Hospitalisation associated with the 2009 H1N1 pandemic and seasonal influenza in Hong Kong, 2005 to 2010

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Reliable estimates of the morbidity burden caused by the 2009 pandemic influenza (pH1N1) are important for assessing the severity of the pandemic. Poisson regression models were fitted to weekly numbers of cause-specific hospitalisation in Hong Kong from 2005 to 2010. Excess hospitalisation associated with the 2009 pandemic and seasonal influenza was derived from the model by incorporating the proxy variables of weekly proportions of specimens positive for the pandemic influenza A(H1N1)pdm09, seasonal influenza A (subtypes H3N2 and H1N1) and B viruses. Compared with seasonal influenza, pH1N1 influenza was associated with higher hospitalisation rates for acute respiratory disease (ARD) among children younger than 18 years and adults aged between 18 and 64 years, but among the elderly aged 65 years and older the hospitalisation rates were lower for pH1N1 than for seasonal H3N2 and H1N1 influenza. Hospitalisation rates for chronic diseases associated with pH1N1 influenza were generally higher than those associated with seasonal influenza. The reported hospitalised cases with laboratory-confirmed pandemic infections accounted for only 16% of pH1N1 influenza-associated hospitalisations for ARD in the age group 75 years and older, and 5–66% of hospitalisations for chronic diseases in those older than 40 years. The 2009 H1N1 influenza pandemic was associated with a dramatically increased risk of hospitalisation among children and young adults. The morbidity burden of pandemic was underreported in old people and in those with chronic conditions.

Introduction

In April 2009 a novel influenza A(H1N1) virus of swine-origin (referred to as pH1N1 hereafter) emerged and quickly spread worldwide [1]. Previous studies have reported that annual hospitalisation rates with laboratory-confirmed pandemic infections ranged from 3 to 110 per 100,000 person-years [2-4]. However, it is likely that these rates seriously underestimated the true burden of the pandemic, as many cases were not tested for pandemic infections due to limited laboratory capacity [5]. Furthermore, the tests could have been biased towards children and young adults in whom the pH1N1 infection rates were reported to be higher, but severe outcomes after infections were more likely to occur in the elderly aged 65 years or older [6,7]. Previous studies have further found that few pandemic-associated fatalities in persons older than 65 years were captured by intensive laboratory tests [8,9]. Given the potential underreporting of pandemic cases, it is necessary to compare excess hospitalisation associated with seasonal and pandemic influenza to assess the severity of 2009 H1N1 pandemic. We and others have demonstrated that excess hospitalisation estimated from Poisson models can provide reliable estimates for true morbidity burden of seasonal influenza [10,11].

Two subtypes of seasonal influenza A(H3N2) and (H1N1) (referred to as sH1N1 hereafter), as well as influenza B viruses, have been circulating in humans for many years [12]. There is evidence that these viruses are distinct in terms of transmission efficiency and risk of hospitalisation or mortality [13,14]. However, few studies have compared disease burden associated with different types or subtypes of seasonal influenza and pandemic viruses. In this study, we aimed to comprehensively assess the age-specific hospitalisation burden associated with each type (or subtype) in subtropical city Hong Kong which had a population of 7.07 million in 2011 [15].

Methods

Data

Hospitalisation records from 2005 to 2010 were obtained from the electronic health record system of the Hospital Authority (HA), which manages all 41 public hospitals and covers 78% of hospital-bed days in the entire territory of Hong Kong [16]. We aggregated the records into weekly hospitalisation numbers by all discharge diagnoses (up to 15 diagnoses) that were coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) [17].

We considered the following disease categories: acute respiratory disease (ARD; ICD9 460–466, 480–487), pneumonia and influenza (P&I; ICD9 480–487) for the age groups of 0–5, 6–17, 18–39, 40–64, 65–74, and ≥75 years, and cardiovascular disease (CVD; ICD9 390–459), diabetes (ICD9 250), ischaemic heart disease (IHD; ICD9 410–414), and stroke (ICD9 430–438) for the age groups of 40–64, 65–74, and ≥75 years. Mid–year population by age groups was obtained from the Census and Statistics Department for the study period.

We obtained the weekly numbers of detected influenza viruses reported by the Public Health Laboratory Centre, Hong Kong from the weekly report 'Flu Express' available on the website of the Centre for Health Protection at the Department of Health (DH) (http://www.chp.gov.hk/en/guideline1_year/441/304.html). The numbers of specimens were estimated from the summary tables of the Centre's Sentinel Surveillance website (http://www.chp.gov.hk/en/sentinel/26/44/292.html). The respiratory specimens were collected from hospitalised patients and outpatients from the public and private healthcare sectors in Hong Kong and were tested by viral culture and subtyped by haemagglutination inhibition tests. As the online reports for other respiratory viruses were not publicly available from the DH during the study period, we also obtained the virology surveillance data for respiratory syncytial virus (RSV), adenovirus and parainfluenza viruses from the microbiology laboratory of Queen Mary Hospital.* This single laboratory covered 21% of all specimens for the DH surveillance network during the study period, and the influenza virology data from these two sources were highly correlated (r=0.81) during that period. The seasonal patterns of these viruses were also consistent with those from the DH [18]. Meteorological data for temperature and relative humidity were obtained from the Hong Kong Observatory.

