Estimation of excess mortality and hospitalisation associated with the 2009 pandemic influenza

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KEY MESSAGES

1. We estimated the excess mortality and hospitalisation associated with influenza strain A(H1N1)pdm09 using the classical Poisson model and the Poisson prediction modelling approach.
2. During the first wave of the pandemic from May to December 2009, 127 all-cause excess deaths were associated with the A(H1N1)pdm09, of which 115 were due to cardiovascular and respiratory diseases and 22 were due to pneumonia and influenza.
3. During the whole pandemic period from May 2009 to July 2010, 10 377 hospitalisations secondary to acute respiratory diseases and 7204 secondary to pneumonia and influenza were associated with A(H1N1)pdm09 infections.
4. An age shift towards children and younger people was found in A(H1N1)pdm09-associated excess hospitalisation for acute respiratory diseases and its subcategory pneumonia and influenza.
5. The age pattern of A(H1N1)pdm09-associated excess mortality was similar to that for seasonal influenza, with high mortality risk observed in people aged ≥65 years. This suggests that control measures adopted by the government were effective in reducing the mortality risk in younger age-groups.

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Introduction

In 2009, a novel A(H1N1) influenza strain, later termed as A(H1N1)pdm09, emerged to cause an influenza pandemic. To assess the severity of this pandemic, it is critical to reliably estimate the mortality and morbidity burden associated with A(H1N1)pdm09. Hospitalisations and deaths due to influenza in health records represent only the tip of the iceberg for influenza-associated disease burden, owing to its non-specific symptoms and the lack of timely laboratory tests. The Poisson regression model has been used to quantify influenza disease burden by estimating excess mortality/hospitalisation, which is defined as the difference in deaths/hospitalisation during epidemic periods compared with baseline periods when influenza viruses are not circulating.[1] Given the potential underreport of pandemic cases, it is necessary to compare excess hospitalisation associated with seasonal and pandemic influenza to accurately assess the severity of the 2009 H1N1 pandemic.

This study aimed to estimate the excess mortality or hospitalisation associated with A(H1N1)pdm09 using a valid modelling approach, and to evaluate the severity of the pandemic by comparing the disease burden of this pandemic with past seasonal influenza epidemics, and to identify the susceptible age-groups in the H1N1 pandemic by comparing laboratory-confirmed cases.

Methods

Weekly numbers of cause-specific deaths for the age-groups <20, 20-39, 40-64, 65-84, and ≥85 years were obtained from the Census and Statistics Department; three categories were considered: cardiovascular and respiratory, pneumonia and influenza, and all-cause. Hospitalisation records were obtained from the electronic health record system of the Hospital Authority. We aggregated the records into weekly hospitalisation numbers based on any-listed discharge diagnoses (up to 15 diagnoses) for the following disease categories: acute respiratory disease, pneumonia and influenza for the age-groups of 0-5, 6-17, 18-39, 40-64, 65-74, ≥75 years; and cardiovascular disease, diabetes, ischaemic heart disease, and stroke for the age-groups of 40-64, 65-74, ≥75 years.

Virology data were retrieved from: (1) the dataset of weekly numbers of laboratory-confirmed cases for influenza type A (two seasonal subtypes A(H3N2) and A(H1N1), the pandemic strain A(H1N1)pdm09) and type B during the period of 2005-2010 from the Public Health Laboratory Centre's weekly report 'Flu Express' at http://www.chp.gov.hk/en/guideline1_year/441/304.html; and (2) the Microbiology Laboratory of Queen Mary Hospital for influenza A, influenza B, respiratory syncytial virus, adenovirus, parainfluenza (type 1, 2 and 3) during the period of 1998-2009, as influenza

subtypes data before 2005 and other respiratory viruses other than influenza were not available to the public.

We developed a Poisson prediction method to estimate influenza-associated mortality by modifying the classical Poisson models for disease burden of influenza. The first step was to detrend the weekly mortality data of entire study period. In the second step, a Poisson regression model with the predictor variables of temperature, humidity, and an influenza proxy variable of weekly proportions of specimens positive for influenza (influenza proportions) was fitted to the detrended mortality data of 1998-2008. This 10-year Poisson model was then used to predict a mortality level for the assessment year, with the data of temperature and humidity taking the values as observed in that year and the influenza variable simultaneously set to zero. Then the time trend removed in the first step was added back to the predicted mortality to derive the baseline mortality. Excess mortality for the assessment year was then calculated by deducting the baseline mortality from the observed mortality data in that year.

