Infection Fatality Risk of the Pandemic A(H1N1)2009 Virus in Hong Kong


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One measure of the severity of a pandemic influenza outbreak at the individual level is the risk of death among people infected by the new virus. However, there are complications in estimating both the numerator and denominator. Regarding the numerator, statistical estimates of the excess deaths associated with influenza virus infections tend to exceed the number of deaths associated with laboratory-confirmed infection. Regarding the denominator, few infections are laboratory confirmed, while differences in case definitions and approaches to case ascertainment can lead to wide variation in case fatality risk estimates. Serological surveillance can be used to estimate the cumulative incidence of infection as a denominator that is more comparable across studies. We estimated that the first wave of the influenza A(H1N1)pdm09 virus in 2009 was associated with approximately 232 (95% confidence interval: 136, 328) excess deaths of all ages in Hong Kong, mainly among the elderly. The point estimates of the risk of death on a per-infection basis increased substantially with age, from below 1 per 100,000 infections in children to 1,099 per 100,000 infections in those 60–69 years of age. Substantial variation in the age-specific infection fatality risk complicates comparison of the severity of different influenza strains.

death; human influenza; severity

Abbreviations: CI, confidence interval; IFRc, infection fatality risk based on deaths of confirmed cases; IFRe, infection fatality risk based on excess influenza-associated deaths; ILI, influenza-like illness; LAB, laboratory; pH1N1, pandemic influenza A(H1N1)pdm09.

The severity profile of a pandemic influenza virus, in combination with its transmissibility, determines the impact it will have in a population (1). One commonly reported measure of severity at the individual level is the risk of death among people infected by the virus, and this conditional measure is referred to as the “case fatality risk” or, sometimes, as the “case fatality rate” or “ratio.” There are well-known complications in quantifying both the numerator and the denominator of the case fatality risk (2). Regarding the numerator, deaths of individuals with confirmed infection would underascertain all deaths associated with infection (3–6). Instead of directly counting “confirmed” deaths, it is also possible to statistically estimate excess deaths (5–9). Regarding the denominator, most influenza infections are mild; laboratory testing has limited capacity, is expensive, and is often unnecessary for clinical management; and therefore few infections would be laboratory confirmed (10, 11).

It is feasible to estimate the incidence rates of infections in a population if relevant surveillance data are available (12, 13), and the estimated cumulative incidence of infection may provide more unbiased denominators of case fatality risk that address the unobservability of infection and minimize ascertainment bias. In the present study, we propose such a severity measure referred to as the “infection fatality risk” and define it as the number of influenza-associated deaths divided by the number of infections in a population or subgroup. The infection fatality risk is expected to permit comparisons (e.g., across age groups and risk groups), and we investigate the infection fatality risk based on deaths of confirmed cases (IFRc) as well as the infection fatality risk based on excess influenza-associated deaths (IFRe). IFRc involves ascertainment and underreporting biases, while IFRe assumes full description of observed data by statistical modeling.
The first objective of our study was to estimate the number of excess deaths associated with the first wave of pandemic influenza A(H1N1)pdm09 (pH1N1) in Hong Kong. The second objective was to estimate the age-specific severity profiles of IFRc and IFRe and to investigate the differences between them.

MATERIALS AND METHODS
Sources of data
Information on age-specific all-cause deaths and the corresponding annual midyear populations from 2001 through 2009 was obtained from the Hong Kong Government Census and Statistics Department (14, 15). Information on age-specific hospitalizations and deaths associated with laboratory-confirmed pH1N1 infection from May 1, 2009, through December 31, 2009, was provided by the Hong Kong Hospital Authority. Surveillance data on influenza-like illness (ILI) from around 50 sentinel general practitioners were available as the weekly proportion of outpatients reporting a fever of >37.8°C plus a cough or sore throat (denoted “ILI data” hereafter), along with local laboratory (LAB) data on the weekly proportion of specimens from sentinel outpatient clinics and local hospitals that tested positive for influenza (denoted “LAB data” hereafter) (16). Surveillance data stratified by age were not available. Data on temperature and humidity were obtained from the Hong Kong Observatory (17). Age-specific estimates of the cumulative incidence of pH1N1 infection in the first wave were determined in separate serological surveillance studies (18, 19) and used as the denominators for estimation of IFRc and IFRe.