Statistical analysis

We fitted the following quasiPoisson regression models to weekly numbers of hospitalisation from 2005 to 2010 for each age–disease category.

$$\begin{cases} Y_t \sim quasiPoisson(\mu_t, \phi\mu_t) \\ \log(\mu_t) = \beta_0 + \beta_1 SH1_t + \beta_2 H3_t + \beta_3 B_t + \beta_4 PH1_t \\ \quad + \beta_5 RSV_t + \beta_6 Adeno_t + \beta_7 P1_t + \beta_8 P2_t + \beta_9 P3_t \\ \quad + s(t) + s(Temp_t) + s(Hum_t) + \beta_{10} D_t + \beta_{11} D_t \times PH1_t \end{cases}$$

where Yt denotes the number of hospitalisations in week t (t=1,2,…,312) which was assumed to follow a quasiPoisson distribution with an over-dispersion parameter ϕ. $SH1_t$, $H3_t$, B_t and $PH1_t$ denote the weekly proportions of specimens tested positive for sH1N1, H3N2, influenza B and pH1N1, respectively. These proxy variables were added to quantify the effects of each type/subtype. RSV_t, $Adeno_t$, $P1_t$, $P2_t$ and $P3_t$ were proportions of specimens positive for RSV, adenovirus and three types of parainfluenza viruses. As nearly all annual total numbers of cause-specific hospitalisation almost doubled during the study period, we adjusted for the long-term and seasonal trends of hospitalisation data by adding a natural cubic spline $s(t)$ into the model. Because the time series of acute respiratory diseases (ARD and P&I) tend to show greater seasonal variations than those of chronic diseases, we decided to use 3 degrees of freedom (*df*) per year (totally 18 *df* during the whole study period) in ARD and P&I, but to use a minimum of 2 or 3 *df* in total for the whole period for CVD, IHD, stroke and diabetes. $s(Temp_t)$ and $s(Hum_t)$ were the natural cubic spline of temperature and relative humidity with *df*=3 to adjust for the variation of meteorological factors. During the containment phase of the 2009 pandemic (26 April to 27 June 2009), every pH1N1 case was admitted regardless of the disease severity. To adjust for the change in hospitalisation admission thresholds during this period, we added the dummy variable D_t for the period of this containment phase, and its product term with the pandemic virus proxy D_tx$PH1_t$, into the model to allow a different hospitalisation risk during the containment phase.

Morbidity burden of influenza was measured by excess hospitalisation rate associated with each influenza type or subtype. We first defined the baseline hospitalisation number as the number of expected hospitalisations when the proxy variables for pH1N1, sH1N1, H3N2 and B viruses were set to zero. Excess hospitalisation number was then calculated as the difference between the baseline and predicted hospitalisation numbers with all variables taking the observed values. The 95% confidence intervals (CI) were calculated by bootstrapping the weekly excess hospitalisation numbers and subsequently refitting the same models 1,000 times. We also calculated the annual excess rate by dividing the average annual total numbers of excess hospitalisation by the annual age-specific population sizes derived from the 2001, 2006 and 2011 censuses [15,19,20] through linear interpolation.

Model validation

On 1 May 2009 the HA established an electronic reporting system 'e-flu' in response to the influenza A(H1N1) pandemic. Patients with acute respiratory symptoms were routinely tested for influenza A(H1N1) by RT-PCR. The e-flu data recorded outpatient visits, hospitalisation and deaths with laboratory-confirmed influenza A(H1N1) infections [21]. Given the intensive laboratory screening for influenza A(H1N1)pdm09 infections during the pandemic, the hospitalised pH1N1 cases reported by the e-flu system could be regarded as the low boundary of true burden. Hence we calculated the disease-specific laboratory-confirmed pandemic hospitalisation according to any-listed discharge diagnosis. As the e-flu surveillance was relaxed after the first wave, we compared these numbers with our estimates of age- and cause-specific excess numbers during

Table 1

Virology surveillance data and annual hospitalisation rate (per 100,000 person-years) in Hong Kong, 2005–2010

	2005	2006	2007	2008	2009	2010
Virology data n (% of total influenza-positive specimens)						
Total specimens	39,580	37,108	40,258	44,171	12,5100	69,680
Total influenza-positive specimens	6,204	4,196	6,422	4,786	30,576	8,773
Seasonal influenza A(H1N1)	413 (6.7)	3,047 (72.6)	133 (2.1)	1,490 (31.1)	2,821 (9.2)	1 (0.0)
Influenza A(H3N2)	4,751 (76.6)	225 (5.4)	4,845 (75.4)	2,039 (42.6)	8,165 (26.7)	4,484 (51.1)
Influenza A(H1N1)pdm09	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19,279 (63.1)	2,022 (23.0)
Influenza B	1,040 (16.8)	924 (22.0)	1,444 (22.5)	1,257 (26.3)	311 (1.0)	2,266 (25.8)
Hospitalisations						
ARD	1,023.5	903.9	986.0	1,247.0	1,417.5	1,606.8
P&I	682.6	616.7	665.8	905.2	1,072.2	1,217.0
CVD	1,963.2	1,940.3	2,012.9	2,813.2	3,864.4	4,810.9
IHD	507.1	496.5	502.4	683.8	935.4	1,167.3
Stroke	427.6	411.5	427.7	666.1	914.8	1,115.2
Diabetes	534.1	513.5	550.6	844.6	1,408.2	1,772.6

ARD: acute respiratory disease; CVD: cardiovascular disease; IHD: ischaemic heart disease; P&I: pneumonia and influenza.

The annual figures in this Table were obtained by cumulating weekly data from week 1 to 52 (or 53) of each year.*

the first wave of the pandemic from 1 May 2009 to 2 January 2010.

The ethical approval for this study was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UV11-264). All analyses were conducted using R package version 2.12.2 (R Development Core Team).

