Risk factors for severe outcomes following 2009 Influenza A (H1N1) infection: A Global Pooled Analysis

Short title: Risk Factors for H1N1pdm Severity

AUTHORS

WHO Working Group for Risk Factors for Severe H1N1pdm Infection†

†Maria D Van Kerkhove1,2 Katelijn AH Vandemaele1, Vivek Shinde1, Giovanna Jaramillo-Gutierrez1, Artemis Koukounari2, Christl Donnelly2, Luis O. Carlin3, Rhonda Owen4, Beverly Paterson5, Louise Pelletier6, Julie Vachon7, Claudia Gonzalez8, Yu Hongjie9, Feng Zijian8, Shuk Kwan Chuang8, Albert Au8, Silke Buda9, Gerard Krause9, Walter Haas9, Isabelle Bonmarin9, Kiyosu Taniguchi10, Kensuke Nakajima11, Tokuaki Shobayashi11, Yoshihiro Takayama12, Tomi Sungaw12, Jean Michel Heraud13, Arnaud Orelle13, Ethel Palacios14, Marianne AB van der Sande15, CCH Lieke Wielders15, Darren Hunt16, Jeffrey Cutter17, Vernon Lee16,17 Juno Thomas16, Patricia Santa-Olalla18, Maria J. Sierra-Moros19, Wanna Hanshaoworakul20, Kumnuan Ungchusak20, Richard Pebody21, Seema Jain21, Anthony W Mounts2*Corresponding author

Key Words (5 max): pandemic H1N1, risk factor, severe disease, hospitalizations, deaths

Corresponding author

Anthony W Mounts
Global Influenza Programme, World Health Organization
20 Appia Way, Geneva 1200 Switzerland
Email: mountsa@who.int
Tel: +41 22 791 1062

1 Global Influenza Programme, World Health Organization
2 MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London UK
3 Ministerio de Salud de la Nación, Buenos Aires, Argentina
4 Influenza Surveillance Section, Surveillance Branch, Office of Health Protection, Department of Health and Ageing, Australia
5 Influenza Surveillance Section, Public Health Agency of Canada, Ontario, Canada
6 Departamento de Epidemiología, División de Planificación Sanitaria, Ministerio de Salud de Chile
7 Office for Disease Control and Emergency Response, Chinese Center for Disease Control and Prevention Beijing, P.R. China
8 Surveillance and Epidemiology Branch, Centre for Health Protection, Centre for Health Protection of Department of Health, Hong Kong SAR
9 Department of Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
10 Département des maladies infectieuses, Institut de Veille Sanitaire, Saint-Maurice Cedex, France
11 Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan
12 Ministry of Health, Labour and Welfare Japan
13 Virology Unit, Institut Pasteur from Madagascar, Antananarivo, Madagascar
14 Directorate General of Epidemiology, FCO, De P. Miranda, Mexico City, Mexico
15 Epidemiology and Surveillance Unit, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands
16 New Zealand Ministry of Health, Wellington, New Zealand
17 Communicable Diseases Division at the Ministry of Health, Singapore
18 Biodefence Centre, Ministry of Defence, Singapore
19 Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
20 Epidemiology and Surveillance Unit, Respiratory Virus Unit, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa
21 Coordinating Centre for Health Alerts and Emergencies, Dirección General de Salud Pública y Sanidad Exterior Ministerio de Sanidad y Política Social, Spain
22 Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand
23 Health Protection Agency, England
24 Epidemiology and Prevention Branch, Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA
Abstract

Background: Since the start of the 2009 influenza A pandemic (H1N1pdm), WHO and its member states have gathered information to characterize the clinical severity of H1N1pdm infection and to assist policy makers to determine risk groups for targeted control measures.