We fitted classical Poisson regression models to weekly numbers of hospitalisation for each age-disease category in Hong Kong, as described in our previous study.[2] The virus proxies of weekly proportions of specimens tested positive for A(H1N1), A(H3N2), influenza B, and A(H1N1) pdm09 were simultaneously added to assess the effects of these viruses. The variables of weekly average temperature, relative humidity, weekly proportions of specimens positive for respiratory syncytial virus, adenovirus and three types of parainfluenza viruses were added into the model as confounding factors. For hospitalisation, we also added the dummy variable for the period of this containment phase, and its product term with the pandemic virus proxy into the model to allow a different hospitalisation risk during the containment phase. Baseline hospitalisation number was first calculated as the number of expected hospitalisation when the proxy variables for A(H1N1)pdm09, A(H1N1), A(H3N2), and influenza B viruses were set to zero, respectively. Excess hospitalisation number was then calculated as the difference between the baseline and predicted hospitalisation numbers with all variables set as observed.

In terms of calibration and validation of models, we compared the estimates from different models with the hospitalisation rates directly observed from a prospective cohort of paediatric patients to justify the choice of dummy variables and degrees of freedom for smoothing functions of confounding variables.[3] The model with the estimates closest to these observed rates for each age-disease category was then chosen as the best and used for subsequent analyses.

Since 1 May 2009, the Hospital Authority and Department of Health had routinely tested nearly all the suspected cases with acute respiratory symptoms for A(H1N1)pdm09 by RT-PCR and established an electronic reporting system 'eFlu' in response to the H1N1 pandemic. Because laboratory tests were intensively conducted in suspected cases during the first wave of pandemic from 1 May 2009 to 2 January 2010, the total numbers of hospitalised or fatal cases with laboratory-confirmed A(H1N1)pdm09 infections could be regarded as the lower bound of the true burden.

Results

We estimated that there were 127 excess deaths attributable to A(H1N1)pdm09, with underlying cause of cardiovascular and respiratory and its subcategory pneumonia and influenza being estimated to be 115 and 22, respectively, corresponding to the excess rates of 1.6 and 0.3 per 100 000 population, respectively. The higher mortality rate attributable to the pandemic was observed in the age-groups of 65-84 and ≥85 years for all-cause, cardiovascular and respiratory, and pneumonia and influenza (Table 1). In 2009, the age-standardised annual crude mortality rate was 9.4 per 100 000 population, which was within the range of annual rates in the preceding years (5.1-13.9).

After age standardisation, annual excess hospitalisations were higher in 2009 than in other years for acute respiratory disease, pneumonia and influenza, and ischaemic heart disease, but were slightly lower than in 2010 for cardiovascular disease, stroke, and diabetes (Table 2). A total of 10 377 acute respiratory disease hospitalisation and 7204 pneumonia and influenza were attributable to A(H1N1)pdm09 during the whole pandemic period from May 2009 to July 2010. 60% of these hospitalisations occurred in children and 13% in the elderly. For chronic diseases, the total numbers of A(H1N1)pdm09-associated hospitalisation were 1676, 848, 359, and 1550, for cardiovascular disease, ischaemic heart disease, stroke, and diabetes, respectively. More than 80% of these hospitalisations occurred in people aged ≥65 years. Overall, 80% of A(H1N1)pdm09-associated hospitalisation occurred during the first wave of the pandemic from May 2009 to January 2010.

