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Risk Factors Associated with Severe Clinical Outcomes of Pandemic H1N1 Infection

Abstract

The clinical outcome of pandemic H1N1 influenza infection is dependent on the interplay of virus and host factors. Influenza virus infections can range from relatively mild infections of the upper respiratory tract to fatal disease of the lower respiratory tract. A range of host factors play a role in the severity of clinical disease in pdm(H1N1)09 infection. With the exception of neonates age was directly proportional to the severity of clinical outcome; obesity, COPD and pregnancy play a key role in clinical outcome of infection. An important determinant in the pathogenesis of influenza infection is the tissue tropism of the influenza virus. The D222G and D222N mutations of pdm(H1N1)09 influenza appear to have an increased tropism for the tissues of the lower respiratory tract and are disproportionally associated with severe clinical disease. These α2-3 salicylic acid tropic mutations, which have been associated with fatal cases of influenza infection, have also been preferentially selected for during sequential passage in embryonated eggs and viruses of avian origin.

Keywords

Influenza; Pandemic; H1N1; pdm(H1N1)09; Oseltamivir

Review Article

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Abbreviations

ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; CFR: Case Fatality Ratio; HA: Haemagglutanin; HPA: Health Protection Agency; ICU: Intensive Care Unit; NDA: No Detectable Antibody; pdm(H1N1)09: Pandemic 2009 H1N1 Influenza; SAE: Serious Adverse Event

Introduction

The current H1N1 influenza vaccine strain A/California/7/2009 has a surprisingly high no detectable antibody (NDA) rate of approximately 52% in a population of 200 subjects screened (unpublished data). Studies have shown that the A/California/7/2009 strain of pandemic H1N1 influenza causes alveolar haemorrhage in the ferret model [1,2]; similar "swine flu" viruses A/Mexico/4482/2009 and A/Netherlands/602/2009 also presented severe pathology in the ferret model [3,4]. As a consequence it is clear that infection with this group of viruses represents a significant risk of a severe clinical outcome. Furthermore, the severe symptoms that are associated with a subset of A/California/7/2009 infections are atypical for previous seasonal influenza infections.

Co-morbidities and their impact on clinical outcome of infection

The clinical outcomes of infection by pdm(H1N1)09 are considerably affected by one or more host factors and co-morbidities. Here we discuss these co-morbidities and the impact that they have on clinical consequences to infection.

Case fatality ratios

By July 2009 63,479 cases of influenza like illness were reported in Mexico; of these cases 11% (6,945) were confirmed as H1N1 influenza; 92% of confirmed positive cases (6,407) were treated as outpatients, 7% (475) were admitted to hospital and survived and <1% died (63) [5]. During the early phase of the pandemic the case fatality ratio (CFR) was calculated to be approximately 0.4-0.6% [6]. In the UK an estimated 540,000 people had symptomatic H1N1 infection during a study period with a CFR of (0.026%) 26 deaths per 100,000 [7]. There is little published information for the CFRs of seasonal H1N1 or H3N2 influenza. However using data from the Health Protection Agency (HPA) we were able to determine the CFR for influenza infections admitted to intensive care units (ICU).

Figure 1 demonstrates that the CFR of H3N2 infections were higher than pdm(H1N1)09 infections over the period of 2012/2013.

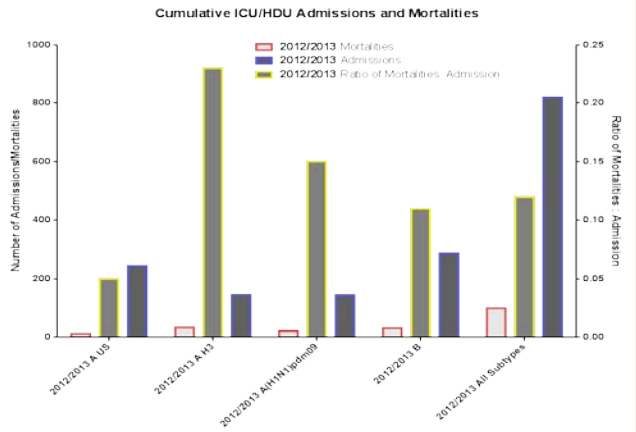

Figure 1: Case ratios of hospital admissions and fatalities for pdm(H1N1)09, H3N2 and B virus infections over the season of 2012/2013.