Statistical analysis
We assume that all excess deaths are truly associated with pH1N1. To address the uncertainty, 4 statistical models were used to estimate the excess deaths, namely, time-series regression, linear regression, and Poisson regression with log links and identity links. In each approach, we compared excess death estimates based on 4 different proxy measures of local influenza activity including the following: 1) weekly incidence rates of pH1N1 infection, 2) weekly ILI data, 3) weekly LAB data, and 4) the product of weekly ILI and LAB data. Incidence rates of pH1N1 infection were estimated by deconvoluting the time series of hospitalizations associated with pH1N1, allowing for the delay from infection to hospitalization and scaling to serial cross-sectional serological data (Web Appendix available at http://aje.oxfordjournals.org/) (18).

We applied each regression model to the time series of weekly all-cause mortality rates from 2001 through 2009, excluding February–September of 2003, which was affected by the Severe Acute Respiratory Syndrome epidemic. The data were stratified into 8 age groups: 0–4 years, 5–14 years, 15–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, and ≥70 years. In each regression model, we included one of the measures of influenza activity as a covariate, lagged by 1 week to allow for a delay between infection and death, and also adjusted for covariates including seasonal influenza activity, respiratory syncytial virus activity, mean temperature, and absolute humidity (Web Appendix). Trigonometric components were included to allow for cyclic annual seasonality. The influenza-associated excess mortality rates were calculated by subtracting the predicted mortality rate estimated from each fitted regression model setting influenza activity as zero from the predicted mortality rate from the same model based on the observed weekly influenza activity. Further details of the statistical methods are described in the Web Appendix. All analyses were conducted in R, version 2.13.1, language and environment (20).

RESULTS
The first wave of pH1N1 in Hong Kong began in the summer and peaked in September 2009 before activity declined to low levels (Figure 1). Local all-cause mortality rates generally increased in the winter, and there was no obvious increase in all-cause deaths during the peak of the pandemic (Web Appendix). Because the patterns of age-specific pH1N1 incidence rates were similar in each age group (Figure 1), we directly standardized these age-specific pH1N1 incidence rates using the Hong Kong population. The resulting age-standardized incidence rates were then used as a single proxy measure of influenza activity.

We compared the correlation between the ILI data, the LAB data, and the product of ILI and LAB data versus age-standardized incidence rates (Figure 2). ILI data tended to overestimate the lower levels of pH1N1 incidence rates, as did the LAB data to a lesser extent, while the product of ILI data and LAB data had the strongest correlation with pH1N1 incidence rates.

Using age-standardized pH1N1 incidence rates as the proxy of influenza activity, we estimated that the overall number of excess deaths associated with the first wave of pH1N1 was 232 (95% confidence interval (CI): 136, 328) under the time-series regression model with most of the excess deaths in the elderly (Table 1, Web Table 1). Estimates of excess deaths were similar in each of the 4 regression models (Table 1, Web Table 1). Estimates of excess mortality based on proxy measures of influenza activity gave estimates similar to those based on estimated pH1N1 incidence rates (Table 1, Web Table 1). In comparison, there were 54 deaths in patients with laboratory-confirmed pH1N1 before December 31, 2009 (7). In sensitivity analyses, point estimates of the excess deaths were lower when influenza activity was lagged by 2 weeks and when it was not lagged (Web Table 2).

Based on deaths of patients with laboratory-confirmed pH1N1, point estimates of the IFRc increased with age from 0.4 to 164 deaths per 100,000 infections for individuals from 5–14 years to 60–69 years of age (Table 2). Similarly, based on estimated excess deaths by the time-series regression model using age-standardized incidence rates as the proxy measure of influenza activity, point estimates of the IFRe increased from approximately zero (point estimate −1.1, 95% CI: −6.1, 4.2) deaths per 100,000 infections in
those 5–14 years of age to 1,100 (95% CI: 180, 4,700) deaths per 100,000 infections in those 60–69 years of age.