Among all the virus types/subtypes, A(H1N1)pdm09 was associated with the highest annual excess rate of acute respiratory disease hospitalisation, followed by A(H3N2), influenza B, and A(H1N1). Excess rates of acute respiratory disease and pneumonia and influenza were found higher in children aged <5 years for A(H1N1)pdm09, A(H1N1), or influenza B, whereas the rates were higher among persons aged >75 years for A(H3N2). For acute respiratory disease and pneumonia and

TABLE 1. Annual excess rate of all-cause mortality (per 100 000 population) associated with influenza for different age-groups, estimated by the Poisson prediction model

Year	Excess rate (95% confidence interval) of all-cause mortality associated with influenza						
	<20 y	20-39 y	40-64 y	65-84 y	≥85 y	All age-groups (crude)	All age-groups (standardised)*
1998	0.3 (–1.1 to 1.6)	0.1 (–1.4 to 1.8)	3.6 (–0.8 to 7.7)	29.4 (2.8 to 55.2)	175.2 (12.0 to 327.7)	4.4 (0.5 to 7.9)	5.1 (–1.3 to 11.2)
1999	0.7 (–0.4 to 1.8)	–0.8 (–2.2 to 0.6)	–0.7 (–4.2 to 2.9)	45.0 (21.1 to 68.3)	142.1 (–10.9 to 284.1)	7.6 (4.2 to 11.0)	9.0 (3.4 to 14.5)
2000	0.6 (–0.5 to 1.8)	–0.5 (–2.0 to 1.0)	1.6 (–2.4 to 5.2)	51.4 (24.3 to 76.3)	159.0 (–7.2 to 315.5)	7.6 (3.6 to 11.2)	8.7 (2.5 to 14.4)
2001	0.1 (–1.1 to 1.3)	0.3 (–1.3 to 1.8)	1.4 (–2.2 to 4.8)	29.4 (5.3 to 52.6)	75.4 (–63.4 to 202.1)	5.0 (1.1 to 8.7)	5.6 (–0.3 to 11.0)
2002	1.0 (0.1 to 2.1)	0.1 (–1.5 to 1.6)	3.3 (0.1 to 6.4)	44.6 (20.9 to 66.0)	204.5 (68.2 to 327.8)	8.8 (4.8 to 12.2)	9.6 (4.0 to 14.9)
2003	–0.6 (–1.7 to 0.5)	0.0 (–1.7 to 1.6)	1.5 (–2.2 to 4.9)	51.2 (26.9 to 76.1)	130.9 (–33.9 to 276.4)	7.6 (3.4 to 11.5)	8.4 (2.1 to 14.0)
2004	0.7 (–0.3 to 1.6)	0.7 (–0.7 to 2.0)	–0.4 (–3.4 to 2.5)	31.4 (9.3 to 54.1)	191.8 (47.1 to 334.1)	6.3 (2.5 to 10.1)	6.8 (1.5 to 12.0)
2005	0.4 (–0.7 to 1.6)	–0.3 (–1.9 to 1.2)	5.3 (2.2 to 8.7)	69.4 (44.5 to 94.1)	258.2 (90.8 to 429.1)	13.2 (8.5 to 17.3)	13.9 (7.7 to 20.0)
2006	0.4 (–0.8 to 1.5)	–0.2 (–1.6 to 1.2)	0.6 (–2.6 to 3.6)	28.3 (6.5 to 52.2)	183.7 (35.0 to 336.6)	6.4 (2.2 to 10.4)	6.7 (1.1 to 12.3)
2007	0.4 (–0.6 to 1.3)	0.8 (–0.5 to 1.9)	0.9 (–2.0 to 3.9)	55.5 (34.9 to 76.2)	196.8 (62.0 to 332.7)	10.0 (6.2 to 13.6)	10.3 (5.2 to 15.4)
2008	–0.2 (–1.5 to 1.0)	–0.9 (–2.3 to 0.4)	1.0 (–2.3 to 4.0)	29.5 (7.8 to 51.0)	298.7 (142.6 to 455.8)	8.1 (3.8 to 11.9)	8.4 (2.5 to 13.7)
2009	0.4 (–0.6 to 1.3)	0.0 (–1.2 to 1.1)	1.3 (–1.6 to 4.3)	34.1 (13.0 to 55.7)	276.2 (157.1 to 396.4)	9.1 (5.2 to 13.0)	9.4 (4.2 to 14.5)

* The 2009 mid-year population was used as standard population

TABLE 2. Age-standardised annual excess rate of hospitalisation (per 100 000 population) associated with influenza in 2005 to 2010