Methods and findings: Data were collected on approximately 70,000 H1N1pdm laboratory-confirmed hospitalized patients, 9,700 patients admitted to ICU and 2,500 deaths reported between April 2009 and January 2010 from 19 countries or administrative regions – Argentina, Australia, Canada, Chile, China, France, Germany, Hong Kong SAR, Japan, Madagascar, Mexico, the Netherlands, New Zealand, Singapore, South Africa, Spain, Thailand, the United States, and United Kingdom – to characterize and compare the distribution of risk factors among H1N1pdm patients at three levels of severity: hospitalizations, intensive care unit (ICU) admissions and deaths.

The median age of patients increased with severity of disease. The highest per capita risk of hospitalization was among patients <5 and between 5–14 years old (RR=3.3 and 3.2, respectively, compared to the general population), whereas the highest risk of death per capita was in the 50–64 and >65 year old age groups (RR=1.5 and 1.6, respectively, compared to the general population). Similarly, the ratio of H1N1pdm deaths to hospitalizations increased with age and was the highest in the >65 year old age group, indicating that while infection rates have been observed to be very low in the older age group, risk of death in those over the age of 65 years who became infected was higher than in younger groups. The proportion of H1N1pdm patients with ≥1 reported chronic condition increased with severity (median 31.1%, 52.3% and 61.8% of hospitalized, ICU and fatal H1N1pdm patients, respectively). With the exception of asthma, pregnancy and obesity, the proportion of patients with each risk factor increased with severity level. For all levels of severity, pregnant women in their third trimester consistently accounted for the majority of the total of pregnant women. Our findings suggest that morbid obesity might be a risk factor for ICU admission and fatal outcome (RR=36.3).

Conclusions: Our results demonstrate that risk factors for severe H1N1pdm infection are similar to seasonal influenza with some notable differences, such as younger age groups, and obesity, and reinforces the need to identify and protect groups at highest risk of severe outcomes.

Conclusion

In late April 2009, a novel strain of influenza A H1N1 was identified from Mexico and the United States. This virus quickly spread globally and on June 11, 2009, the World Health Organization (WHO) declared the pandemic alert phase 6, indicating that the first influenza pandemic of the 21st century had begun [1,2,3]. Many Northern hemisphere temperate countries passed their first wave during their spring and summer months of 2009, followed by an early 2009 fall influenza season. Southern hemisphere temperate countries passed their first wave during their winter of 2009 and at the time of writing are finishing their winter 2010 season. By the end of 2009, the peak of the local influenza epidemic had passed in most countries across the world [4].

Since the start of the pandemic, WHO and member states have been gathering information to characterize the clinical picture and patterns of risk associated with the new 2009 pandemic influenza A H1N1 (H1N1pdm) virus infection to assist public health policy makers to target vaccination strategies, antiviral use and other control measures. Risk factors for severe disease following seasonal influenza infection have been well documented in many countries, and include chronic medical conditions such as pulmonary, cardiovascular, renal, hepatic, neuromuscular, hematologic, and metabolic disorders, some cognitive conditions, and immunodeficiency [5,6,7]. The risk associated with pregnancy in seasonal influenza is less well documented but in previous pandemics, pregnant women were identified as at increased risk of adverse outcomes and many countries include healthy pregnant women among the seasonal high risks groups as well [8,9,10,11]. However, early in the 2009 H1N1 pandemic, risk factors for severe disease following infection were largely unknown. Following a series of teleconferences organized by WHO with clinicians treating H1N1pdm patients around the world, it appeared that the most common risk factors for severe H1N1pdm disease were similar to those for seasonal influenza infection; however, several new factors (e.g., obesity, and tuberculosis [TB]) were also observed with high frequency in some countries. It was also noted that members of indigenous/aboriginal communities in some countries appeared to be over represented among severe cases [12].

While many countries have recently reported data on the association between severe H1N1pdm influenza and the presence of a variety of underlying risk factors (e.g., [1,3,4,5,6,7,8,9,10,11,12]), these data are presented in different formats making direct comparisons across countries difficult and no clear consensus has emerged for some conditions. This paper presents data from approximately 70,000 lab-confirmed hospitalized and 2,500 fatal cases in 19 countries or administrative regions – Argentina, Australia, Canada, Chile, China,
France, Germany, Hong Kong SAR, Japan, Madagascar, Mexico, the Netherlands, New Zealand, Singapore, South Africa, Spain, Thailand, United States, and United Kingdom – in order to characterize and compare the distribution of underlying risk factors among H1N1pdm confirmed patients who were hospitalized, admitted to an intensive care unit (ICU) or died and to assess the frequency and distribution of known and new potential risk factors for severe H1N1pdm infection.