Results

Descriptive statistics

Annual total numbers of specimens collected by the DH ranged from 37,108 to 125,100 during the study period (Table 1). Influenza A(H3N2) was dominant in 2005 and 2007, while in 2006 and 2008, seasonal influenza A(H1N1) and B viruses were isolated more. The pandemic pH1N1 virus first emerged in May 2009, reached a peak around September and remained at a low level after November. A few specimens positive for seasonal influenza were found during the pandemic period from May to November 2009. Influenza B became dominant after March 2010, followed later by influenza A(H3N2) followed. During the study period from 2005 to 2010, the average annual hospitalisation rate was 1,197.4, 859.9, 2,900.8, 715.4, 660.5 and 937.3 per 100,000 person-years, for ARD, P&I, CVD, IHD, stroke and diabetes, respectively (Table 1). Persons aged 75 years and older had the highest hospitalisation rate for all the disease categories.

Annual excess hospitalisation associated with influenza

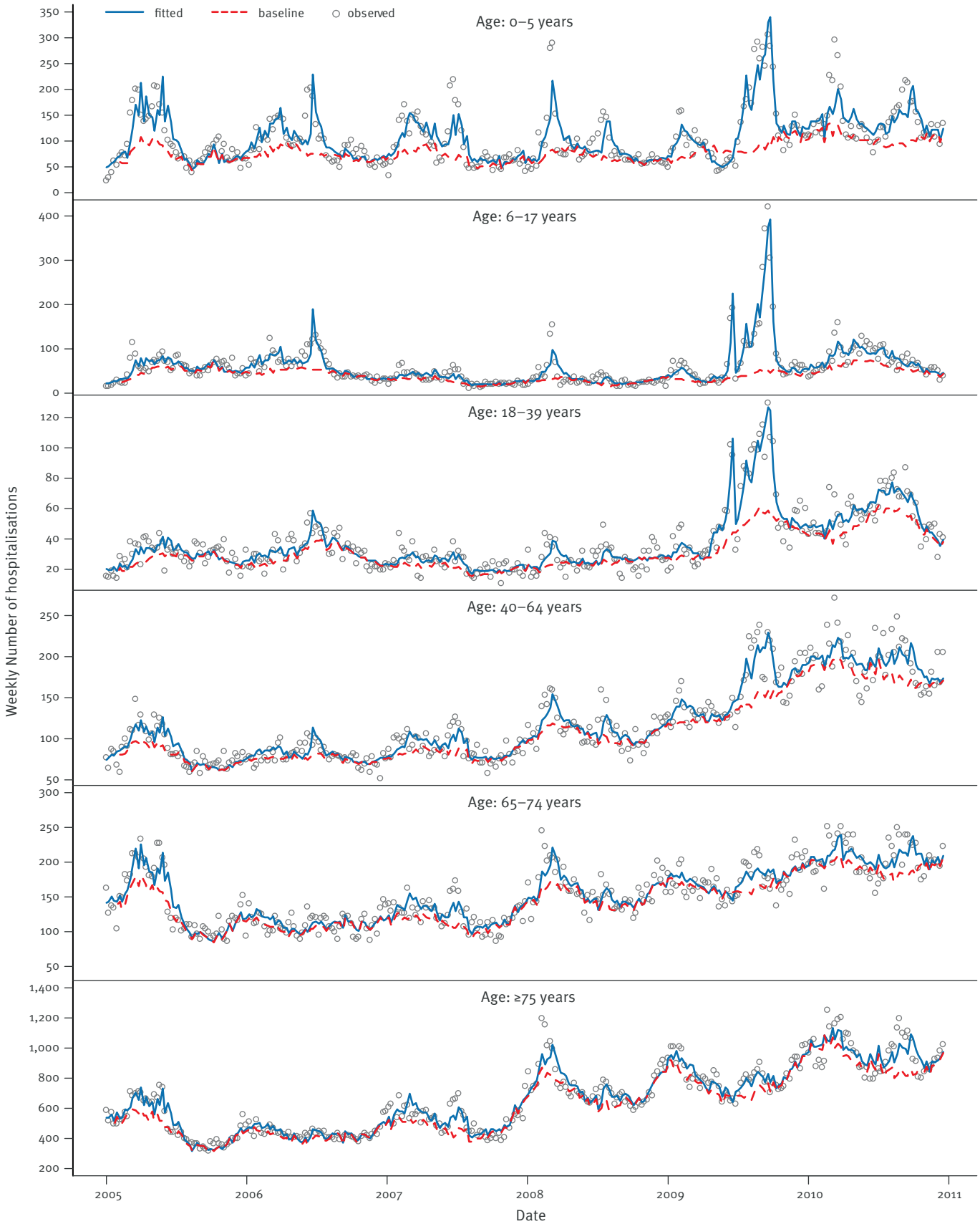
An example of model fit by weekly observed and fitted numbers of P&I hospitalisation is shown in Figure 1. Significant association of influenza virus types (or subtypes) with hospitalisation was found in most age–disease categories studied ($p<0.05$). Annual age-specific excess hospitalisation rates showed great year-to-year variations in all the disease categories. Across the six-year study period, the highest annual excess rate for ARD, P&I and IHD was observed in 2009, and for CVD, stroke and diabetes in 2010, after adjustment for age structure by age standardisation (Table 2). During the study period, the highest annual excess rates of ARD and P&I hospitalisation were found in the pandemic year 2009 for children and adults aged 18–64 years. For old people, excess rates of hospitalisation associated with influenza markedly increased during the post-pandemic year of 2010 for most disease categories, whereas the rates in 2009 remained at the level similar to or slightly higher than those in the preceding interpandemic years (data now shown).

