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The Infection Attack Rate and Severity of 2009 Pandemic H1N1 Influenza in Hong Kong

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Background. Serial cross-sectional data on antibody levels to the 2009 pandemic H1N1 influenza A virus from a population can be used to estimate the infection attack rates and immunity against future infection in the community.

Methods. From April through December 2009, we obtained 12,217 serum specimens from blood donors (aged 16–59 years), 2520 specimens from hospital outpatients (aged 5–59 years), and 917 specimens from subjects involved in a community pediatric cohort study (aged 5–14 years). We estimated infection attack rates by comparing the proportions of specimens with antibody titers $\geq 1:40$ by viral microneutralization before and after the first wave of the pandemic. Estimates were validated using paired serum samples from 324 individuals that spanned the first wave. Combining these estimates with epidemiologic surveillance data, we calculated the proportion of infections that led to hospitalization, admission to the intensive care unit (ICU), and death.

Results. We found that 3.3% and 14% of persons aged 5–59 years had antibody titers $\geq 1:40$ before and after the first wave, respectively. The overall attack rate was 10.7%, with age stratification as follows: 43.4% in persons aged 5–14 years, 15.8% in persons aged 15–19 years, 11.8% in persons aged 20–29 years, and 4%–4.6% in persons aged 30–59 years. Case-hospitalization rates were 0.47%–0.87% among persons aged 5–59 years. Case-ICU rates were 7.9 cases per 100,000 infections in persons aged 5–14 years and 75 cases per 100,000 infections in persons aged 50–59 years, respectively. Case-fatality rates were 0.4 cases per 100,000 infections in persons aged 5–14 years and 26.5 cases per 100,000 infections in persons aged 50–59 years, respectively.

Conclusions. Almost half of all school-aged children in Hong Kong were infected during the first wave. Compared with school children aged 5–14 years, older adults aged 50–59 years had 9.5 and 66 times higher risks of ICU admission and death if infected, respectively.

The 2009 pandemic influenza A H1N1 virus emerged in Mexico in early 2009 and rapidly spread around the world [1]. By January 2010, most countries had experienced at least one substantial epidemic wave. Vaccines against the novel H1N1 influenza strain became

available toward the end of 2009. Timely serologic data are important to facilitate identification of the target groups for whom pandemic vaccine would be most useful prior to subsequent waves, because some population groups may have substantial immunity following the first wave. We conducted a prospective sero-epidemiological study using serial cross-sectional data as well as longitudinal cohort data to estimate age-specific H1N1 influenza infection attack rates (IARs) in the community during the first wave of the pandemic. We used our IAR estimates to infer the severity of the pandemic strain, including the age-specific proportion of infections that led to laboratory confirmation, hospitalization, intensive care unit (ICU) admission, and death [2–5].

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METHODS

Subjects

Blood donors, aged 16–65 years. From 12 June through 31 December 2009, blood donors from the 4 largest blood donation centers (Mongkok, Causeway Bay, Kwun Tong, and Tsuen Wan) of the Hong Kong Red Cross Blood Transfusion Service were invited to participate in our serologic surveillance study. Eligible donors were healthy adults aged 16–65 years and weighing >41 kg. Repeated participants were identified using their unique Blood Transfusion Service identification numbers. A total of 12,217 serum samples were tested. Paired serum specimens from before the first pandemic wave (before 1 August 2009) and after the first pandemic wave (after 15 November 2009) were collected from 324 blood donors. Blood donors did not receive any remuneration or compensation.

Hospital outpatients, aged 5–59 years. From 2 September through 31 December 2009, we invited patients visiting the Pediatric and Adolescent Medicine outpatient clinic and the Medicine outpatient clinic at Queen Mary Hospital to participate in our serologic surveillance study. Patients with acute respiratory infections or immunosuppression (including patients receiving chemotherapy for various malignancies, post-transplant or cirrhotic patients, or any patients receiving systemic immunosuppressants) at recruitment were excluded from participation. A total of 2520 serum samples were tested.