**Methods**

This study compares data primarily obtained from surveillance programs of the Ministries of Health or National Public Health Institutes of 19 countries or administrative regions covering the period April 2009 to January 2010. Countries were asked to provide risk factor data on laboratory-confirmed cases using a standardized format for this analysis. The data were collected in the course of routine surveillance, methods of which varied from country to country [27,28,29,30,31,32,33,34,35,36,37,38,39, 40,41,42,43,44,45,46,47,48,49], and were reported anonymously and as aggregate data; hence no ethics approval was required. Potential risk conditions were grouped into four categories: age; chronic medical illnesses, pregnancy (by trimester); and other conditions that were not previously considered as risk conditions for severe influenza outcomes, such as obesity, membership in a vulnerable social or ethnic group, and TB. Details of the standardized format and definitions of each of the conditions are provided in the supplemental information (SI).

Risk factor information was collected separately for three levels of severity of illness in laboratory-confirmed patients: hospitalizations, admissions to ICU, and fatalities by country. Details of the available data from countries by risk factor and severity level are provided in the supplemental information. For each risk factor, except for pregnancy, the percentage of patients hospitalized, admitted to ICU and died was calculated using the total number of cases reported in each severity category. To evaluate the risk associated with pregnancy, the ratio of pregnant women to all women of childbearing age (age 15–49 years) in each level of severity was used to describe the differences between levels. The overall median and interquartile ranges (IQR) were calculated for each risk factor using all available data. In addition, where available, countries provided baseline comparison data for prevalence of the risk factor in the general population (details and sources provided in the SI). Data on age were provided by age groups (<5, 5–14, 15–24, 25–49, 50–64 and ≥65 years old).

**Risk of severe disease**

Where data were available, we calculated the risk for severe H1N1pdm outcomes (hospitalization, admission to ICU and death) compared to the prevalence of risk factors in the general population (relative risk of hospitalization [RRhosp], relative risk of ICU admission [RRICU], relative risk of death [RReath]) by country. See supplemental information for more information and formulae.

For pregnancy, we first calculated the proportion of women of childbearing age who were pregnant in each severity category by dividing the number of pregnant women in that category by number of women of childbearing age in that category. As individual case data were not available, we calculated the number of fertile women in each level of severity using the numbers of patients in each level of severity in the age range between 15 and 49 years multiplied times the percentage for that severity level that was female. Unless provided by the country, the point prevalence of pregnant women in the general population (the denominator of the RR calculation) was calculated using crude birth rate and 2010 UN population estimates [50] to derive the annual number of pregnancies, multiplied by 40/52 and without adjusting for seasonality of pregnancies, abortions, miscarriages, early deliveries, or multiple births. We also calculated the country-specific odds ratios (OR) and 95% confidence intervals (CI) for death given hospitalization separately for each risk factor (i.e., the odds of death given hospitalization and a specific risk factor), thereby comparing the odds of death in one group (for example, among hospitalized patients with asthma) with the odds of death in all other hospitalized patients combined (for example, among hospitalized patients without asthma) (individual country ORs not shown). We then used the I² statistic to quantify the percentage of variation across countries that is due to true underlying heterogeneity in the OR rather than chance variability [51]. The I² statistics for all examined risk factors indicated that there was substantial true underlying variation between ORs from different countries (Figure 3). We undertook meta-analyses with and without random effects in parallel to describe the distribution of the OR estimates across the countries for which data were available for analysis. As expected, given the heterogeneity observed between countries, the random-effects meta-analysis yielded wider confidence intervals. We conservatively report the pooled estimates from the random effects meta-analysis to describe the distribution of the OR estimates across the countries for which data were available for analysis. Underlying the random effects approach is the assumption that, although the individual countries give rise to different OR estimates, these estimates arise from a distribution with a central value, the estimate of which is referred to as the “pooled OR”, and normally distributed variability around this value.
All and meta-analyses techniques were performed using STATA v10 (StataCorp, College Station, Texas).

