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# Real-time estimation of the hospitalization fatality risk of influenza A(H1N1)pdm09 in Hong Kong

J. Y. WONG, P. WU*, E. H. Y. LAU, T. K. TSANG, V. J. FANG, L.-M. HO AND B. J. COWLING

*School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China*

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## SUMMARY

During the early stage of an epidemic, timely and reliable estimation of the severity of infections are important for predicting the impact that the influenza viruses will have in the population. We obtained age-specific deaths and hospitalizations for patients with laboratory-confirmed H1N1pdm09 infections from June 2009 to December 2009 in Hong Kong. We retrospectively obtained the real-time estimates of the hospitalization fatality risk (HFR), using crude estimation or allowing for right-censoring for final status in some patients. Models accounting for right-censoring performed better than models without adjustments. The risk of deaths in hospitalized patients with confirmed H1N1pdm09 increased with age. Reliable estimates of the HFR could be obtained before the peak of the first wave of H1N1pdm09 in young and middle-aged adults but after the peak in the elderly. In the next influenza pandemic, timely estimation of the HFR will contribute to risk assessment and disease control.

**Key words**: Epidemiology, influenza A.

## INTRODUCTION

During the early stage of an epidemic of a novel influenza strain, timely and reliable estimates of the severity of infections are important for predicting the impact that the influenza viruses will have in the population, and for calibrating the public health response [1]. The hospitalization fatality risk (HFR), a measure of the severity of infection, is defined as the probability of death in cases who required hospitalization for medical reasons [2, 3]. A well-known complication with the estimation of severity of infection in 'real time' during an epidemic is the uncertainty about the final outcomes of some patients that remain in hospital at the time of analysis [4]. This led to substantial underestimation of the HFR of H7N9 early in the outbreak in China in 2013 [2], and similar issues were also documented in the 2009 influenza pandemic [5] and the 2003 epidemic of SARS [4, 6, 7].

The first objective of this study was to estimate the HFR of pandemic influenza A(H1N1)pdm09 virus infections (H1N1pdm09) during the first wave in Hong Kong in 2009. The second objective was to compare different statistical methods for real-time estimation of the HFR.

## METHODS

### Sources of data

Data on individual patients with laboratory-confirmed H1N1pdm09 infection from 30 June 2009

* Author for correspondence: Dr P. Wu, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Hong Kong Special Administrative Region, China.
(Email: pengwu@hku.hk)

to 31 December 2009 were obtained from the Hong Kong Hospital Authority (the e-flu database) [8]. Epidemiological information was provided in the database, including age, dates of laboratory confirmation, first hospital admission, death and discharge. In this analysis we used data on all patients for whom laboratory confirmation of H1N1pdm09 was obtained from 7 days preceding to 28 days after hospital admission.

### Statistical analysis

We used three alternative statistical methods to estimate the HFR in real time, i.e. (1) division of cumulative deaths by cumulative cases ($HFR_1$); (2) division of cumulative deaths by cumulative resolved cases ($HFR_2$); and (3) the method proposed by Garske *et al.* [5], which is based on the cumulative cases and deaths and a fitted Weibull distribution ($HFR_3$) for the hospitalization-to-death distribution. The three estimators are defined as follows:

$$\mathrm{HFR}_1(t) = \frac{D(t)}{C(t)},$$

$$\mathrm{HFR}_2(t) = \frac{D(t)}{D(t)+R(t)},$$

$$\mathrm{HFR}_3(t) = \frac{D(t)}{\sum_{u=0}^{t} c(u)F(t-u)},$$

where $\mathrm{HFR}_j(t)$ is the hospitalization fatality risk estimated on day $t$ under method $j$; $D(t)$ is the cumulative number of deaths on day $t$; $C(t)$ is the cumulative number of hospitalized cases on day $t$; $R(t)$ is the cumulative number of recovered cases on day $t$; $c(t)$ is the number of hospitalized cases on day $t$; $F(.)$ is the Weibull cumulative distribution function of time from hospitalization to death based on data available at time $t$.

$HFR_1$ includes all hospitalized patients in the denominator, and will tend to underestimate the true HFR if there are many unresolved cases [4, 6]. $HFR_2$ includes only patients with known outcome (i.e. death/recovery) and may not be able to estimate the HFR in the early stages of an epidemic. $HFR_3$ allows for unresolved outcomes by accounting for the interval between hospital admission and death [5], assuming that the distribution of the interval from hospital admission to death for unresolved patients is consistent with the distribution observed from patients with known outcomes.