**DISCUSSION**

We estimated that, during the first wave of the pandemic, pH1N1 was associated with 232 excess deaths among individuals at all ages, mostly among the elderly (Table 2). Among the elderly, we estimated that there were around 10 times as many excess deaths as deaths in patients with confirmed pH1N1 (21). Although the population-wide estimate involves a large standard error due to overall small age-specific estimates and large variations in the estimates by age group, previous estimates of the excess mortality associated with pH1N1 in Hong Kong were similar to those presented here (7). Excess deaths typically exceed confirmed

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**Figure 1.** All-cause deaths, pandemic A(H1N1)2009 virus (pH1N1) hospitalizations and deaths, and estimated pH1N1 incidence rates in Hong Kong, 2009. A) Weekly number of all-cause deaths; B) weekly number of hospitalizations of patients with confirmed pH1N1; C) weekly number of deaths of patients with confirmed pH1N1; D) age-specific estimated incidence rates of pH1N1 infection, estimated by deconvoluting hospital admission rates and scaling to serological surveillance data. Incidence rates by age group: 5–14 years (dot-dash-dot); 15–19 years (long dash); 20–29 years (double dash); 30–39 years (thick solid); 40–49 years (short dash); and 50–59 years (dotted), respectively, and the age-standardized incidence rates (thick solid), expressed as rates per 100,000 population per week. Incidence rates were standardized to the local Hong Kong population. Three-letter names and abbreviations on the inner label of the x-axis represent months of the year.
deaths because some deaths occur in individuals who do
not present to the health-care system, while others occur in
patients who are tested for pH1N1 only after cessation of
detectable viral shedding or who never receive a laboratory
test (3–6). In particular, excess influenza deaths in the
elderly tend to exceed confirmed deaths because of non-
specific presentation of influenza infections and the associ-
ation with nonrespiratory causes of deaths in this age
group (22, 23).

Although caution must be exercised in attempting causal
interpretation of statistical estimates of excess deaths due to
their ecological nature, 4 different statistical methods each
gave similar estimates of the excess deaths associated with
pH1N1 (Table 1). The ILI × LAB proxy, a measure of the
proportion of ILI due to pH1N1 among outpatients, was
highly correlated with the estimated incidence rates of
pH1N1 infection, suggesting that it may be a better proxy
of influenza activity than either the ILI data or LAB data
alone (Figure 2) (24, 25).

Using estimates of the excess deaths and the cumulative
incidence of infection, we found that the risk of death on a
per-infection basis increased substantially with age, with the
IFRe varying from below 1 per 100,000 infections in chil-
dren to the order of 1,100 per 100,000 infections in those
60–69 years of age. Combining information from a serologi-
cal study in the Netherlands (26) with excess death estimates
(21), we found that it is possible to obtain very similar esti-
mates of the IFRe, varying from 2.1 to 2,900 deaths per
100,000 infections for individuals from 5–24 years to 65–74
years of age. Although the incidence of infection was very
low among the elderly, probably due to preexisting immu-
nity associated with historical exposures to similar viruses
(27), we found that the high severity in this age group led to
a substantial impact on mortality (Table 2). We did not iden-
tify substantial differences between IFRc and IFRe for indi-
viduals below the age of 60 years.

Other studies provided a wide range of estimates of the
case fatality risk of pandemic influenza (3, 11, 19, 28–31).
The earliest study of the severity of pH1N1 did not account for age and estimated that the case fatality risk was 400 deaths per 100,000 infections (29). Another study from Mexico estimated that the fatality risk varied from 3 to 30 deaths per 100,000 cases with ILI in individuals aged 1–9 years and ≥70 years, respectively (30). In the United Kingdom, the infection fatality risk was estimated to range from 5 to 9 deaths per 100,000 infections for all ages (28). Studies on previous influenza pandemics in 1918, 1957, and 1968 estimated the fatality risk among clinically apparent illnesses to be 100–2,500 per 100,000 patients (31). However, estimates of the cumulative incidence of symptomatic infection are likely to vary depending on the case definition as well as health-care–seeking behaviors and surveillance systems. The IFRe, measured by using the cumulative incidence of infection derived from the serological data as the denominator and statistically estimated deaths as the numerator, may provide a more consistent and less biased approach for comparatively assessing the severity of infection than case fatality risk estimates.