**Results**

Data were collected on approximately 70,000 patients requiring hospitalization, 9,700 patients admitted to ICU and 2,500 fatal patients from 19 countries and administrative regions across the Americas, Asia, Europe and Africa.

**Age and gender**

Approximately half of all patients included in this analysis in each level of severity were female (49.8%, 47.0% and 44.7% of all hospitalized, ICU and fatal H1N1pdm patients, respectively). This proportion did not vary significantly by country (Table 1). Age was associated with increased risk of poor outcome as indicated by several different parameters. The median age of patients increased with increasing levels of severity (Table 1). Among hospitalized patients, the median age within each country ranged from 7 years old in Japan to 38 years old in Spain with a median reported value among all countries, which provided data (n=14) of 19 years old (IQR 14.8–27.5); among patients admitted to ICU, the median age within each country ranged from 28 years old in China to 49.5 years old in Hong Kong SAR with a median value among all countries, which provided data (n=9) of 42 years old (IQR 35.0–45.0); and among fatal cases, median age within each country ranged from 30 years old in China to 56 years old in Hong Kong SAR with a median value among all countries, which provided data (n=13) of 46 years old (IQR 37.0–42.0). When the age distribution of the proportion of patients in each level of severity was compared to the distribution in the general population, the RR was highest in the <5 and 5–14 year age groups (RRhosp=3.3 and 3.2, respectively) but the RR of death was highest in the <5 and 5–14 year age groups (RRdeath=1.6 and 1.7, respectively) (Figure 1). The ratio of H1N1pdm deaths to hospitalizations increased with age and was the highest in the ≥65 year old age group in all countries from which data were available (Figure 2).

**Chronic illness**

The proportion of H1N1pdm patients with at least one chronic medical condition generally increased with severity (median among all countries which provided data of 31.1% [n=14], 52.3% [n=10] and 61.8% [n=16] of hospitalized, ICU and fatal H1N1pdm patients, respectively (Table 1). This pattern was observed for most countries (individual country data not shown). For nearly every individual risk factor under study, the prevalence increased significantly with severity level. Chronic respiratory conditions excluding asthma (median of 10.3%, 17.2%, 20.4%, respectively) and asthma (median of 17.6%, 9.8%, 5.3%, respectively) were the risk factors most often reported among severe cases, followed closely by diabetes (median of 9.0%, 13.6%, 14.4%, respectively) and chronic cardiac conditions (median of 7.1%, 10.9%, 12.1%, respectively). The pooled OR for death given hospitalization was significantly above one for each risk factor listed with the exception of asthma, and was highest for chronic liver disease and immunocompromised patients (Figure 3).

The risk of severe disease due to H1N1 infection, including hospitalization and death, was elevated for every chronic condition for which there was data available (Table 1). Notably, the RR for fatal disease due to H1N1pdm infection was also elevated for asthma (median RRdeath=1.7 [IQR 1.5–2.1]) and not markedly different from the RR associated with hospitalizations (median RRhosp=1.8 [IQR 1.2–2.6]). Data on chronic illness rates in the general population was not available from enough countries to permit an assessment of the relative magnitude of risk associated with various conditions with certainty.

**Pregnancy**

The proportions of women of child-bearing age who were hospitalized with H1N1 and were pregnant as part of all hospitalizations (median of all country data 17.4% [IQR 13.5%–30.2%]); who were admitted to ICU (median of all country data 15.0% [IQR 9.4–24.2%]); and who died (median of all country data 6.9% (0.0–9.1%) varied within each country. Pregnant women in their third trimester consistently accounted for more than half of all pregnant women among hospitalized, ICU-admitted, and fatal cases. However, with the exception of China, Thailand, and USA, the proportion of pregnant women decreased with increasing level of severity and the pooled OR for death given hospitalization during pregnancy was below 1 (pooled OR=0.6, 95% CI 0.2–2.5).