Symptoms

A meta-analysis of H1N1 pandemic influenza infection showed that the most common symptoms were cough (84.9 %), fever (84.7%), headache (66.5%), runny nose (60.1%) and muscle pain (58.1%) [8].

Factors associated with death or hospitalisation

Of those admitted to intensive care, up to 98% of patients and 91% of fatalities of pdm(H1N1)09 associated deaths were related to at least one co-morbidity [6,7,9-11] such as; age, chronic lung disease, obesity, pregnancy, diabetes, cardiac disease and immunosuppression. However a study of those admitted to ICUs in Australia and New Zealand found that 31.7% had no underlying condition [12].

Age: Generally patients with a non-severe clinical outcome were younger than those admitted to ICUs, who were also younger than those who died Table 1. According to one Canadian study, the median age was 23 years for all patients, 18 years for those with non-severe outcome, 34 years for those admitted to ICUs and those aged over 45 years were significantly more likely to die [13]. The greatest frequency of hospital admissions was in children aged 0-1 year followed by adults in the 50-64 year age group [12]. While studies suggest that children and young people had the highest cases of hospital admission, CFRs were highest in the over 65 year age group [5,7,9,10,13].

Lung disease: Chronic lung disease, asthma in particular, appears to be a common co-morbidity in severe cases of pdm(H1N1)09 infection including those requiring intensive care and those resulting in death [6,12,13]. Data on admissions to ICUs related to H1N1 influenza infection in Australia and New Zealand in 2009 showed that 32.7% of admissions had asthma or chronic pulmonary disease [12] and in Canada 41.1-47% of the critically ill also displayed these co-morbidities [11,13]. In Canada it was also shown that 22.6-38% of the critically ill were or had been smokers [11,14]. In California in 2009, 41% of fatal influenza cases had chronic lung disease [10] while in Germany it was reported to be 23.1% [15].

Obesity: Obesity has commonly been reported in ICU submissions and patients dying from pdm(H1N1)09 [6,11,12,15-18] and has been identified as a predictor of outcome in acute respiratory infection [19], possibly as a consequence of a defective cellular immune response to infection [20]. Of those admitted to an ICU in Australia and New Zealand in 2009, 28.6% (of which data was available) had a BMI of 35 kg/m^2 or greater [12]. In Canada 33.3% of the critically ill were obese (BMI ≥30) [11], and in one region of Canada the figure was as high as 62% [14]. In California, 66% of fatal adult cases involved obesity (BMI ≥30) [10] while in Germany the 23.1% of reported fatalities involved obesity (BMI >30)[15].

Pregnancy: Pregnancy has frequently been reported in cases of hospital admission related to pdm(H1N1)09 into ICUs. Pregnancy conveys a 4-5 fold increased rate of serious illness and hospitalisation with influenza [21]. During previous influenza outbreaks, pregnancy has also been associated with increased mortality and morbidity [22,23]; particularly if infection occurs during the third trimester [23]. Of those admitted to ICUs in Australia and New Zealand in 2009 9.1% were pregnant women [12] and 7.7-12% of the critically ill in Canada were pregnant [11,14]; in California 6% of fatal cases involved pregnancy [10] and in Germany there were 1.2% [15].

Diabetes: Diabetes triples the risk of hospital admission following pdm(H1N1)09 infection and quadruples the risk of ICU admission once hospitalised [24]. From the total number of admissions to ICUs in Australia and New Zealand in 2009, 16% had diabetes [12] as well as 20.8% of the critically ill in Canada [11] and with one region as high as 44% [14]. In Germany 17.2% of fatal cases were associated with diabetes [15].

