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2009 Pandemic H1N1 influenza: Risk factors for severe and fatal manifestations

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ABSTRACT

Introduction: Most of the confirmed 2009 H1N1 pandemic cases showed mild influenza like illness similar to seasonal influenza. However, there were also severe and fatal cases. Knowledge of the risk factors associated with severe and fatal cases is important. This study assessed the risk factors for severe and fatal manifestations. **Materials and Methods:** Search of Medline/PubMed (search period unrestricted) using keywords '*Pandemic*', '*H1N1 influenza'*, '*risk factor*', '*severe and/or fatal*' was performed. **Results:** The incidence of severe and fatal cases ranged from 20 to 100% and from 0.7 to 39% respectively. Studies on age as a factor showed mixed results but generally showed the younger age group to be at higher risk, different to that of seasonal influenza. Various co-morbid conditions such as pregnancy, obesity, diabetes mellitus, chronic pulmonary and cardiac disease, being immune suppressed, nutritional status, and delay in treatment have been shown to be important risk factors for severe disease. One study showed *Streptococcus pneumoniae* and *Human respiratory syncytial* virus A co-infection to have a role in the severity of the disease. Indirect racial study suggested that genetic factors are important. Other factors that may be important and required further research such as associated preexisting conditions such as arterial hypertension, active tuberculosis and neurological disease, in addition to over-responsive innate immune response, viral dose, alcohol consumption, and environmental factors. **Conclusion:** In the 2009 H1N1 influenza pandemic, risk factors for severe and fatal cases include preexisting medical conditions, obesity, underweight, pregnancy, and delay in antiviral treatment. Respiratory co-infection may be important.

Keywords: Influenza, influenza A virus, H1N1 subtype, hospitalisation, mortality, pandemics

INTRODUCTION

In 1998, triple-reassortant swine influenza A (H1) viruses that contained genes from swine, avian and human influenza viruses emerged among pig herds in North America. From December 2005 through February 2009, 11 cases of human infection with the triple-reassortant viruses in the United States were reported to the Centers for Disease Control and Prevention (CDC). [1, 2] In late March 2009

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the first human case was reported in Mexico and this was followed by an outbreak that marked the start of the latest influenza pandemic. [3] In April 2009, a strain of the outbreak causing virus that is closely related to the triple-reassortant viruses was identified. Then, the virus was called the novel swine origin H1N1 influenza virus, and the disease was called swine origin H1N1 influenza. [2, 4] The outbreak spread very fast, and WHO raised the pandemic level for swine origin H1N1 influenza from level 4 to level 5 on 29th April 2009. [2] Finally, WHO raised the pandemic level to level 6 on 11th June 2009, [5] the first in 41 years since the pandemic of influenza A (H3N2) in 1968. [2] Since, the disease was referred to as pandemic H1N1 2009 influenza. [6]

Most of the confirmed cases showed mild influenza-like illness similar to typical seasonal influenza cases. However, there were also severe and fatal cases, especially in Mexico. Knowledge of risk factors for severe and fatal cases is very important to provide more attention to those at high risk. To date, few studies on the 2009 pandemic H1N1 influenza cases provide information on the risk factors for severe and fatal cases. Therefore this study aimed to provide a more complete picture of the risk factors for severe and fatal manifestations.

MATERIALS AND METHODS

Search in Medline/PubMed without time restriction was carried out using the keywords '*Pandemic*', '*H1N1 influenza*', '*risk factor*', '*severe and/or fatal*'. The total number of articles identified from the search was screened for original and reviews articles concerning the pandemic H1N1 influenza. Articles concerning H1N1 influenza and environmental factors were also searched. Abstracts of identified articles were screened for conditions or risk factors that may be associated with severe and/or fatal manifestations. The relevant original articles that contained these data were included in this study, classified according to the extracted data and source, noted and tabulated. Review articles which contained additional data that were not reported in the original articles were also included.