Each estimator was applied to the time series of daily hospitalization data from June to December 2009. The data were stratified into three age groups: 20–44 years (young adults), 45–64 years (middle-aged adults) and ⩾65 years (elderly). For each age group, estimates were compared based on the three different statistical methods. In each method, a real-time dataset was reconstructed at different time points incorporating reporting delays in laboratory confirmation, but assuming no reporting delay on outcomes. Estimates using $HFR_1$ and $HFR_2$ were made starting from the first death, while estimates using $HFR_3$ were started after five deaths had occurred because the estimated hospitalization-to-death distribution was unstable with fewer deaths. The HFRs and interval distribution were estimated in a Bayesian framework in order to retain uncertainty in the hospitalization-to-death distribution for $HFR_3$. Uniform priors over the entire range of possible values for all parameters were used for all parameters. Convergence of Markov Chain Monte Carlo algorithms was judged using the R-hat criteria [9]. Posterior medians and 95% credible intervals (CrI) are reported. All analyses were conducted with R version 3.0.2 (R Foundation for Statistical Computing, Austria).

## RESULTS

H1N1pdm09 virus emerged in Hong Kong in May 2009 and caused one major epidemic wave peaking in September–October in that year (Supplementary Fig. S1). A total of 6458 hospitalized patients were included in the e-flu database with laboratory-confirmation from 7 days before to 28 days after admission. Mortality in hospitalized patients was 0·02% (1/4309), 1·29% (13/1005), 3·38% (24/710), and 4·61% (20/434) in the <20, 20–44, 45–64 and ⩾65 years age groups, respectively. HFRs were only estimated for age groups aged ⩾20 years because there was only one death in the <20 years age group.

We examined the hospitalization-to-death intervals using age-specific data from June to December 2009 (Supplementary Fig. S2). The mean hospitalization-to-death intervals were 7·68 days (95% CrI 3·95–23·10), 7·40 days (95% CrI 4·85–12·49) and 12·59 days (95% CrI 8·16–23·54) in the 20–44, 45–64 and ⩾65 years age groups, respectively. However, the Weibull distribution might underestimate the probability of long hospitalization-to-death intervals earlier in the epidemic with fewer deaths (Supplementary Fig. S3).

Point estimates of age-specific $HFR_1$ at the end of 2009 gradually increased with age from 1·36% in the 20–44 years age group to 4·76% in the ⩾65 years age group (Fig. 1). The final $HFR_3$ estimates were

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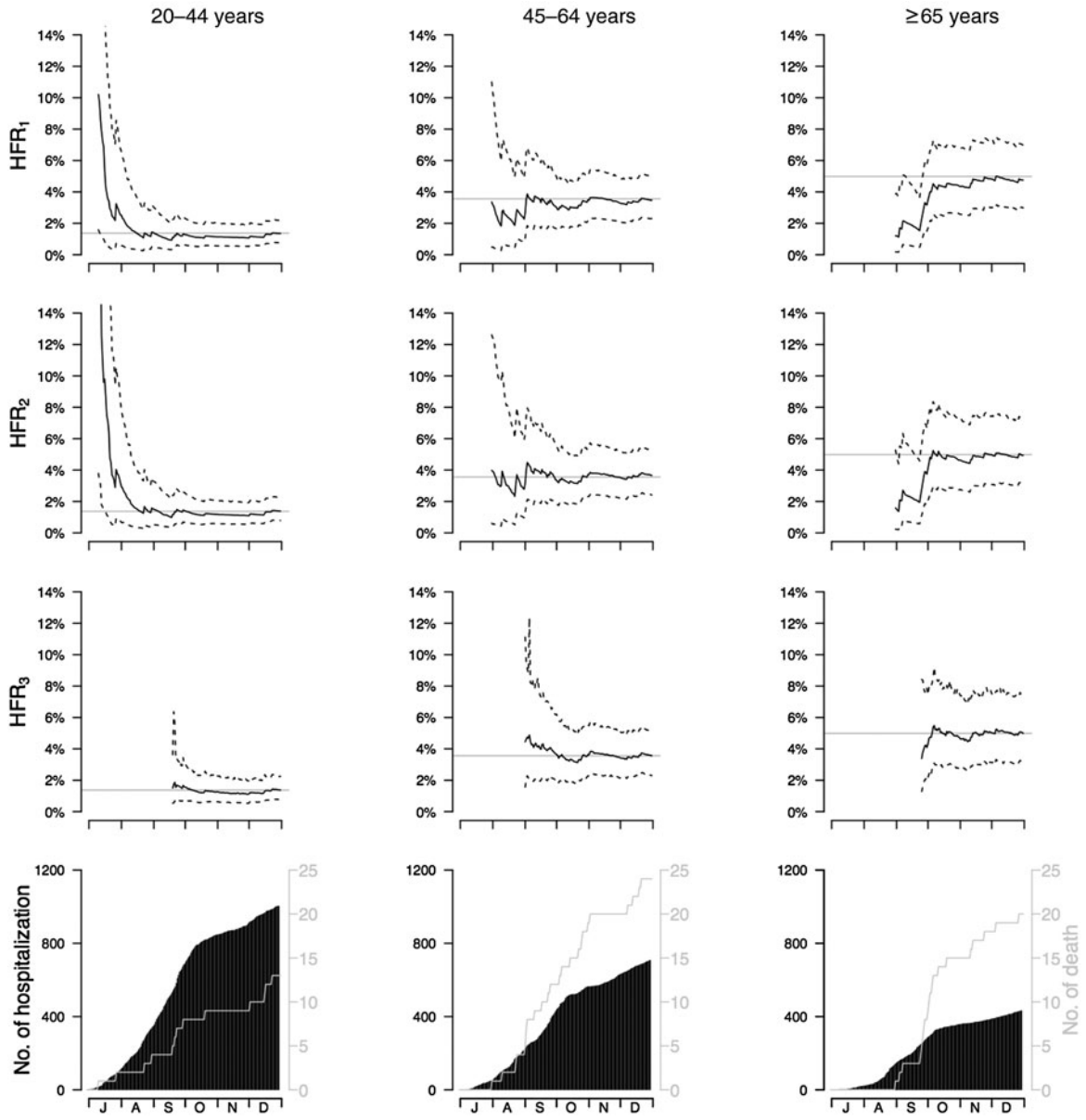