Excess hospitalisation associated with the pandemic

During the whole pandemic period from May 2009 to July 2010, a total of 10,377 hospitalisations with ARD and 7,204 with P&I were associated with pH1N1 influenza. Of these, 60% occurred in children and 13% in the elderly (Table 3). For chronic diseases, the total numbers of pH1N1-associated hospitalisation were 1,676, 848, 359 and 1,550, for CVD, IHD, stroke and diabetes, respectively. More than 80% of these hospitalisations

Figure 1

Weekly observed (squares) and fitted (solid blue line) hospitalisations with any-listed diagnosis of pneumonia and influenza Hong Kong, 2005–2010



Broken red line indicates the baseline when all the influenza proxies were assumed zero.

Table 2

Age-standardised annual excess rate per 100,000 person-years of hospitalisation associated with influenza, with the 2006 population as standard, Hong Kong, 2005–2010

Disease	2005	2006	2007	2008	2009	2010
	ER (95% CI)	ER (95% CI)	ER (95% CI)	ER (95% CI)	ER (95% CI)	ER (95% CI)
ARD	115.9 (70.2; 157.0)	80.5 (39.8; 120.3)	116.1 (70.3; 158.8)	96.7 (51.7; 138.1)	166.8 (109.5; 221.7)	152.7 (96.3; 204.9)
P&I	76.2 (44.3; 105.1)	56.6 (27.9; 84.4)	75.0 (44.1; 104.0)	64.9 (33.7; 94.1)	130.9 (88.0; 170.3)	109.5 (67.5; 147.6)
CVD[a]	30.4 (-24.9; 84.2)	51.1 (10.2; 90.3)	31.5 (-10.7; 71.9)	48.3 (-2.3; 99.5)	63.3 (-3.9; 125.9)	102.3 (6.6; 192.4)
IHD[a]	3.7 (-15.5; 21.9)	8.8 (-6.2; 23.4)	3.3 (-11.8; 17.7)	6.0 (-11.1; 21.9)	19.4 (-2.6; 39.7)	12.6 (-21.0; 44.4)
Stroke[a]	8.5 (-6.0; 21.5)	12.0 (1.6; 22.2)	8.1 (-2.9; 18.6)	12.3 (-1.7; 25.4)	18.9 (0.5; 35.5)	19.4 (-6.5; 43.1)
Diabetes[a]	9.2 (-9.7, 27.9)	16.5 (1.6; 30.6)	9.3 (-6.3; 24.0)	16.7 (-2.9; 36.6)	36.7 (7.9; 63.6)	50.6 (8.2; 91.4)

ARD: acute respiratory disease; CI: confidence interval; CVD: cardiovascular disease; ER: excess rate; IHD: ischaemic heart disease; P&I: pneumonia and influenza.

[a] Excess rates are assumed zero in the age groups younger than 40 years.

occurred in people aged 65 years and older. In the group including all ages, around 80% of pH1N1-associated hospitalisations for all the disease categories studied occurred during the first wave of the pandemic from May 2009 to January 2010.

To compare our estimates with the total numbers of laboratory-confirmed pH1N1 cases requiring hospitalisation, we calculated the ratio of the admission numbers reported by the e-flu system to excess hospitalisation associated with pH1N1 influenza in the same age–disease groups during the first wave. The ratio ranged from 0.72 to 0.92 for ARD and from 1.05 to 1.68 for P&I in the age groups younger than 75 years (Table 3). In persons 75 years and older, the confirmed hospitalised cases reported by e-flu for ARD and 45% for P&I in the same age group only accounted for 16% of excess hospitalisations that were estimated from the statistical models to be attributable to pH1N1 influenza. For the chronic diseases CVD, IHD, stroke and diabetes, the total numbers of confirmed pH1N1 hospitalisation accounted for only 25–66%, 11–28%, 5–15% of pH1N1-associated excess hospitalisation, for the age groups of 40–64, 65–74 and ≥75 years, respectively.

Comparison of type- or subtype-specific excess hospitalisation

In the group including all ages, pH1N1 influenza was associated with the highest annual excess rate of ARD hospitalisation (95.9 per 100,000 person-years; 95% CI: 66.9–122.1), followed by influenza A(H3N2) (49.4; 95% CI: 36.7–61.5), B (38.3; 95% CI: 21.7–54.2) and sH1N1 (18.3; 95% CI: 10.4–26.2). A similar pattern was also observed for P&I hospitalisation. Across different age groups, excess rates of ARD and P&I associated with pH1N1, sH1N1 or B influenza were higher among children under the age of five years, whereas the rates associated with H3N2 influenza were higher among persons older than 75 years (Figure 2). Excess rates associated with pH1N1 influenza were 2–5 times as high as those with seasonal influenza in children younger than five years, 5–12 times as high in children aged 6–17 years, but 50% and 70% lower than the rates of seasonal influenza A(H3N2) in persons aged 65–74 and ≥75 years.

Of three seasonal influenza viruses, H3N2 accounted for a higher proportion of ARD and P&I hospitalisation than the other two viruses in all the age groups except the groups aged 6–17 and 18–39 years, in which influenza B had higher rates. For chronic diseases, pH1N1 was associated with higher excess rates of diabetes, CVD and IHD, but the rates were similar to those of other seasonal viruses for stroke. The fractions of all-ages excess hospitalisation in the total numbers of corresponding cause-specific hospitalisation ranged from 0.4% to 9.4% for pH1N1 and from 1.7% to 8.8% for seasonal influenza A and B combined (Table 4). Compared with the age-specific proportions of seasonal influenza A and B combined, the proportions of pH1N1 were markedly higher in the age group of 6–17 years for ARD and in the age groups 6–17 and 18–39 years for P&I, but lower in the age groups older than 40 years for all the disease categories studied except diabetes.