The search identified 44 articles and eight of which were review articles. The data extracted included factors (proven or probable) reported to be associated with severe or fatal H1N1 influenza cases, the number of cases, the age (median and range), numbers or percentage of cases, odds ratios, relative risks and 95% confidence interval of those factors were noted, and tabulated. Finally, the results were reviewed in detail, summarised and the various risk factors were presented in a comprehensive way. For the analyses of factors that were associated with severe and fatal cases, 14 original articles, one animal study and one review article that provided adequate data and fulfilled the inclusion criteria were included. [5-31] The factors analysed included: age [5, 7-12, 18], underlying co-morbid conditions [13, 14, 23], pregnancy and post partum [17, 24-28], co-infections [21, 22], obesity [15, 29, 30], time of treatment [6] and other factors. [16, 31]

RESULTS

The incidence of severe and fatal cases ranged from 20 to 100% and 0.7 to 39% respectively (Table 1). Conditions or factors that may be associated with severe and/or fatal manifestations were age, preexisting medical conditions that included nutritional

Table 1: Data on age of severe and fatal cases.

Origin of study	Number of patients	Severity	Age range (yrs)	Median/MSD
Mexico [7]	18	Severe *: 18 (100) Fatal: 7 (39)	9 to 52 **	45 **
Mexico [11]	2,582	Severe *: 821 (32) Fatal: 100 (4)	5 to 59 ***	NA
Argentina[8]	199	Severe *: 39 (20) Fatal: 20 (10)	<6 and >55 *	27.8 ±21.6*
USA [9]	272	Severe *: 67 (25) Fatal: 19 (7)	1 to 86 * 1.3 to 57 **	29 * 26 **
Canada [10]	1,479	Severe *: 308 (21) Fatal: 72 (5)	≥ 20 * ≥ 45 **	34 * 51 **
South Africa [12]	12,331	Severe: NR Fatal: 91 (0.7)	<1 to 70 **	33 **

Legends: MSD; mean ± standard deviation, NA; not available, NR; not reported* severe cases included fatal cases, ** fatal cases, *** from 71% of severe cases, and 87% of fatal cases.

status, pregnancy, time of treatment, bacterial co-infection, and genetics and other factors. Some studies on the age as a factor that increase the risk of severe and/or fatal outcome showed mixed results as can be seen in Table 1. With the exception of the study from Argentina that showed an age pattern similar to that of seasonal influenza, most studies have shown the age commonly affected was younger than 65 years old.

Preexisting conditions such as arterial hypertension, diabetes mellitus, chronic pulmonary and cardiac disease, active tuberculosis infection, neurological disease, immunosuppression or HIV infection, obesity, underweight, and pregnancy were associated with the severity of the disease (Table 2). One study showed that bacterial and viral co-infections contribute to the severity of the disease (Table 3).

In addition, time of treatment, genetic and other factors were also shown as risk factors for severe and fatal cases (Table 4).

DISCUSSION

There are many factors that had influenced the severity of the 2009 pandemic H1N1 influenza. Factors that have been associated with severe or fatal manifestations included preexisting medical conditions, pregnancy, poor nutritional status, immunosuppression, delay in initiating antiviral treatment, co infections (bacterial or viral), genetic predispositions and age. In addition, some factors from a theoretical point of view might have also influenced the severity and outcomes of the disease, and require further studies.

In seasonal influenza, the high risk age groups for severe and fatal manifestations have been the young and the elderly (65 years and over). [18] However in the recent H1N1 pandemic, data from WHO showed that the majority of severe and fatal cases had occurred in the 30 to 50 age group. [5] In Mexico, findings showed that 87% of fatal and 71% of severe cases occurred in those aged between the 5 to 59 years. [7, 11] In Canada, age 20 years or older was found to be associated with higher risk of severe manifesta–

tions. [10] In the United States, only 5% of those affected were 65 years of age or older. [9] Interestingly in Argentina, a pattern similar to those seen in seasonal influenza were reported. [8] Generally, most studies showed that age group distribution of mild, moderate and severe to fatal cases in this pandemic is different from those of seasonal influenza. [19]