**Fig. 1.** Age-specific real-time estimates of the hospitalization fatality risk from three different methods in Hong Kong, 2009. Black solid lines represent the posterior median, dotted lines show the 95% credible interval, and the grey solid line represents the posterior median of $HFR_3$ on 31 December 2009. HFR, Hospitalization fatality risk.

very similar, increasing from 1·37% (95% CrI 0·78–2·25) to 4·94% (95% CrI 3·12–7·37) for individuals aged 20–44 to ⩾65 years, respectively (Fig. 1) using a Weibull distribution fitted to the hospitalization-to-death intervals.

We applied the three different estimators to the H1N1pdm09 data in real time from August 2009 onwards and found that the HFR estimate was relatively stable (Fig. 1), and HFR estimates were similar for the three methods at different time points (Supplementary Table S1). Estimators that accounted for censoring ($HFR_2$–$HFR_3$) tended to perform better than the $HFR_1$ estimator without adjustment (Fig. 1), and quite consistent estimates of HFR could be obtained from the beginning of September for adults, and early October for the elderly with a much smaller number of hospitalizations.

## DISCUSSION

During an ongoing influenza epidemic, final outcomes of some hospitalized cases will not be known at the

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time of data analysis. This was ignored in some early studies that determined the HFR of H1N1pdm09 and could lead to an inaccurate estimation of the HFR [4–6]. We used two methods, with and without adjustment for censoring, to estimate the HFR of H1N1pdm09 virus infection in 2009 in Hong Kong. Estimators allowing for censoring performed better than models without although we did not find substantial difference in estimates of HFR in real time between these two methods. However, in the SARS epidemic, substantial differences were identified between crude and adjusted estimates [4].

Previous studies showed that the elderly were at a particular high risk of developing severe illness if infected with H1N1pdm09, indicated by a higher estimate of infection hospitalization risk compared to younger individuals [10, 11]. Together with the age-stratified estimates of HFR from our study showing a higher risk of fatality in hospitalized elderly, this suggested that H1N1pdm09 infection was more likely to lead to fatal events in the elderly. Early treatment and better medical support to reduce severe complications after infection for this age group are needed. In addition, we were able to obtain a timely estimate of HFR for adults in early September, before the peak of the first pandemic wave, while such an estimate could only be achieved for the elderly after the peak. This could be due to the smaller number of confirmed deaths in the elderly.

There are several limitations of this study. First, HFR was assumed to be constant over the course of the epidemic. However, this assumption may be violated if there are changes in case ascertainment or improvements in treatment. Further work could explore methods for estimation of changes in the HFR over time, and the optimal timing and sample size necessary to obtain reliable HFR estimates. When moving from the containment phase to mitigation phase in the 2009 pandemic, there was change in hospital admission guidelines and it is possible that the earliest estimates would bias downwards because mild cases were also admitted to hospitals for isolation during the containment phase [1, 5]. Therefore, we only analysed patients admitted to hospitals after the containment period (i.e. 1 May 2009 to 29 June 2009). Improvement in treatment of influenza would also decrease HFR estimates over time [6]. Second, HFR estimates might be biased by the choice of distribution functions for the hospitalization-to-death interval. The choice of distribution is uncertain and it may be censored [5]. Finally, the lack of information on the date of official announcement for each confirmed case prevented us from fully simulating the real-time situation during the epidemic, therefore we used the best available data instead as an alternative, i.e. dates of laboratory confirmation, instead.

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268815003179.

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## DECLARATION OF INTEREST

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