Table 3

Age- and cause-specific excess hospitalisation associated with the 2009 influenza A(H1N1) pandemic, Hong Kong, 2005–2010

Diseases	Age group (years)	Whole pandemic period[a]				First wave[b]				e-flu[c]		Ratio[d]
		Excess number		Excess rate		Excess number (95% CI)		Excess rate		Number	Rate	
ARD	0-5	2,829	(1,875; 3,819)	763.7	(505.9; 1,030.8)	2,330	(1,496; 3,183)	1,027.5	(659.8; 1,404.1)	2,153	949.6	0.92
	6-17	3,408	(3,050; 3,836)	315.4	(282.2; 355.0)	3,003	(2,678; 3,369)	454.2	(405.1; 509.4)	2,506	379.0	0.83
	18-39	1,585	(1,213; 1,930)	54.1	(41.4; 65.9)	1,515	(1,181; 1,823)	84.5	(65.9; 101.7)	1,096	61.2	0.72
	40-64	1,134	(639; 1,658)	32.8	(18.5; 47.9)	1,008	(580; 1459)	47.6	(27.4; 68.9)	902	42.6	0.89
	65-74	233	(-295; 744)	38.8	(-49.0; 123.7)	192	(-270; 648)	52.1	(-73.2; 176.1)	171	46.5	0.89
	≥75	1,186	(-642; 2,942)	209.7	(-113.4; 519.9)	1,009	(-515; 2,525)	291.4	(-148.8; 729.4)	159	45.9	0.16
	All ages	**10,377**	**(5,840; 14,930)**	**133.3**	**(97.2; 168.4)**	**9,057**	**(5,150; 13,007)**	**187.9**	**(135.3; 238.5)**	**6,987**	**126.8**	**0.77**
P&I	0-5	1,916	(1,394; 2,450)	517.2	(376.1; 661.2)	1,921	(1,512; 2,349)	847.4	(666.8; 1,036.1)	2,074	914.8	1.08
	6-17	2,707	(2,439; 3,001)	250.5	(225.7; 277.7)	2,334	(2,093; 2,594)	353.0	(316.5; 392.3)	2,454	371.1	1.05
	18-39	834	(647; 1,014)	28.5	(22.1; 34.6)	631	(472; 773)	35.2	(26.3; 43.1)	1,062	59.3	1.68
	40-64	777	(384; 1,177)	22.5	(11.1; 34.0)	642	(344; 935)	30.3	(16.2; 44.2)	883	41.7	1.38
	65-74	174	(-276; 606)	28.9	(-45.9; 100.7)	154	(-159; 478)	41.9	(-43.1; 129.9)	169	45.9	1.10
	≥75	796	(-812; 2,390)	140.7	(-143.6; 422.4)	354	(-968; 1,502)	102.3	(-279.7; 433.9)	158	45.6	0.45
	All ages	**7,204**	**(3,775; 10,637)**	**102.6**	**(74.2; 130.9)**	**6,036**	**(3,293; 8,632)**	**134.3**	**(98.2; 167.2)**	**6,800**	**123.4**	**1.13**
CVD	40-64	337	(-958; 1,512)	9.7	(-27.7; 43.7)	314	(-749; 1,315)	14.9	(-35.4; 62.1)	206	9.7	0.66
	65-74	483	(-634; 1,428)	80.3	(-105.4; 237.5)	407	(-532; 1,205)	110.5	(-144.5; 327.4)	87	23.6	0.21
	≥75	857	(-1,581; 3,248)	151.4	(-279.5; 574.0)	711	(-1,315; 2,703)	205.5	(-379.7; 780.8)	82	23.7	0.12
	All ages	**1,676**	**(-3,174; 6,188)**	**17.0**	**(-33.6; 66.2)**	**1,432**	**(-2,595; 5,224)**	**23.3**	**(-45.9; 90.6)**	**375**	**6.8**	**0.26**
IHD	40-64	181	(-320; 673)	5.2	(-9.2; 19.5)	115	(-262; 485)	5.4	(-12.4; 22.9)	29	1.4	0.25
	65-74	164	(-225; 537)	27.2	(-37.4; 89.3)	138	(-189; 454)	37.5	(-51.3; 123.5)	38	10.3	0.28
	≥75	503	(-269; 1347)	88.9	(-47.5; 238.0)	415	(-221; 1,112)	119.9	(-63.8; 321.1)	20	5.8	0.05
	All ages	**848**	**(-813; 2,557)**	**1.6**	**(-15.9; 17.6)**	**668**	**(-672; 2,051)**	**2.2**	**(-21.7; 24.1)**	**87**	**1.6**	**0.13**
Stroke	40-64	33	(-258; 312)	1.0	(-7.4; 9.0)	31	(-212; 269)	1.5	(-10.0; 12.7)	20	0.9	0.65
	65-74	129	(-204; 400)	21.4	(-34.0; 66.6)	109	(-172; 339)	29.6	(-46.8; 92.2)	17	4.6	0.16
	≥75	197	(-512; 909)	34.8	(-90.5; 160.6)	164	(-427; 758)	47.4	(-123.4; 218.9)	24	6.9	0.15
	All ages	**359**	**(-974; 1,621)**	**1.8**	**(-10.5; 13.8)**	**304**	**(-811; 1,367)**	**2.4**	**(-14.4; 19.0)**	**61**	**1.1**	**0.20**
Diabetes	40-64	365	(-228; 916)	10.6	(-6.6; 26.5)	307	(-192; 773)	14.5	(-9.1; 36.5)	101	4.8	0.33
	65-74	449	(-128; 949)	74.7	(-21.2; 157.8)	376	(-107; 794)	102.1	(-29.0; 215.8)	41	11.1	0.11
	≥75	736	(-150; 1,635)	130.1	(-26.4; 288.9)	611	(-124; 1,359)	176.4	(-35.7; 392.5)	39	11.3	0.06
	All ages	**1,550**	**(-505; 3,499)**	**17.7**	**(-3.4; 38.1)**	**1,294**	**(-422; 2,926)**	**24.2**	**(-4.6; 52.2)**	**181**	**3.3**	**0.14**

ARD: acute respiratory disease; CI: confidence interval; CVD: cardiovascular disease; IHD: ischaemic heart disease; P&I: pneumonia and influenza.