It is not exactly known why the certain age groups are more affected in both seasonal influenza and the recent H1N1 pandemic. In general, children and young adults are more likely to be in public places (schools and work places) and be exposed to the seasonal flu-like illnesses. As a result, these groups may have certain degrees of immunity. However, it has been shown that previous seasonal flu exposures do not confer any protection against the recent H1N1 pandemic. [20] Chowell *et al.* postulated that in this H1N1 pandemic, one reason why the elderly populations were less affected and at lower risk for severe manifestations was probably due to immunity from previous exposure to H1N1 strains before the 1957 pandemic. [11] This was proven by the presence of cross reactive anti–bodies in elderly. [20]

In Mexico, bacterial co-infection was not shown to be a contributory factor to the severity of the disease. [7] A larger study that

Table 2. Preexisting conditions in severe and fatal cases.

Pre-existing conditions	**Percentage/proportion of preexisting Condition among severe/fatal cases**	**Odd Ratio (OR), Relative Ratio (RR), 95% Confidence Interval (CI)**
Arterial hypertension	Proportion: 3/18 [7]	Not reported
Diabetes mellitus	Proportion: 2/18, [7] 15%* [12]	RR= 2.2, 95% CI= 1.7-2.7[10] OR**= 2.3*, 95% CI= 0.8-7.0* [13]
Chronic pulmonary disease (Asthma or COPD)	Proportion: 2/18, [7] 28% [9]	RR=1.8*, 95% CI= 1.1-3.1*[10] OR** (C)=4.38, 95%CI (C)=1.81-10.60 [14]
Active tuberculosis	10%* [12]	Not reported
Chronic cardiac disease	13%* [12]	RR= 2.1, 95%CI= 1.6-2.7[10] OR***= 6.6*, 95%CI= 1.7-26.0* [13]
Neurological disease	18%[9]	Not reported
Immunosuppression/ HIV infection	18%, [9] 53%* [12]	RR= 1.5, 95%CI= 1.1-2.0 [10] OR***= 3.5*, 95%CI= 1.02-11.9* [13]
Obesity (BMI ≥30 Kg/m2)	22%* [12]	OR***= 9.1[13] 95%CI= 4.4-18.7 [13] OR***= 2.6*[13] 95%CI= 0.97-7.0* [13] OR (MO) = 4.7 [15,] 95%CI (MO)=1.3-17.2[15] OR (MO) =7.6* [15,] 95%CI (MO) = 2.1-27.9* [15] OR (A) = 3.1* [15] 95%CI (A) = 1.5-6.6* [15]
Underweight		OR (B) = 5.5 [15] 95%CI (B) = 1.3-22.5 [15]
Pregnancy	9%,[9] 28%* [12]	RR (NP)= 5.2, [a] 6.5, [b] 1.4* [16] 95%CI (NP)= 4.6-5.8,[a] 4.8-8.8,[b] 0.4-4.5* [16]
Combinations	Proportion: 1/18 [7]	

Legends: COPD= chronic obstructive pulmonary disease, *for fatal outcome, **age adjusted, ©; children, ***; adjusted for age and other confounding factors, (MO); morbidly obese (BMI ≥ 40 Kg/m2), age ≥ 20 years, without preexisting chronic medical condition, (A); age ≥ 20 years, without preexisting chronic medical condition, (B) age 2-19 years, without preexisting chronic medical condition, (NP) compared to non pregnant women, [a] for hospitalisation, [b] for ICU admission

Table 3: Impact of co-infection on severity of H1N1 infections.