Subjects of a community study, aged 5–14 years. From 1 November 2008 through 31 October 2009, we conducted a cohort study of pediatric seasonal influenza vaccination and household transmission of influenza. A total of 151 children aged 5–14 years were recruited and provided baseline serum samples in November and December 2008. From September through December 2009, an additional 766 children aged 5–14 years were recruited and provided baseline serum samples for the second phase of the study. For the present study, we tested the 151 serum samples collected before the first pandemic wave and the 766 serum samples collected after the first wave.

Informed Consent

Written informed consent was obtained from all participants. Parental consent was obtained for participants aged ≤ 15 years, and children aged 8–15 years gave written assent. All study protocols were approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Data on Hospitalization, ICU Admission, and Death

Age-stratified data on virologically confirmed outpatient consultations, hospitalizations, ICU admissions, and deaths associated with H1N1 influenza from 29 April 2009 through 15 November 2009 were provided by the Hong Kong Hospital Au-

thority (the e-flu database) [6]. From May 2009 onward, patients admitted with acute respiratory illnesses routinely underwent laboratory testing for H1N1 influenza virus by molecular methods. Population-size data by age were obtained from the Hong Kong Government Census and Statistics Department.

Laboratory Methods

Serum samples were tested for antibody responses to A/Cali-
fornia/4/2009 by viral microneutralization [7]. Further details of our laboratory methods are provided in the Appendix, which appears only in the electronic version of the journal.

Outcomes

Most individuals infected with influenza develop antibody titers $\geq 1:40$ by viral microneutralization after recovery [8]. We defined the H1N1 influenza seroprevalence rate as the proportion of individuals who had antibody titers $\geq 1:40$. While microneutralization antibody titers ≥ 40 are not by themselves conclusive evidence of H1N1 influenza virus infection in all age groups, we have assumed that the increase in cross-sectional seroprevalence from the time period before the first wave of pandemic influenza (hereafter, “pre–first-wave”) to the time period after the first wave (hereafter, “post–first-wave”) is evidence of recent H1N1 influenza infection. Seasonal influenza A infection or vaccination is not typically associated with an increase in antibody titers to H1N1 influenza [7, 9], and H1N1 influenza was the predominant circulating strain [10]. In analysis of paired serum samples, we defined the seroconversion rate as the proportion of individuals with antibody titers of $\leq 1:10$ pre–first-wave and $\geq 1:40$ post–first-wave (ie, ≥ 4 -fold increase in antibody titer; titers of $\leq 1:10$ were taken as 1:10 in our calculations).

The IAR was defined as the proportion of individuals infected with H1N1 influenza during the first wave. The case-confirmation rate, case-hospitalization rate, case-ICU admission rate, and case-fatality rate were defined as the proportion of H1N1 influenza infections that led to laboratory confirmation, hospitalization, ICU admission, and death, respectively. Because of containment efforts until 29 June 2009, all patients with laboratory-confirmed cases were required to be hospitalized for isolation, regardless of disease severity; therefore, only surveillance data from June 30 onward were used to estimate severity measures.

Statistical Methods

We estimated the IAR as the difference between the pre–first-wave and post–first-wave seroprevalence rates. To validate this approach, we compared the IAR estimates with the seroconversion rates in paired serum samples available from a subset of 324 blood donors aged 15–59 years. We used the estimated IAR as the denominator for calculating the case-confirmation

rate, case-hospitalization rate, case-ICU admission rate, and case-fatality rate from the e-flu surveillance data. We obtained the posterior distributions of age-specific IARs, case-confirmation rates, case-hospitalization rates, case-ICU admission rates, and case-fatality rates using Monte Carlo Markov Chain methods with noninformative priors for all parameters. Further details of the statistical methods are provided in the Appendix.