[a] May 2009 to July 2010.

[b] May 2009 to January 2010.

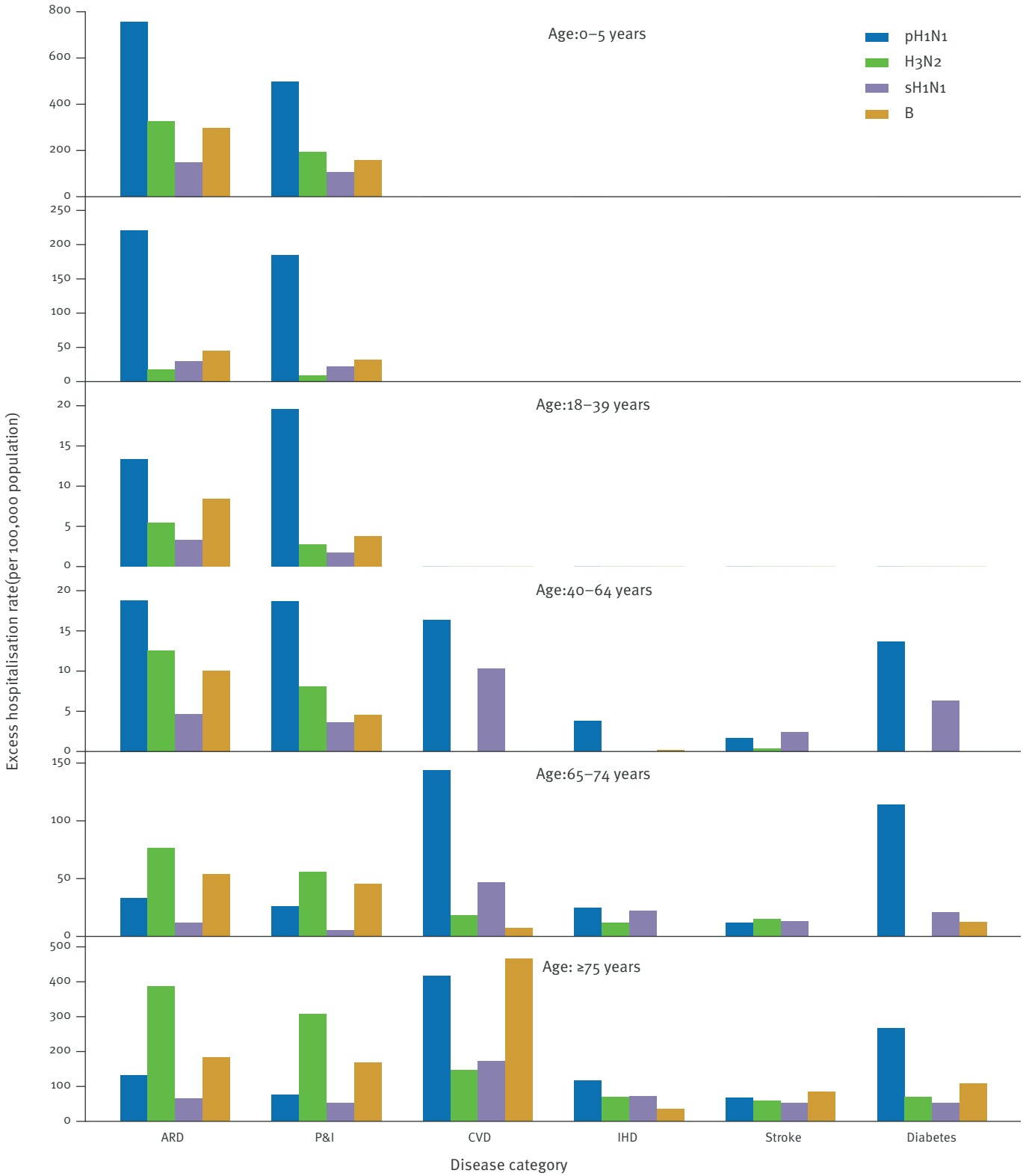
[c] The total numbers of laboratory-confirmed pandemic hospitalisation during the first wave were obtained from the e-flu database managed by the Hospital Authority. The cause-specific cases were grouped by any-listed diagnoses.

[d] Ratio=numbers of hospitalised cases with laboratory confirmed pH1N1 infection/excess numbers of hospitalisation associated with influenza A(H1N1)pdm09 during the first wave.

