and adults 25 to 64 years of age[28,42]. In Australia, 27% of all hospitalised cases and 16% of patients admitted to ICU were pregnant women, with a mortality rate of 4%[10]. Other published reports confirm that, compared to a normal influenza season, a higher number of pregnant women and adults of a younger age were admitted to ICU following an infection by the pandemic H1N1 influenza virus[14,16,26,43,44].

Australian and New Zealand ICUs recorded a large increase in the use of extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS)[45]. New South Wales reported that over 10% of patients admitted to ICU with confirmed H1N1 pandemic influenza needed treatment with ECMO due to severe respiratory failure[46]. The mortality in patients treated with ECMO was 21%, but this number was substantially lower than mortality rates documented from patients with ARDS of heterogeneous aetiology[47,48]. The authors concluded that the young age of patients and also the cause of the ARDS (ARDS secondary to viral pneumonia) contributed to the better survival rate.

Underlying medical risk factors

It is well known that individuals with underlying medical problems, such as chronic respiratory, cardiovascular and neurological diseases, are more susceptible to complications of influenza. With pandemic H1N1, about 50–75% of hospitalised patients had an underlying medical risk factor[11,17]. In Australia, the proportion of hospitalised cases with at least one comorbidity was 46% and if one adds two more vulnerable groups (Indigenous persons and pregnant women) this increases to 58%[10]. The PAEDS surveillance data also showed a pre-existing disease in 52.7% of children admitted to hospital. Among ICU cases, the percentage with a comorbidity was 64% (Elliot, E.J. *et al.*, personal communication). By contrast, the systematic review showed that only 18% of all confirmed cases (but many were out-patients) with pandemic influenza H1N1 had a pre-existing and chronic health condition while data from Ontario, Canada (again pertaining to in- and out-patients) reported less than 10% of confirmed cases as having underlying chronic conditions[21]. However, this also means there were many healthy people with no comorbidities being admitted to ICU. Pandemic H1N1 infection seems to be more pathogenic than seasonal influenza ,causing severe infection and complications in relatively young, otherwise healthy individuals[42,49,50]. Studies in mammalian models suggest that the cause for the higher pathogenicity of the pandemic H1N1 virus lies in its ability to replicate better in lungs which might cause diffuse alveolar damage with subsequent hospitalisation and death, even where no underlying medical condition exists[51].

Obesity as an underlying risk factor for more severe infection due to the pandemic H1N1 influenza is discussed in several publications[42,52,53]. It has not been associated with seasonal influenza in previous years, but it was already known from a mouse model that diet-induced obese mice had a 6.6-fold higher mortality rate post-infection with a seasonal influenza strain[54]. Morbid obesity (BMI ≥ 40) was associated with hospitalisation from pandemic H1N1 infection among adults with, but also without, chronic medical conditions[52,53]. Also, obese (BMI 30.0–39.9) or morbidly obese individuals were at greater risk of death than individuals with a body mass index (BMI) <30.

Data from Australia and New Zealand reported that 28.6% of patients with confirmed critical illness related to 2009 H1N1 influenza had a BMI >35[42].

Conclusion

Recent research has helped us to understand the differences between the pandemic H1N1 2009 influenza and seasonal influenza. A higher burden of severe disease was recorded in children and healthy adults. The elderly were relatively spared, but if infection occurred the case fatality rate was high. In general, clinical features of the newly evolved pandemic H1N1 influenza strain were similar to what has been observed in previous influenza seasons. However, cases with pandemic H1N1 more often presented with gastrointestinal symptoms such as vomiting and diarrhoea. Similar to seasonal influenza, shortness of breath was a characteristic of more severe infection with a higher possibility of being admitted to an ICU. As seen with seasonal influenza, persons with underlying medical conditions were at increased risk of complications associated with the pandemic strain. In particular, morbid obesity and pregnancy were identified as risk factors for more severe disease. Although overall the 2009 pandemic due to H1N1 influenza A has been, in retrospect, a less severe pandemic than anticipated, the available epidemiological and clinical evidence gathered during that period has confirmed a high pathogenicity in a small minority and has provided information to increase preparedness for future influenza pandemics.

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