Heart disease: Of the total number of admissions to ICUs in Australia and New Zealand in 2009, 10.5% had chronic heart failure [12] and 14.9% of the critically ill had cardiac disease in Canada [11] and in addition 23% of fatal cases in California [10] and 27.2% in Germany [15] had chronic heart disease.

Respiratory failure and immunosuppression: Although multi-organ failure has been reported in patients with

Table 1: Age specific indices of incidence of and mortality from pandemic pdm(H1N1)09 by Donaldson [7]. All population and case estimates rounded to nearest 1000.

Age Group (years)	Population *(1000s)	Cases (Estimated)		No of Deaths			Case Fatality Rate Deaths Per 100,000 Cases (Range)	Population Risk of Deaths. Deaths Per 100,000 Population (Exact 95% CI)
		No. Range (1000s)	Cumulative Incidence Per 100,000 Population	Total	Male	Female		
<1	641	7 (3-13)	1000	2	1	1	30 (2-260)	3.1 (0.3 to 11.3)
1- 4	2398	26 (12-53)	1100	7	3	4	27 (3-120)	2.9 (1.1 to 6.1)
5-14	5961	187 (86-381)	3100	20	7	13	11 (3-36)	3.4 (2.0 to 5.2)
15-24	6812	144 (67-297)	2100	17	8	9	12 (3-40)	2.5 (1.4 to 4.0)
25-44	14 460	125 (58-297)	850	37	21	16	30 (10-88)	2.6 (1.8 to 3.5)
45-64	12 661	45 (21-92)	350	29	21	8	65 (21-200)	2.3 (1.5 to 3.3)
≥ 65	8159	3 (1-5)	30	26	14	12	980 (300-3200)	3.2 (2.0 to 4.7)
All ages	51 092	536 (247-1097)	1100	138	75	63	26 (11-66)	2.7 (2.2 to 3.2)

*From Office of National Statistics mid-population estimates 2007

pdm(H1N1)09infections, the majority of severe illness relates to respiratory failure. Pneumonia can complicate clinical infection and is associated with severe clinical outcome. Immunosuppression was associated with the critically ill in 19. 6-21% of the critically ill in Canada in 2009 [10,14] and 33% and 30% of fatal cases in California [14] and Germany [15].

No known associated risk factor

During the 2009 pandemic there was a "substantial minority" of fatalities in patients that were previously healthy [7]. While the main cause of death was usually acute respiratory distress syndrome (ARDS) in patients with an underlying co-morbidity, there have been several reported cases of critical illness or death in patients, resulting from myocarditis, with no underlying condition [25-33].

There have also been cases of myocarditis resulting from seasonal influenza infection [34-36]. For patients with no underlying condition, the risk of a severe outcome was greatest among those 30-49 years old and those aged 60 and older [13]. The time from onset of illness to admission was 2-7 days with a median time of 3-4 days [12,13].

The classically reported influenza syndromes were:

- Viral pneumonitis or associated respiratory distress syndrome 48.8%
- Secondary bacterial pneumonia 20.3%
- Exacerbation of airflow limitation 13.9%
- Intercurrent illness or other illness 17.1% [13]

In general symptomology was similar to seasonal influenza, Webb et al. [12] did not find that the proportion of patients that died in hospital was any higher than that of patients who died from seasonal influenza who were admitted to an ICU [37]. With the exception of 0-1 year old group in general the severity of clinical outcome appeared to be directly proportional to age [5,7,9,10,12,13]. Other key risk factors leading to severe clinical outcomes were asthma, COPD and obesity [10-15]although there were a number of severe clinical cases with no known underlying condition [7,25-33].

The virus

In addition to the host factors which play an important role in the clinical outcome of pdm(H1N1)09 infection, the virus genotype also plays a role in the severity of clinical outcome. Antiviral resistance can have an important role in the efficacy of treatment to infection while other mutations can alter the virus tropism leading to an increase in this verity of virus pathogenicity.

Antiviral resistance

H275Y: Antiviral resistance to the neuraminidase inhibitor oseltamivir can be conferred by the well-characterised resistance mutation in the neuraminidase gene H275Y [38,39]. All current seasonal H1N1 (not H1N1 pdm) strains are genotypically (H275Y) and phenotypically resistant to oseltamivir [40,41].