Note: The total numbers of all ages may not be equal to the sum of each age group due to roundup

Figure 2

Annual age- and cause-specific excess rate per 100,000 person-years of hospitalisation associated with A(H1N1)pdm09, seasonal influenza A(H3N2), A(H1N1) and B, Hong Kong, 2005–2010



ARD: acute respiratory disease; CVD: cardiovascular disease; IHD: ischaemic heart disease; P&I: pneumonia and influenza

Table 4

Percentage of excess hospitalisation in total cause-specific hospitalisation, Hong Kong, 2005–2010

Disease	2005–2010						1996–2000[a]
	Age group (years)	Seasonal influenza A(H1N1)	Influenza A(H3N2)	Influenza B	Influenza A(H1N1)pdm09	Seasonal influenza A+B	Seasonal influenza A+B
ARD	0-5	2.5	5.4	4.9	12.5	12.8	9.3[b]
	6-17	4.9	3.1	7.5	36.7	15.5	9.3[b]
	18-39	2.0	3.3	5.1	8.0	10.4	7.2[c]
	40-64	1.4	3.8	3.1	5.7	8.3	11.0
	65-74	0.6	3.8	2.7	1.7	7.1	11.5
	≥75	0.7	4.1	1.9	1.4	6.7	8.7
	All ages	**1.5**	**4.1**	**3.2**	**8.0**	**8.8**	**10.9**
P&I	0-5	5.4	9.7	7.9	25.0	23.0	14.7[b]
	6-17	6.3	2.8	9.2	53.3	18.3	14.7[b]
	18-39	2.0	3.1	4.4	22.6	9.5	10.5[c]
	40-64	1.5	3.4	1.9	7.8	6.8	8.7
	65-74	0.3	3.3	2.7	1.5	6.3	11.0
	≥75	0.6	3.6	2.0	0.9	6.2	7.1
	All ages	**1.6**	**4.0**	**2.9**	**9.4**	**8.5**	**11.6**
CVD	40-64	0.5	NA[d]	NA[d]	0.9	NA[d]	NA
	65-74	0.5	0.2	0.1	1.6	0.8	NA
	≥75	0.7	0.6	1.9	1.7	3.2	NA
	All ages	**0.6**	**0.3**	**0.8**	**1.3**	**1.7**	**NA**
IHD	40-64	NA[d]	NA[d]	0.0	0.8	NA[d]	2.0
	65-74	0.8	0.4	NA[d]	1.0	NA[d]	0.8
	>75	1.2	1.2	0.6	1.9	3.0	3.2
	All ages	**0.9**	**0.6**	**NA[d]**	**0.4**	**NA[d]**	**1.8**
Stroke	40-64	0.7	0.1	NA[d]	0.5	NA[d]	0.8
	65-74	0.6	0.7	NA[d]	0.5	NA[d]	1.4
	≥75	0.8	0.9	1.3	1.0	3.0	2.4
	All ages	**0.7**	**0.7**	**0.6**	**0.4**	**2.0**	**1.5**
Diabetes	40-64	0.9	0.0	NA[d]	2.0	NA[d]	3.5
	65-74	0.6	0.0	0.4	3.3	1.0	3.0
	≥75	0.7	1.0	1.6	3.8	3.3	5.4
	All ages	**0.8**	**0.3**	**0.6**	**3.1**	**1.7**	**3.5**

ARD: acute respiratory disease; CVD: cardiovascular disease; IHD: ischaemic heart disease; NA: not available; P&I: pneumonia and influenza.

[a] Adapted from reference [34].

[b] Age group 0–14.

[c] Age group 15–39.

[d] Not estimated because of negative excess risk estimates.

The fraction of ARD and P&I excess hospitalisation in the group of 0–5 year-olds was comparable between pH1N1 and seasonal influenza.

Discussion

There are lots of obstacles in obtaining the estimates on hospitalisation due to influenza simply based on surveillance of symptomatic cases, because many suspected cases were not tested in a timely manner due to limited laboratory capacity in most countries. Presanis and colleagues estimated that only 20–30% of hospitalised pH1N1 cases in the United Kingdom confirmed by the laboratory surveillance during the 2009 pandemic [22]. In the present study we used a Poisson regression model, which has been widely adopted for estimation of the influenza disease burden [23-25], to assess excess hospitalisation associated with seasonal influenza. We estimated that during the pandemic period of May 2009 to February 2010, 7,856 admissions for ARD in children and adults younger than 65 years were attributable to pH1N1 infections. This estimate was close to the total number of 6,657 laboratory-confirmed pH1N1 cases hospitalised for ARD in Hong Kong. The close match between model-derived and laboratory-confirmed cases in young age groups is not surprising as they were immediately identified as high risk groups at the beginning and underwent intensive laboratory screening for pH1N1 infections throughout the pandemic period. We found that the estimated in old population groups, excess hospitalisations associated with pH1N1 were dramatically higher than the numbers of confirmed hospitalised cases, for both acute and chronic diseases. This is in agreement with our previous findings that the mortality burden of pH1N1 in children and young adults was fully captured by intensive screening, but seriously underreported in the elderly [8]. We speculated that the neglected burden in the old population could be due to their low antibody and viral titres after infection, or the time lag between primary infection and hospital admission for exacerbated underlying conditions. To capture these cases, it is necessary to enhance the surveillance at community level so as not to miss the time when the symptoms of primary infection are evident.

A shift in the age of severe and fatal cases towards younger age groups has been observed in historical influenza pandemics. Consistent with many other studies [26-28],our estimates demonstrated that for ARD and P&I, the influenza A(pH1N1)pdm09 virus was associated with dramatically elevated excess hospitalisation in children and young adults compared with the seasonal viruses, whereas its impact on the elderly was less than that of influenza A(H3N2), although comparable to sH1N1 and influenza B. A study in Denmark also found significantly higher hospitalisation rates for pH1N1 among persons younger than 65 years, but the rates among the elderly were similar for the pandemic and seasonal viruses [29]. That old people are less affected by pH1N1 infection could be explained by their preexisting immunity against pH1N1 [30]. Despite a low attack rate of pH1N1 in elderly people in Hong Kong living in the community, a large proportion of the hospitalised and fatal cases still occurred in old people, who had markedly higher case–intensive care unit and case–fatality rates according to data from the e-flu database [31].