RESULTS

Virological surveillance data suggested that the first wave of pandemic H1N1 influenza in Hong Kong occurred from August to October, and evidence of infection had largely decreased by mid-November 2009 (Figure 1). Most of the laboratory-confirmed cases of infection in this first wave occurred in individuals aged <25 years; this age group accounted for >72% of the laboratory-confirmed cases and hospitalizations, 32% of ICU admissions, and 6% of deaths. Taking into account a delay of 2–3 weeks for antibody titers to appear during convalescence [8], we found that these virological surveillance data were consistent with our serial cross-sectional seroprevalence data, which indicated a sharp increase in seroprevalence among individuals aged 5–25 years from September to November 2009 and a plateau thereafter (Figure 2). This justified our decision to base the pre-first-wave and post-first-wave seroprevalence estimates on serum samples collected in June 2009 and November–December 2009, respectively. More than 90% of H1N1 influenza-associated hospitalizations from 30 June through 15 November 2009 occurred after 1 August. This justified our use of 1 August 2009 as the pre-first-wave cutoff date for our paired serum samples.

Among individuals aged 5–14 years, the seroprevalence rates across time were similar between pediatric outpatients and pediatric cohort study subjects (Figure 2). Similarly, for older age groups, the seroprevalence rates were largely similar between blood donors and hospital outpatients (except for those aged 20–29 years in November–December). This provided some evidence that despite potential biases in our convenience sampling scheme, the resulting serologic data provided a reasonably representative description of seroprevalence in the community.

Prior to the first pandemic wave (June 2009), seroprevalence was uniformly low among individuals aged 5–59 years but increased substantially among younger age groups during the first wave (Table 1 and Figure 2). Comparing the pre-first-wave and post-first-wave seroprevalence rates (ie, the serial cross-sectional method), we estimated that the IAR was 43.4% among individuals aged 5–14 years, 15.8% among individuals aged 15–19 years, 11.8% among individuals 20–29 years, 4.3% among individuals aged 30–39 years, 4.6% among individuals aged 40–49 years, and 4.0% among individuals aged 50–59 years (Table 1). These IAR estimates were broadly consistent with the IARs estimated from seroconversion rates in paired serological analysis of blood donor samples (Appendix). Overall, we estimated

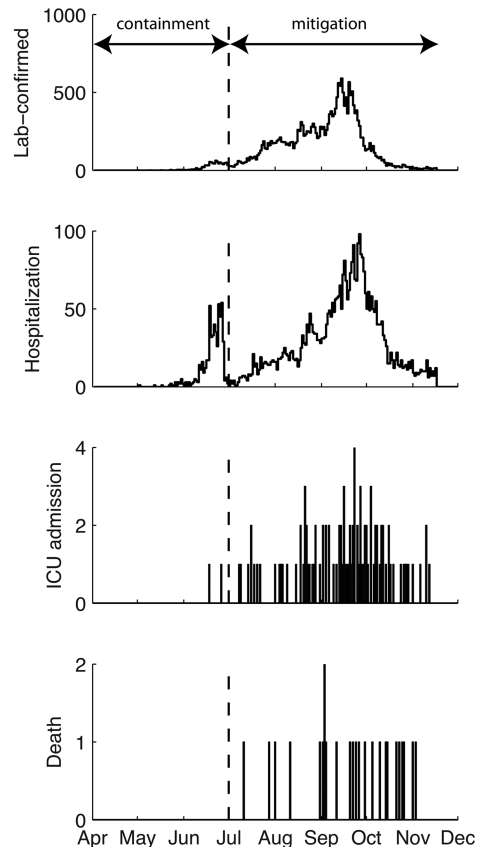


Figure 1. Epidemiologic surveillance data for the first wave of H1N1 influenza in Hong Kong, 2009. ICU, intensive care unit.

a population-weighted IAR of 10.7% (95% confidence interval [CI], 9%–12%) among individuals aged 5–59 years through the first wave in Hong Kong.