A small proportion (1%-1.5%) of pdm(H1N1)09 virus strains are oseltamivir resistant, almost exclusively due to a H275Y mutation in the neuraminidase protein. It has been observed that the Y275 mutation was present as a minor variant in infected hosts before the onset of therapy. There is also evidence for the co-transmission of this drug-resistant variant with drug-susceptible viruses [42].

There is conflicting data on the presence of compensatory mutations. Four mutations have been identified that can either fully (R194G, E214D) or partially (L250P, F239Y) compensate for the fitness deficiency of the H274Y mutant. These compensatory mutations appear to restore replication efficiency of the virus which can be negatively impacted when conferring oseltamivir resistance. The compensatory effect of E214D is applicable in both seasonal influenza virus strain A/New Caledonia/20/1999 and 2009 pandemic swine influenza virus strain A/California/04/2009 [43].

S247N: S247N is a novel, naturally occurring N1 neuraminidase mutation that reduces oseltamivir sensitivity and greatly potentiates oseltamivir resistance in the context of the H275Y mutation. It has been shown that highly oseltamivir-resistant viruses pdm(H1N1)09 containing both the S247N and H275Y mutations transmit efficiently in the guinea pig transmission model [44] indicating the increased potential of proliferation of oseltamivir resistant strains. The prevalence of oseltamivir resistant viruses is increasing globally.

Other resistance mutations

Originally, seasonal influenza H1N1 viruses were resistant to oseltamivir but mostly sensitive to amantadine. However, as a consequence of the emergence of the pdm(H1N1)09 virus that carried the S31N mutation in M2, virtually all currently circulating human influenza (pdm(H1N1)09 and H3N2 viruses are resistant to amantadine [45].

Mutations affecting pathogenicity

D222G*: The D222G mutation in the haemagglutinin gene has been shown to present an increased severity of infection and increased likelihood of a SAE [46-52].The D222G mutation was reported by the WHO to have an overall prevalence of <1.8% but with a prevalence of 7.1% in fatal cases [53]. Kilander et al. [47] showed that the D222G mutation was isolated from 18% of (61) cases with severe influenza infection and from 0% of (205) cases with mild disease. Puzelli et al. [49] also showed that 5.8% of (52) severe cases and in 0.9% of (117) mild cases possessed the D222G mutation.

The mutation presents an alteration in the tissue tropism of the virus with a reduced affinity for α2-6 receptors and an increased affinity for α2-3 receptors [48,51,54-56] so increasing the affinity for the lower respiratory tract. This has been demonstrated by the higher frequency of D239G mutants detected in viruses isolated from patients with fatal outcomes and in isolates from lungs [57].

It has been shown in ferrets that viruses containing the D222G

mutation presented similar pathology compared to that of the wild type virus with respect to lethargy, weight loss, replication efficiency and transmission. In mice inoculated intranasally with D222G, a greater weight loss and viral replication were observed than with wildtype virus. In the human cell model the D222G virus replicated with reduced kinetics but to a higher titre [51].

Memoli et al. [58] isolated virus from the nasal wash of a severely ill immunocompromised patient at the time of diagnosis and from a bronchoalveolar lavage later in the course of infection. The nasal wash contained D222 and the lavage contained predominantly G222 virus. When compared to plaque purified G222 virus in a ferret model, the G222 predominant clinical isolate was the most pathogenic and developed most diversity during infection, indicating that increased diversity and not signal polymorphism was the most important in predicting pathogenic potential.

D222E*: The mutation D222E in the haemagglutinin gene has been identified in a previously healthy 30 year old who suffered from Guillain–Barré Syndrome [59], however it is not clear whether the Guillain–Barré Syndrome was a result of the D222E. The D222E mutation was also detected by Puzelli et al. [49] & Miller et al. [60]. Puzelli et al. [49] found that the D222E mutation was evenly distributed between mild (31.6%) and severe cases (38.4%) of infection.