Pregnant women with H1N1pdm infection were at higher risk of hospitalization compared to women of child bearing age in the general population without H1N1pdm infection with an unadjusted RR of hospitalization ranging from 3.5 in Germany to 25.3 in France (median RRhosp 6.8, n=10 countries). The unadjusted RR of death, while elevated compared to non-pregnant women in more than half of countries, was generally lower than that for hospitalization with a median RRdeath 1.9, (n=11 countries). Four areas (Japan, the Netherlands, Hong Kong SAR, and Singapore) had a RRdeath of zero.

**Other risk factors**

The proportion of patients with obesity (BMI≥30 or clinically judged as obese) increased with increasing disease severity and represented a median of 6%, 11.3% and 12.0% of all hospitalized, ICU and fatal H1N1pdm patients, re-
respectively, and this pattern was also observed for morbid obesity (BMI > 40) with 3.0%, 5.0% and 15.2% respectively (Table 1). However, this pattern was not consistently reported in each country. For example, France, Thailand, and China observed similar proportions of obese patients among ICU and fatal cases, while Hong Kong, SAR, reported a lower prevalence of obesity among fatal cases than ICU admissions. Using data from all countries, the pooled OR for death given hospitalization for obesity (BMI ≥ 30 or clinically judged as obese) was 2.9 (95% CI 1.3–6.6; Figure 3). Compared to the general population in the two countries from which data were available, the risk of death associated with morbid obesity was increased (mean RRdeath 36.3 [IQR 22.4–50.1] n=2).

Canada, Australia, and New Zealand reported significant disparities in the burden of severe H1N1pdm disease across different ethnic groups. In these three countries, indigenous population groups were overrepresented among severe H1N1pdm cases requiring hospitalization and among fatal patients. In contrast, in Thailand and Mexico, minority groups were underrepresented among severe H1N1pdm cases. Taken together, the unadjusted median RR hospitalization of H1N1pdm patients among minority groups was 1.0 (IQR 0.2–3.7) and median RR death was 2.4 (IQR 1.2–3.8). TB data were reported from three countries and increased slightly with level of severity. The disease was reported in a median of 1.7%, 1.3% and 2.6% of hospitalized, ICU and fatal H1N1pdm patients, respectively. We were not specifically able to evaluate HIV because of a paucity of data on HIV in H1N1pdm patients.

Discussion

Our results demonstrate that a significant portion of severe and fatal cases had preexisting chronic illness, and that the presence of chronic illness increased the likelihood of death. It was notable, however, that approximately 2/3 of hospitalized cases and 40% of fatal cases did not have any identified preexisting chronic illness. However, it is unknown how many of these cases had other risk factors, such as pregnancy, obesity, and substance abuse (including smoking and alcohol), for which we were had insufficient information in this study. These figures are also dependent on the completeness of available data for recorded risk factors. As with seasonal influenza, the most common underlying chronic conditions among hospitalized patients were respiratory disease, asthma, cardiac disease, and diabetes. Interestingly, we found that although asthma was frequently associated with both hospitalization and death in most countries with an increased RR for both, the OR for death given hospitalization suggested that a higher proportion of hospitalized cases survived compared to other conditions. This may represent the occurrence of manageable influenza induced exacerbations of asthma prompting admission which do not progress to viral pneumonia or other fatal complications and the younger age in which asthma tends to occur [61].