Disease	Age-standardised excess rate (95% confidence interval) of hospitalisation associated with influenza					
	2005	2006*	2007	2008	2009	2010
Acute respiratory disease	115.9 (70.2 to 157.0)	80.5 (39.8 to 120.3)	116.1 (70.3 to 158.8)	96.7 (51.7 to 138.1)	166.8 (109.5 to 221.7)	152.7 (96.3 to 204.9)
Pneumonia and influenza	76.2 (44.3 to 105.1)	56.6 (27.9 to 84.4)	75.0 (44.1 to 104.0)	64.9 (33.7 to 94.1)	130.9 (88.0 to 170.3)	109.5 (67.5 to 147.6)
Cardiovascular disease	30.4 (–24.9 to 84.2)	51.1 (10.2 to 90.3)	31.5 (–10.7 to 71.9)	48.3 (–2.3 to 99.5)	63.3 (–3.9 to 125.9)	102.3 (6.6 to 192.4)
Ischaemic heart disease	3.7 (–15.5 to 21.9)	8.8 (–6.2 to 23.4)	3.3 (–11.8 to 17.7)	6.0 (–11.1 to 21.9)	19.4 (–2.6 to 39.7)	12.6 (–21.0 to 44.4)
Stroke	8.5 (–6.0 to 21.5)	12.0 (1.6 to 22.2)	8.1 (–2.9 to 18.6)	12.3 (–1.7 to 25.4)	18.9 (0.5 to 35.5)	19.4 (–6.5 to 43.1)
Diabetes	9.2 (–9.7 to 27.9)	16.5 (1.6 to 30.6)	9.3 (–6.3 to 24.0)	16.7 (–2.9 to 36.6)	36.7 (7.9 to 63.6)	50.6 (8.2 to 91.4)

* The 2006 mid-year population was used as standard population

influenza hospitalisation, excess rates associated with A(H1N1)pdm09 were 200% to 500% of influenza rates in children aged <5 years and 500% to 1200% of those in children aged 6-17 years, but 50% and 70% of seasonal A(H3N2) rates in persons aged 65-74 years and ≥75 years, respectively.

Discussion

Combined with our estimates of excess mortality as numerators and the estimated attack rates from the previous serological studies,[4] the case fatality risk per infection case was 0.01% and 1.8% for the all-ages and ≥60 years age-groups, respectively. This suggests that the 2009 A(H1N1)pdm09 pandemic was much less severe than the previous pandemics.

Our estimates of the pandemic-associated excess mortality (particularly in children and young adults) in Hong Kong are generally lower than those for most of other countries/regions, but the rates of excess hospitalisation were markedly higher. Most pandemics in history were characterised with an age shift of mortality towards younger people. Some studies in other regions/countries also showed that most fatal cases occurred in younger age-groups. Nonetheless, there was no strong evidence of such an age shift in Hong Kong, given that the elderly had significantly higher mortality risk of A(H1N1) pdm09 than younger population.

In contrast, we observed a clear age shift of hospitalised cases towards younger age-groups in Hong Kong. Such discrepancy may simply reflect regional heterogeneity in disease severity and

population susceptibility, but could also suggest that the control measures adopted by the government were effective in reducing the mortality risk of younger age-groups.

The upper bound of our estimates for both hospitalisation and mortality all matched laboratory-confirmed cases of younger age-groups reported by eFlu. This indicates that the true mortality burden of influenza in these age-groups could be obtained through intensive virological surveillance. Surprisingly, we found a big gap between the numbers of reported fatal/hospitalised cases and our model estimates in older population, although the suspected cases were intensively screened for pandemic infection by virological tests. The underestimation of influenza-related illness in this age-group requires further investigation. We speculate that many influenza-initiated mortalities are attributed to secondary bacterial complications and exacerbation of underlying chronic respiratory and cardiovascular diseases. Although some evidence suggests that older persons were protected by pre-existing immunity against A(H1N1)pdm09,[5] those who were fragile and susceptible could have acquired infections and were more likely to have had serious complications. Our findings highlight a need to enhance the laboratory surveillance at the community level, particularly in older people.

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