A total of 23,643 laboratory-confirmed H1N1 influenza cases among individuals aged 5–59 years were reported from 29 April through 15 November 2009. Before 30 June, 567 (67%) of the 849 laboratory-confirmed cases were isolated in hospitals as part of containment-phase measures. These data were excluded from our analysis of severity estimates. From 30 June onward, hospital admission was based on medical need, and 4253 (19%) of the 22,794 individuals aged 5–59 years with laboratory-confirmed H1N1 influenza were admitted to hospitals from 30 June through 15 November. There were 103 ICU admissions and 26 deaths among patients aged 5–59 years with laboratory-confirmed H1N1 influenza. On the basis of our estimated IAR of 10.7% among individuals aged 5–59 years (equivalent to 597,000 cases of infection in Hong Kong), we estimated that ~3.9% (95% CI, 3.5%–6.2%) of infections were reported and were laboratory confirmed and that ~0.73% (95% CI, 0.66%–1.22%) of infected individuals required hospitalization (Table 2). The rate of ICU admissions and deaths were ~17.6 cases

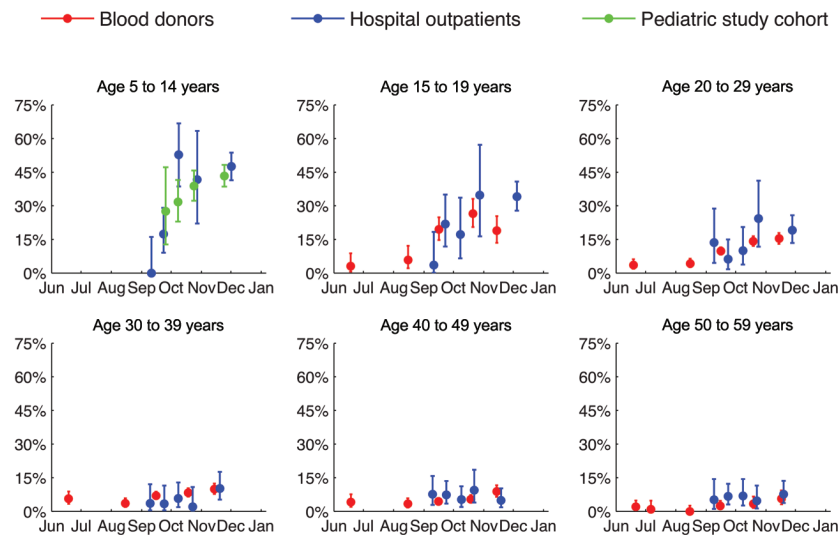


Figure 2. Age-specific proportions of individuals with antibody titers $\geq 1:40$ by viral microneutralization between June 2009 and January 2010. Each data point corresponds to an average over multiple days, and vertical bars indicate 95% confidence intervals estimated by the exact binomial method. Data points with sample size < 10 are not shown. All subjects (151 persons aged 5–14 years) in the pediatric cohort study had antibody titers $< 1:40$ by viral microneutralization in April 2009 (data not shown).

(95% CI, 13.3–50.1 cases) and 4.4 cases (95% CI, 3.2–17 cases) per 100,000 infections, respectively (Table 2).

Case-hospitalization rates were $\sim 0.47\%$ – 0.87% among individuals aged 5–59 years (Table 2 and Figure 3). Rates of H1N1 influenza-associated ICU admission were 7.9 cases (95% CI, 5.2–12.6 cases) per 100,000 infections among individuals aged 5–14 years and 75 cases (95% CI, 32.7–281 cases) per 100,000 infections among individuals aged 50–59 years. Rates of H1N1 influenza-associated mortality (case-fatality rates) followed a similar trend, with 0.4 deaths (95% CI, 0.1–2.3 deaths) per

100,000 infections among individuals aged 5–14 years and 26.5 deaths (95% CI, 10.4–109 deaths) per 100,000 infections among individuals aged 50–59 years. Compared with children aged 5–14 years, adults aged 50–59 years were 9.5 and 66 times more likely to be admitted to the ICU and die if infected, respectively.