Early data suggested that pregnancy might be an important risk factor for severe disease with H1N1pdm [21,25,62,63]. Our analysis is consistent with these reports and more recent studies [47,64], which found an overall trend that pregnant women, mainly in their third trimester, have a higher incidence of hospitalization than the general population. Several published studies have also shown that pregnancy is associated with a higher risk of ICU admission and fatal outcome [53,57,65,66]. In our analysis, the risk associated with pregnancy was elevated for both hospitalization and fatality when compared to women of child bearing age, though the latter was not consistently observed in every country. As with asthma, the proportion of pregnant women generally decreased with severity level for most of the countries. Our results suggest that pregnant women with H1N1pdm are approximately 7 times more likely to be hospitalized and 2 times more likely to die than non-pregnant women with H1N1pdm. The greater risk for hospitalization than death from pregnancy may have resulted from a lower threshold for admitting pregnant women and/or a more aggressive approach to antiviral or other treatment for pregnant women. In addition, the occurrence of non-respiratory complications of pregnancy, such as hypertension, pre-eclampsia, and premature labor provoked by infection may increase the risk of hospitalization but not result in death [67]. This would be consistent with published reports of case series of pregnant patients list complications of pregnancy as a common cause of admission [62,68,69]. The data set did not allow us to ad-
just for underlying conditions in pregnant women, and thus to distinguish between risks for healthy pregnant women, and pregnant women with underlying medical conditions; however, we believe that the results support and approach of early intervention with pregnant women who develop influenza.

Early in the 2009 pandemic, clinicians from the US reported a surprisingly high prevalence of morbid obesity, a risk factor not previously reported with severe outcomes for seasonal influenza infection, in patients with severe complications of H1N1pdm infection [70]. Subsequent studies in several countries, including the US, Mexico, Canada, Spain, Greece, France, Australia and New Zealand, reported high proportions of obesity among ICU admissions and fatal patients [13,20,57,63,71,72,73,74,75,76]. Our results provide supportive evidence that obesity may be a risk factor for severe disease, as seen in the increasing proportion of morbidly obese patients with severity level and the associated elevated odds ratio. Our findings also suggest that morbidly obese patients with H1N1pdm are more likely to die if hospitalized; however, the results in our analysis were not consistent across all countries. The association between obesity (or morbid obesity) and severe outcomes may reflect direct causation (e.g. due to greater respiratory strain on obese individuals), causation through other known risk factors (e.g. obesity causes diabetes and heart disease, which pose an increased risk for severe outcome [36], or a noncausal association, if some other factor (e.g. genetic or dietary) caused both morbid obesity and increased risk of severe outcome. Unfortunately our dataset did not allow us to distinguish among these non-exclusive alternatives. Indigenous populations and ethnic minorities have been reported to experience a disproportionately high burden of severe H1N1pdm infection, particularly in the Americas [14,21,23,36,63,74,77,78,79] and the Australasia-Pacific region [79,80,81,82], similar to reports during the 1918 influenza pandemic [83,84,85]. Our analysis of Australian, New Zealand, and Canadian data concur with these published reports, and while compelling, were not universal. Both Thailand and Mexico did not observe a significantly increased burden of severe H1N1pdm disease among indigenous or minority populations. Our data are not sufficient to explain the observed differences in the reported risk of severe disease among minority groups but several hypotheses have been proposed including: a higher prevalence of chronic medical conditions known to increase risk of severe influenza, delayed or reduced access to healthcare, cultural differences in healthcare seeking behaviour and approaches to health, potential differences in genetic susceptibility, and social inequalities [23,77,79]. More research is needed to better understand and quantify the increased risk of severe H1N1pdm disease among these groups. However, an imperfect understanding of the mechanisms of health disparities related to severe H1N1pdm disease should not impede the public health community from undertaking actions to mitigate this risk through appropriate public information, targeted outreach and prevention programs, and involving at-risk population groups in pandemic planning.