Microorganism	Severe	Mild	p value
Streptococcus pneumoniae	56.4%	25.0%	0.0004
Haemophilus influenzae	23.1%	59.4%	0.0001
Staphylococcus aureus	2.6%	25.0%	0.0008
Respiratory syncytial A virus	15.4%	3.1%	0.0085

had studied 574 pandemic H1N1 influenza associated deaths (excluding those in Canada and Australia) also failed to show any correlation with co-infection. [21] In the recent H1N1 pandemic, most of the severe pneumonias were attributed to the H1N1 virus. [22] *Respiratory syncytial A* co-infection was also shown to be significantly higher in severe cases compared to milder cases (p=0.0085). [8] Interestingly, a study from Argentina (n=199) showed that *Streptococcus pneumoniae* co-infection was a risk factor for severe manifestations with adjusted odds ratio of 125.5, and 95% confidence interval 16.95-928.72 (p= 0.0001) in the 6-55 years age group. However, it has to be taken into account that the findings from Argentina in the recent pandemic have been different to others.

In seasonal influenza, cardiac or pulmonary disorders (asthma, cystic fibrosis and bronchopulmonary dysplasia are known to be important risk factors for severe manifestations and poor outcomes. Other chronic diseases such metabolic diseases including diabetes mellitus, renal disease and cancers that lead to immune suppressed states are also risk factors for severe manifestations. [18] In the recent H1N1 pandemic, several studies have shown that co-morbid conditions are important risk factor. These include chronic pulmonary and cardiac diseases, active tuberculosis, diabetes mellitus, immunosuppression and neurological disorders. Even arterial hypertension to be associated with severe and fatal outcome. [7, 9, 10, 12-14] Interestingly, in children, asthma was shown to be a risk factor for severe manifestations with no clear relation to the severity of asthma. [14]

Similar to seasonal influenza, pregnancy has been shown to be an independent risk factor for severe and fatal manifestations in the H1N1 pandemic. [24, 25] A study in

Table 4: Other risk factors for severe and fatal manifestations.

Factor		Relative risk	95% confidence interval
Time of treatment> 48 hrs	Death	4.3	1.4-13.7
Indigenous Australians	Hospitalisations	6.6	6.2-7.2
	ICU admissions	6.2	5.0-7.6
	Death	5.2	3.4-7.9

ICU: Intensive care unit

California on H1N1 infection women of reproductive age who were hospitalised or died: non-pregnant (n=137), pregnant (n=94) and post-partum (n=8) showed only 34% of those who were pregnant had other established risk factors for severe manifestation. The majority (95%) were in the second or third trimester. Eighteen of the pregnant patients (19%) and four of the postpartum cases (50%) required intensive care, and eight died giving a mortality rate after admission to the intensive unit of 36%. [17] Delay in initiating treatment (administered < or = 2 days after symptom onset) was also found to be associated with higher risk for admission to the intensive care unit or death (relative risk of 4.3). A study from Melbourne, Australia looking at confirmed H1N1 hospitalised cases (n=122) showed that 25% of the female patients were either pregnant or postpartum. [27] In the United States, it has also been shown that a higher proportion of pregnant patients had severe manifestations (35.5%, 11 out of 31 confirmed and three probable H1N1 cases) compared to the non-pregnant patients. [26] Of the 45 H1N1-related deaths reported to CDC in this study, six were in healthy pregnant women. The largest study (n=328) on pregnant women hospitalised with H1N1 confirmed that pregnancy as an independent risk factor for severe and fatal manifestations. [16] This may be due to relative immune suppression during pregnancy. One study showed pregnant patients with H1N1 had significantly lower levels of IgG(2) (p=0.001) compared to healthy control pregnant subjects. [28]

In contrast to seasonal influenza, several studies have shown obesity to be associated with poor outcomes during the pandemic H1N1 influenza. [13, 15, 29, 30] A study from Michigan showed nine of 10 H1N1 cases admitted to the intensive care unit for acute respiratory distress were obese. Of this, seven were categorised as extremely obese with body mass index of over 40 kg/m^2. Three of these patients died giving a morality rate of 30%. [29] Interestingly, being underweight was also shown to be an independent risk factor among the 2 to 19 years group in a study that had looked at 361 confirmed H1N1 cases. [15] Therefore, being over or underweight is associated with poorer outcomes.