Our study has a few limitations. First, estimates of IFRe may not be comparable between populations because the severity of infection could be affected by virus mutations, environmental conditions, or host factors that may vary in different countries (32). In addition, estimates of the number of excess deaths may be zero or even negative because of harvesting or virus interference (33, 34) and, in the presence of stronger such effects, the IFRe may not

### Table 1. Estimated Excess All-Cause Deaths by 4 Statistical Methods and 4 Measures of Influenza Activity, Assuming a 1-Week Lag Between Influenza Incidence and Death, in Hong Kong, 2009

<table>
<thead>
<tr>
<th>Age and Statistical Model</th>
<th>Influenza Incidence Proxy</th>
<th>Age-standardized Incidence Proxy</th>
<th>ILI × LAB</th>
<th>ILI</th>
<th>LAB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>95% CI</td>
<td>No.</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-series regression</td>
<td>2</td>
<td>−57, 61</td>
<td>−15</td>
<td>−72, 42</td>
<td>−19</td>
</tr>
<tr>
<td>Linear regression</td>
<td>19</td>
<td>−18, 55</td>
<td>−1</td>
<td>−37, 36</td>
<td>9</td>
</tr>
<tr>
<td>Poisson regression with log link</td>
<td>9</td>
<td>−23, 42</td>
<td>−8</td>
<td>−41, 25</td>
<td>−7</td>
</tr>
<tr>
<td>Poisson regression with identity link</td>
<td>16</td>
<td>−18, 50</td>
<td>−3</td>
<td>−37, 31</td>
<td>7</td>
</tr>
<tr>
<td>≥60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-series regression</td>
<td>231</td>
<td>154, 307</td>
<td>223</td>
<td>149, 298</td>
<td>162</td>
</tr>
<tr>
<td>Linear regression</td>
<td>230</td>
<td>128, 333</td>
<td>223</td>
<td>120, 326</td>
<td>160</td>
</tr>
<tr>
<td>Poisson regression with log link</td>
<td>230</td>
<td>154, 307</td>
<td>221</td>
<td>144, 298</td>
<td>161</td>
</tr>
<tr>
<td>Poisson regression with identity link</td>
<td>248</td>
<td>169, 326</td>
<td>236</td>
<td>158, 315</td>
<td>192</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ILI, influenza-like illness based on consultations with general practitioners; ILI × LAB, general practitioner consultations associated with influenza; LAB, laboratory specimens positive for influenza.

The earliest study of the severity of pH1N1 did not account for age and estimated that the case fatality risk was 400 deaths per 100,000 infections (29). Another study from Mexico estimated that the fatality risk varied from 3 to 30 deaths per 100,000 cases with ILI in individuals aged 1–9 years and ≥70 years, respectively (30). In the United Kingdom, the infection fatality risk was estimated to range from 5 to 9 deaths per 100,000 infections for all ages (28). Studies on previous influenza pandemics in 1918, 1957, and 1968 estimated the fatality risk among clinically apparent illnesses to be 100–2,500 per 100,000 patients (31). However, estimates of the cumulative incidence of symptomatic infection are likely to vary depending on the case definition as well as health-care–seeking behaviors and surveillance systems. The IFRe, measured by using the cumulative incidence of infection derived from the serological data as the denominator and statistically estimated deaths as the numerator, may provide a more consistent and less biased approach for comparatively assessing the severity of infection than case fatality risk estimates.