Our analysis has a number of limitations, not least of which is the wide differences in surveillance systems, case management policies, and antiviral use in the countries studied. The criteria and indications for hospital and ICU admission for certain conditions (e.g., pregnancy, asthma) and by age (e.g., pediatric patients) varied significantly by country, and may have been somewhat dependent on capacity for admission, which likely varied over time. Risk factors are also dependent on the completeness and quality of data on risk factors reported classification of death in the absence of complete testing. These could lead to a bias in the estimate of these conditions among severe cases and could make direct comparisons across countries difficult. Second, our data do not consider multiple risk factors for individual H1N1pdm patients. A lack of individual level data on underlying medical conditions of H1N1pdm patients precludes our ability to sufficiently control for confounding and therefore identify the independent contribution of individual risk factors for severe disease and death. The differences observed in risk factors for hospitalization and death among H1N1pdm patients compared to seasonal influenza risk factors, and the wide range of RR between countries may be explained by differences in age structure in the general population. Several studies have identified important differences in the proportions of underlying conditions by age among hospitalized and fatal cases, including, but not limited to, the UK [15,52], USA [36], Canada [47], and Singapore [39,86].

A third limitation is related to our imperfect calculation of the point prevalence of pregnancy among women of child bearing age in the general population. However, we believe that our findings of the range of RR for hospitalization and death is valid, but may be very slightly inflated because of undercounting in the denominator. The inflationary effect of undercounting is likely greatest on pregnant women in the first trimester, as we didn’t adjust for common first trimester events like abortions, and in this group there is likely substantial undercounting in the numerator as well due to women not knowing they are pregnant in that period. Fourth, the data used in our analysis relied on hospital records, which were not standardized, likely to be incomplete or vary in quality between hospitals or countries. This poses a problem in the direct comparativeness between settings.

Despite these limitations, this analysis is the first to be able to compare risk factors across a variety of countries using data from a very large number of patients and found a great deal of consistency for much of the data. Clearly, cardiac disease, chronic respiratory disease, and
diabetes are important risk factors for severe disease that will be especially relevant for countries with high rates of these illnesses. We provide evidence to support the concern regarding obesity, particularly morbid obesity, as a risk factor, though this clearly needs more study. We found large between country variations with some important risk factors, most notably pregnancy, and the reasons for these differences need more study. There is evidence to suggest that the differences observed with pregnancy might represent differences in case management practices and we believe that the available evidence supports vaccination and early intervention for pregnant women. Our study reinforces the need to identify and target high-risk groups for interventions, such as immunization, information, early medical advice and use of antiviral medications. Experience with the 2009 H1N1 pandemic and the differences observed between countries has highlighted the need for country specific surveillance data, global standardization of case definitions and data collection, and the usefulness of data sharing to aid policy makers in critical decision making for global influenza epidemics.

**Acknowledgements**

The authors would like to recognize the hard work of all the individuals, including GPs, nurses and other healthcare workers, Municipal Health Centres, hospitals, virology laboratories and reference labs, and the Ministries of Health, who provided care to H1N1pdm patients, provided data and information, and kept the public informed. The authors would like to specifically acknowledge: Anna Bramley, MPH, from the Influenza Division at CDC, who has managed and analyzed the US data; Marta Cortes-García, MD, MPH, from the Coordinating Centre for Health Alerts and Emergencies who collected and managed the Spanish data; the Regional Surveillance and Alert Teams from the Autonomous Communities in Spain; Liao Qiaohong and Feng Luzhao from China CDC and Huai Yang from the China–U.S. Collaborative Program on Emerging and Re-emerging Infectious Diseases, Beijing, China; Tessa van ’t Klooster and Tjibbe Donker from the Epidemiology and Surveillance Unit, and Leslie Isken from the Preparedness and Response Unit, for SARI surveillance coordination at the Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands; and Cheryl Cohen from the National Institute for Communicable Diseases, South Africa. The authors also wish to acknowledge the six restructured and six private hospitals in Singapore which provided reports of laboratory-confirmed hospitalized H1N1pdm cases.