During the avian influenza outbreaks of 2005 delay in initiating anti-viral treatment was associated with poor outcomes. Those given treatment early had mild to moderate disease. A study that looked at 22 health-care workers who developed influenza-like illness after caring for the confirmed H1N1 cases and given early anti-viral treatment only developed mild to moderate disease. [7] Similarly, in pregnant and postpartum women, delayed treatment was associated with a higher risk for admissions to the intensive care unit or death. [17] Early presentations were also associated with lower mortality. One study (n=1479 confirmed cases) showed that with median delay of one day from symptom onset to admission increased the risk of death by 5.5% per day. [10] However, in this study early admission did not necessarily mean that patients were given treatment.

Genetic make up of patients may also be important based on ethnicity or racial background. In the Americas and the Pacific region, indigenous populations have been shown to have higher infections rates of developing severe and fatal manifestations (three to six-fold). A study in Australia

showed that the indigenous population had more severe and fatal outcome compared to non-indigenous Australians. [16]

La Ruche *et al*. speculated that family size, crowding, poverty, poor access to health services, and genetic factors might play a role in causing severe and fatal manifestations. [31] During the 1918–1919 pandemic in India, many severe and fatal cases were thought to be due to immune deficits secondary to malnutrition. [32] Reports on HIV infected patients with depressed immune response also showed that they had prolonged symptoms and increased risks for complications. [18] A study in Canada on 1749 H1N1 cases showed that immunosuppression was an independent risk factor for severe manifestations. [10] Another study from France (n=244) among patients admitted to intensive care units compared to 514 cases that were hospitalised in medical wards showed that immunosuppression was a risk factor that was associated with fatal outcome after adjusting for age and other confounding factors. [13]

In theory, apart from the factors discussed, there are other factors that might have contributed to the severity of the disease. These include virulence and viral dose, and environmental factors. Studies are required to assess their contributions. Some of these factors are shown in Table 5.

Fortunately, the end of the 2009 H1N1 pandemic was declared on 10th August 2010 and the world entered the post pandemic period. However, this does not mean that the pandemic virus has disappeared. Past pandemics taught us that the pandemic H1N1 virus will take on the behaviour of a seasonal influenza and will continue to circulate for some coming years. According to the WHO, during the past pandemic, the virus did not mutate to a more lethal form. [34] Therefore, the lessons learnt from the 2009 pandemic will be very valuable in dealing with future possibilities of H1N1 influenza outbreaks, epidemics or even a new pandemic, which may show similarities to the just passed pandemic. These future possibilities stress the importance of identifying the groups that have higher risk of severe or fatal illness.

This pandemic has also shown that progress can be made very quickly such as the development of the vaccine and this may have important implications in future pandemic. In Brunei Darussalam, vaccination was probably effective in reducing the number of cases. Of the 11 confirmed cases reported amongst those who had been vaccinated previously, the majority was only vaccinated few days before the infection. They might not have enough time to develop the antibody against the virus. [33] Whether the pandemic vaccine will provide protective immunity is

Table 5: Theoretical factors that may influence the severity of H1N1 infection.

Factors	**Descriptions**
Ethanol	Inhibit pulmonary CD8 T cell functions
Previous H1N1 exposure	Protective immunity
Viral load	May affect severity
Environmental toxins	Dioxin, arsenic, and cigarette smoke
Dust storms	Microbes, organic and inorganic materials

Note: *For further details on theoretical risk factors, please see supplementary text*.

still to be proven. Studies assessing the level of antibody against H1N1 influenza virus in those patients is required to assess the efficacy of the vaccine.

In conclusion, risk factors for severe and fatal manifestations in the 2009 H1N1 pandemic include pre-existing medical conditions such as chronic respiratory and cardiac diseases, immunosuppression, obesity, pregnancy and delay in initiating treatment. Other risk factors such as co-infections, genetics, arterial hypertension, active tuberculosis and neurological disease may be important and require further studies. Theoretical risk factors include over-responsive innate immune response, viral dose, alcohol consumption, and environmental factors.

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