D222N*: The mutation D222N in the hemagglutinin gene appears to be relatively rare but associated with severe disease; similarly to D222G, D222N appears to alter the tissue tropism of the virus for the lower respiratory tract [48,61]. Kilander et al. [47] found D222N mutations in only 4 of the 266 samples tested but it was present in 3 of those who had severe disease. Mak et al. [48] also found 4/458 samples analysed had the D222N mutation 3/4 cases had severe disease.

*It should be noted that the D222G discussed by most publications is amino acid D239G when counted from the start codon of A/California/4(or 7)2009.

Other mutations

The mutations S162R and T25P were also associated with severe influenza infection [62]. In addition, a meta-analysis of clinical, epidemiological and genomic data from the United States, Canada, United Kingdom, Australia and Japan based on official reports of public health agencies, found that 42.9% of individuals who died from laboratory-confirmed cases of the pdm(H1N1)09 were infected with a virus containing the Q310H mutation in its haemagglutinin [57].

Environmental factors affecting genotype

It has been demonstrated that that serial passage of H1N1 virus in embryonated chicken eggs increased viral growth 32- to 64-fold, coincident with the increased prevalence of G222 or R223 in the HA protein [63]. Ramadhany et al. [64] also showed that the minor genotype of α2,3 tropic viruses in upper airways became dominant after passaging through chicken eggs. The affinity for α2,3 has been exploited by making mutations including D222G to produce a H1N1 live attenuated vaccine with enhanced replication in eggs [65].

The emergence of antiviral resistance to chemotherapy is always a cause for concern particularly when compensatory mutations can negate the biological fitness penalty for resistance [38,39,43]. The fact that viruses containing S247N and H275Y have been demonstrated to be transmissible in an animal model [44] indicates that there is scope for resistant mutations to proliferate in the field. This clearly shows the need for new therapies against these viruses and the careful control of the usage of current antiviral therapies.

While the D222G/N mutations are of low frequency they appeared to have a disproportionate impact on the pathogenesis of disease. These D222G/N do have the potential to impact on the clinical outcome of pdm(H1N1)09 infection even in patients with no underlying condition. D222E however did not appear to have any significant effect on the clinical progression of illness.

Factors contributing to the pathogenic potential of pdm(H1N1)09

During the 2009 pandemic there was a minority of fatalities in patients with no known underlying risk factor [7]. As these fatal cases had no known risk factor, the genotype of the infecting virus may have affected the clinical outcome. It has been well established that mutations in the HA gene (D222G/N) can result in an increased severity of clinical outcome [46-52] and may explain the fatalities in these patients.

Pre-existing immune response to pdm(H1N1)09 infection

It is likely that the severe clinical outcomes from the 2009 pandemic were of the result of a novel virus being exposed to a naive population. Recent papers indicate that cross reactive antibodies from non-pandemic H1N1 strains can elicit an immune response to pandemic influenza infection [66]. Jegaskanda et al. [67] showed that Macaques primed against seasonal H1N1 infection elicit a Natural Killer cell response producing IFN-γ and CD107a in the presence of pandemic H1N1 HA. This response may lessen the severity of infection with pdm(H1N1)09 and could explain why the 2009 pandemic was not as severe as feared; with pre-existing cross reacting antibodies mitigating the more severe outcomes of infection.

Studies to determine the pathogenic potential of D222G/N mutations

Currently there seems to be little or no data available on what proportion of a virus population needs to contain D222G/N mutations to present a severe clinical outcome. This could be determined by titrating a homogeneous stock of D222G/N produced by reverse genetics or plaque purification in a stock of D222 wild type virus. Viruses with differing proportions of D222G/N could then be analysed in the ferret challenge model to determine what levels of D222G/N were required to exert a severe pathogenic effect.

Conclusion

Clearly patients with any underlying health conditions were at higher risk of a severe clinical outcome from infection with age playing an important role in the severity of the clinical outcome. Patients with no underlying condition, the risk of a severe outcome has been reported to be greatest among those aged 30-49 years old and those aged 60 and older [13].

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