DISCUSSION

We estimated that, during the first wave of the pandemic in Hong Kong, 43.4% of school-aged children and 10.7% of in-

Table 1. Estimated Proportion of the Population with Antibody Titers $\geq 1:40$ by Viral Microneutralization against H1N1 Influenza Virus before and after the First Wave of the Pandemic and the Estimated Infection Attack Rate

Age group, years	Before the first wave			After the first wave			Infection attack rate ^{ab} (95% CI), %
	No. of positive specimens/total no. of specimens	Percentage positive (95% CI), %	Source ^a	No. of positive specimens/total no. of specimens	Percentage positive (95% CI), %	Source ^a	
5–14	0/151	0.0 (0.0–2.4)	1	183/422	43.4 (38.6–48.2)	3	43.4 (37.9–47.6)
15–19	3/97	3.1 (0.6–8.8)	2	34/180	18.9 (13.5–25.4)	4	15.8 (8.2–22.1)
20–29	12/336	3.6 (1.9–6.2)	2	135/879	15.4 (13.0–17.9)	4	11.8 (8.4–14.7)
30–39	17/302	5.6 (3.3–8.9)	2	67/676	9.9 (7.8–12.4)	4	4.3 (0.9–7.5)
40–49	10/238	4.2 (2.0–7.6)	2	45/509	8.8 (6.5–11.7)	4	4.6 (1.0–7.9)
50–59	6/352	1.7 (0.6–3.7)	2	14/247	5.7 (3.1–9.3)	4	4.0 (1.1–7.5)
Overall (5–59)		3.3 (2.8–4.7)			14 (13.0–15.4)		10.7 (9.0–12.0)

NOTE. The infection attack rate was calculated using the serial cross-sectional method. CI, confidence interval.

^a Sources of specimens are as follows: (1) Pediatric cohort study, 2–29 April 2009; (2) Hong Kong Red Cross Blood Transfusion Service, 15–22 June 2009; (3) Pediatric cohort study, 6 November to 19 December 2009; and (4) Hong Kong Red Cross Blood Transfusion Service, 1 November to 6 December 2009.

^b Posterior mode.

Table 2. Estimated Age-Specific Proportions of Individuals with H1N1 Influenza Infection Who Were Laboratory Confirmed, Were Hospitalized, Were Admitted to the Intensive Care Unit (ICU), and Died

Age group, years	No. of laboratory-confirmed cases (% of all)	Case-confirmation rate ^a (95% CI), %	No. of hospitalizations (% of all)	Case-hospitalization rate ^a (95% CI), %	No. admitted to the ICU (% of all)	Case-ICU rate ^a (95% CI), per 100,000 infections	No. of deaths (% of all)	Case-fatality rate ^a (95% CI), per 100,000 infections
5–14	10,060 (44.1)	4.0 (3.6–4.6)	2133 (50.2)	0.84 (0.76–0.97)	20 (19.4)	7.9 (5.2–12.6)	1 (3.8)	0.4 (0.1–2.3)
15–19	3673 (16.1)	5.4 (3.9–10.5)	522 (12.3)	0.77 (0.53–1.50)	9 (8.7)	13.3 (7.0–34.4)	2 (7.7)	3 (0.9–13.2)
20–29	4314 (18.9)	3.8 (3.0–5.3)	532 (12.5)	0.47 (0.37–0.66)	7 (6.8)	6.1 (3.0–13.9)	1 (3.8)	0.9 (0.2–5.2)
30–39	1868 (8.2)	4.0 (2.2–18.2)	378 (8.9)	0.80 (0.45–3.66)	12 (11.7)	25.4 (10.7–130.5)	4 (15.4)	8.5 (3.2–53.1)
40–49	1615 (7.1)	2.8 (1.6–12.5)	293 (6.9)	0.51 (0.30–2.26)	21 (20.4)	36.4 (18.8–171.5)	6 (23.1)	10.4 (4.4–57.2)
50–59	1264 (5.5)	2.8 (1.4–10.1)	395 (9.3)	0.87 (0.45–3.16)	34 (33.0)	75 (32.7–281.3)	12 (46.2)	26.5 (10.4–108.9)
Overall (5–59)	22,794 (100.0)	3.9 (3.5–6.2)	4253 (100.0)	0.73 (0.66–1.22)	103 (100.0)	17.6 (13.3–50.1)	26 (100.0)	4.4 (3.2–17)

NOTE. Case-ICU and case-fatality rates are expressed as number of episodes per 100,000 infections. CI, confidence interval.