Our study has a few limitations. First, estimates of IFRe may not be comparable between populations because the severity of infection could be affected by virus mutations, environmental conditions, or host factors that may vary in different countries (32). In addition, estimates of the number of excess deaths may be zero or even negative because of harvesting or virus interference (33, 34) and, in the presence of stronger such effects, the IFRe may not

### Table 2. Severity Profile of Pandemic A(H1N1)2009 Virus During the First Wave in Hong Kong, 2009

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Population, no.</th>
<th>CII, %</th>
<th>95% CI</th>
<th>Confirmed Deaths, no.</th>
<th>IFRc</th>
<th>95% CI</th>
<th>Estimated Deaths, no.</th>
<th>IFRe</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>229,200</td>
<td>NA</td>
<td></td>
<td>0</td>
<td>NA</td>
<td>−8</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5–14</td>
<td>644,200</td>
<td>43.5</td>
<td>39.6, 48.3</td>
<td>1</td>
<td>0.4</td>
<td>0, 1.1</td>
<td>−3</td>
<td>−1.1</td>
<td>−6.1, 4.2</td>
</tr>
<tr>
<td>15–29</td>
<td>1,430,500</td>
<td>16.9</td>
<td>12.4, 21.3</td>
<td>4</td>
<td>1.7</td>
<td>0.3, 3.8</td>
<td>2</td>
<td>0.8</td>
<td>−12.3, 14.6</td>
</tr>
<tr>
<td>30–39</td>
<td>1,114,500</td>
<td>5.8</td>
<td>3.1, 9.7</td>
<td>7</td>
<td>10.8</td>
<td>3.6, 25.5</td>
<td>2</td>
<td>3.1</td>
<td>−40.1, 43.7</td>
</tr>
<tr>
<td>40–49</td>
<td>1,273,000</td>
<td>3.8</td>
<td>1.1, 7.5</td>
<td>6</td>
<td>12.5</td>
<td>3.4, 51.4</td>
<td>8</td>
<td>16.7</td>
<td>−51.2, 119</td>
</tr>
<tr>
<td>50–59</td>
<td>1,085,400</td>
<td>5.0</td>
<td>2.4, 8.3</td>
<td>15</td>
<td>27.9</td>
<td>14.6, 61.7</td>
<td>1</td>
<td>1.9</td>
<td>−59.2, 49.9</td>
</tr>
<tr>
<td>60–69</td>
<td>555,500</td>
<td>0.8</td>
<td>0.2, 4.2</td>
<td>7</td>
<td>164</td>
<td>18, 741</td>
<td>47</td>
<td>1,099</td>
<td>176, 4,657</td>
</tr>
<tr>
<td>≥70</td>
<td>671,400</td>
<td>NA</td>
<td></td>
<td>14</td>
<td>NA</td>
<td>184</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CII, cumulative incidence of infection based on serological surveillance studies (18, 19); IFRc, infection fatality risk based on deaths of confirmed cases; IFRe, infection fatality risk based on excess influenza-associated deaths; NA, not available; pH1N1, pandemic influenza A(H1N1)pdm09.

* Infection fatality risks are expressed as number of deaths per 100,000 infections. The denominators for IFRc and IFRe were the numbers of estimated pH1N1 infections in each age group. A bootstrap method was used to compute 95% confidence intervals. IFRc = deaths in confirmed cases/(CII × population) × 100,000. IFRe = estimated excess deaths/(CII × population) × 100,000.
fully capture the risk of mortality associated with influenza infection. Second, the ILI and laboratory surveillance systems in Hong Kong are not population based, while the laboratory specimens are mostly diagnostic specimens submitted by hospitals rather than routinely collected through the ILI network. Nevertheless, ILI × LAB was highly correlated with pH1N1 incidence rates (Figure 2). Third, it is unclear whether serological surveillance accurately measures the actual cumulative incidence in the population, because serum samples may not be collected from a representative sample of the population, and also because the validity and reliability of using seropositivity or seroconversion as indicators of infection have yet to be explored in detail. Finally, individuals who died would not have had a chance to seroconvert and would not be reflected in the infection fatality risk denominator. This would be a relevant consideration for studies of diseases with much greater severity than pH1N1.

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J.T.W. and B.J.C. are joint senior authors.

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