H3N2 viruses were believed to have more frequent antigenic drift than sH1N1 and influenza B [32]. Previous studies have demonstrated that influenza was associated with markedly more morbidity and mortality during the H3N2-dominated years, than during the years dominated by sH1N1 or influenza B [13]. By simultaneously adding the different virus proxies, regression models allow the separate assessment of the disease burden caused by different influenza types or subtypes. Zhou and colleagues fitted a negative binomial regression model, which is similar to Poisson regression with adjustment for over-dispersion, on weekly hospitalisation data of respiratory and cardiovascular diseases in the United States (US) from 1993 to 2008 [33]. They reported much lower excess rates of hospitalisation associated with sH1N1 and influenza B (1.9 and 17.5 per 100,000 person-years) than with influenza A(H3N2) virus (44.4 per 100,000). Interestingly, our estimates showed that among the three seasonal influenza viruses, H3N2 influenza contributed to higher hospitalisation rates for ARD and P&I. For chronic diseases, however, the hospitalisation rates associated with H3N2 influenza were lower for CVD and diabetes; the rates associated with sH1N1 and H3N2 influenza were similar for IHD and stroke, but those associated with influenza B were slightly lower (Figure 2). Further studies are needed from more countries to compare the virulence of different influenza viruses.

We estimated that during 2005–08, the annual excess rate associated with seasonal influenza ranged from 80.5 to 116.1 per 100,000 person-years for ARD, and from 30.4 to 51.1 for CVD. These rates were higher than the excess hospitalisation rates of 32.6–82.7 for respiratory and circulatory diseases which were estimated from the US study for the same study period [33], although these two sets of estimates may not be directly comparable since we defined disease categories by any-listed diagnosis. Our estimates were the double or triple of the previous estimates using the similar model for the period of 1996–2000 [34] (Table 2). The increased morbidity burden in recent years may not be solely due to more virulent virus strains, as we did not observe any obvious increase in excess mortality associated with influenza in Hong Kong since 1998, except in 2007 when a novel H3N2 strain A/Brisbane/59/2007-like emerged [8]. Instead, this increase is more likely the result of expanding health service capacities and lowering admission criteria due to the aging population of Hong Kong [16]. In fact, overall the proportions of excess hospitalisation in total numbers of cause-specific hospitalisation are quite similar between our present and previous studies, suggesting that the morbidity burden of seasonal

influenza remained comparable during the interpandemic years (Table 4). Interestingly, the percentage of excess hospitalisation associated with seasonal influenza among the total hospitalisations for ARD and P&I among children and young adults was higher during the study period of 2005–2010 than those during 1996–2000. However, it was lower among the elderly, which probably reflects changing health-seeking behaviour of parents and young people, particularly after the outbreak of severe acute respiratory syndrome in 2003 that significantly awakened the public awareness of respiratory viruses.

Surprisingly, we found a heavy morbidity burden of influenza in 2010 in Hong Kong with a similar magnitude as in the pandemic year 2009. However, the majority of influenza isolates since August 2010 have been an H3N2 strain which is an antigenic match to the 2010–2011 vaccine composite strain A/Perth/16/2009. Similar observations were also reported in several European countries [35]. We noticed that in 2010, the summer peak of influenza did not appear until August–September, the months when influenza viruses usually become dormant after the normal peak months of June and July [36]. Most of excess hospital admissions in 2010 were associated with influenza A(H3N2), not pH1N1 that was the dominant strain in the winter peak 2009/10 (data not shown). The potential explanation for altered influenza seasonality after the pandemic could be depletion of the pool of susceptibles by the preceding pandemic, interference of pandemic viruses, or relaxation of the control measures implemented during the pandemic period (border control, designated influenza clinics, etc), all of which certainly warrant further investigations.

There are several limitations to our study. Firstly, our virology data for pH1N1 only covered a period shorter than two years, which might have compromised the power of the Poisson model, as reflected by the non-significant estimates in most age–disease categories. Secondly, other than disease severities there are many unmeasured factors that could have affected hospital admissions, such as influenza vaccination status, health seeking behaviour and admission criteria. Our assessment of cause-specific hospitalisation could be further complicated by varying coding practice of frontline medical practitioners. Although we adjusted for long-term and seasonal trends of hospitalisation in our models to take into account changes in admission threshold and coding practice, this may not be adequate for all the disease categories, as evidenced by some negative estimates and underestimation of P&I excess hospitalisation during the pandemic. Nevertheless, our previous validation study demonstrated that excess hospitalisation derived from the Poisson regression models closely matched the true incidence rates of laboratory-confirmed influenza among a cohort of paediatric patients [10]. Moreover, our estimates were overall larger than the laboratory-confirmed cases requiring hospitalisation, although the difference was not as big as we expected. Therefore, our estimates of excess hospitalisation rates are likely conservative, not exaggerating the true burden of seasonal and pandemic influenza.

In this study we comprehensively assessed the impact of seasonal and pandemic influenza by deriving the age- and cause-specific estimates of excess hospitalisation associated with different types or subtypes of influenza viruses. Compared with seasonal influenza viruses, the pH1N1 virus was associated with dramatically increased hospitalisation risk among children and young adults. Although the attack rate of the pandemic was relatively low in the elderly, their risk of hospitalisation was comparable to the interpandemic years and seriously underreported by the clinical surveillance. This highlights the need to enhance the community surveillance on pandemic outbreaks among old people. Our study provides an approach for reliable assessment of the pandemic severity and also a piece of critical evidence for proper evaluation of control measures implemented during the pandemic.

*Author's correction

On request of the authors, the first three sentences of the second paragraph of the Methods section were replaced and a footnote was added to Table 1. These corrections were made on 14 November 2012.

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