Finally, the authors would also like to thank Matthew Lim and Lyn Finelli for their review of the manuscript and the Medical Research Council (MVK, CD, AK) and Bill and Melinda Gates Foundation (MVK) for funding.
TABLE 1. Risk factors by severity level for select countries and risk of severe disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Severity Level</th>
<th>Relative Risk of Severe Disease (IQR) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospitalized Patients</td>
<td>ICU Patients</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>14</td>
<td>19.0 (14.8–27.5)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>12</td>
<td>49.8 (46.2–51.5)</td>
</tr>
<tr>
<td>Chronic Medical Illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>12</td>
<td>10.3 (5.0–21.7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>11</td>
<td>17.6 (10.0–20.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>9.0 (3.5–12.6)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>12</td>
<td>7.1 (3.7–10.9)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>13</td>
<td>4.0 (2.0–5.1)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>9</td>
<td>1.1 (0.3–2.0)</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>11</td>
<td>4.0 (2.5–7.5)</td>
</tr>
<tr>
<td>Immune compromised</td>
<td>13</td>
<td>5.0 (2.0–7.2)</td>
</tr>
<tr>
<td>Cases with ≥1 of the chronic medical illness</td>
<td>14</td>
<td>31.1 (19.0–47.1)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>7</td>
<td>2.0 (1.0–3.5)</td>
</tr>
<tr>
<td>Second trimester</td>
<td>7</td>
<td>7.0 (3.9–9.3)</td>
</tr>
<tr>
<td>Third trimester</td>
<td>7</td>
<td>9.5 (7.6–21.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>6.0 (1.9–9.3)</td>
</tr>
<tr>
<td>Total (any trimester)</td>
<td>10</td>
<td>17.4 (13.5–30.2)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥30 or clinically obese)</td>
<td>11</td>
<td>6.0 (1.5–7.5)</td>
</tr>
<tr>
<td>Body Mass Index 30–40</td>
<td>3</td>
<td>7.0 (4.4–16.0)</td>
</tr>
<tr>
<td>Body Mass Index &gt;40</td>
<td>5</td>
<td>3.0 (1.4–11.5)</td>
</tr>
<tr>
<td>BMI not measured but judged clinically obese</td>
<td>8</td>
<td>4.3 (1.8–13.3)</td>
</tr>
<tr>
<td>Vulnerable social/ethnic group</td>
<td>4</td>
<td>5.2 (2.3–10.6)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2</td>
<td>1.7 (0.9–1.8)</td>
</tr>
</tbody>
</table>

‡ See Supplemental Information for definitions of risk factors.
† The number of countries providing data for cell directly to the right, full list of countries which provided data for each risk factor is provided in the SI.
NA Not assessed.
A RR hosp and RR death calculated by age group and shown in Figure 1.
B RR hosp = unadjusted relative risk of hospitalization among H1N1pdm patients with the risk factor compared to the risk of hospitalization among H1N1pdm patients without the risk factor and RR death = unadjusted relative risk of death among H1N1pdm patients with the risk factor compared to the risk of death among H1N1pdm patients without the risk factor; range of RR provided if ≥2 countries provided data.
C Denominator = women of child bearing years in each level of severity.
FIGURE 1.
Relative risk of (a) hospitalization, (b) ICU and (c) death by age group compared the general population.
Legend: Countries included in hospitalization (a) and mortality (b) RR: Japan, Hong Kong SAR, China, Singapore, Thailand, Chile, Germany, the Netherlands, Spain, New Zealand, Canada, US, Madagascar (hospitalizations only), and France (deaths only); Countries included in ICU RR (c): Japan, Hong Kong SAR, China, Singapore, Canada, Spain, the Netherlands, USA, New Zealand, South Africa. Bars represent the min/max rate per age group. Dark line represents pooled RR, shaded lines are individual country RR.
FIGURE 2.
Ratio of confirmed H1N1pdm deaths to hospitalizations for selected countries
Legend: Countries included in figure: Spain, Singapore, China, Hong Kong, Canada, the Netherlands, Thailand, Chile, Germany, Japan, USA, New Zealand; Bars represent maximum country ratio.

FIGURE 3.
Pooled odds ratio and 95% CI of risk of death given hospitalization for selected countries
Legend: See supplemental information section 4 for countries included in the pooled risk factor odds ratios.
References