^a Posterior mode.

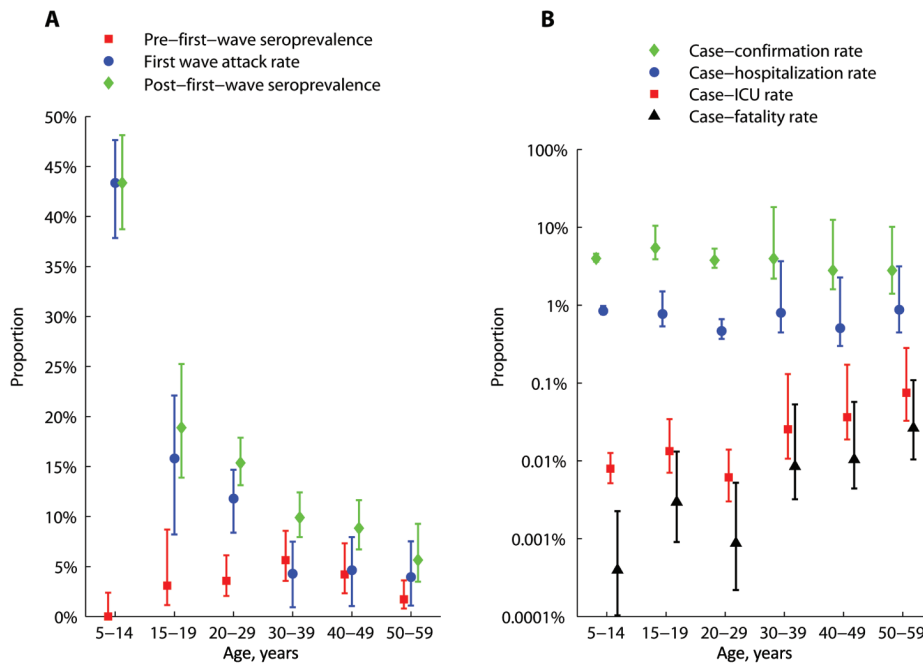


Figure 3. Age-specific infection attack rates and severity measures of H1N1 influenza in Hong Kong. *A*, Pre-first-wave and post-first-wave seroprevalence rates and infection attack rates based on the serial cross-sectional approach. *B*, Proportions of infections leading to laboratory confirmation, hospitalization, intensive care unit (ICU) admission, and fatality. The points and vertical bars indicate posterior modes and 95% confidence intervals based on the fitted model.

dividuals aged 5–59 years were infected with H1N1 influenza. A serologic survey in England found similar IARs in London and the West Midlands [8]. Both studies highlight the importance of including serologic surveys as a component of pandemic surveillance. While our core results are based on data from serial cross-sectional samples, we found similar IARs inferred from participants from whom paired serum samples were available. The geographically compact and homogeneously mixing population in the urban environment of Hong Kong permits some degree of confidence in the validity of our IAR and severity estimates. The detailed H1N1 influenza reporting system, the wide coverage of the public health care system (which includes >90% of all local inpatient days [11]), and the resource investments since the epidemic of severe acute respiratory syndrome have led to routine laboratory testing for all patients hospitalized with fever or pneumonia. This should allow identification of the majority of hospitalizations, ICU admissions, and deaths directly associated with H1N1 influenza infection. Thus, the completeness of the H1N1 influenza surveillance system, the well-defined population denominator, and our large-scale serologic survey provide accurate numerators and denominators for the severity measures.

We based severity estimates for H1N1 influenza on the IAR as the denominator. Some previous studies of H1N1 influenza severity used as the denominator the clinical illness attack rate, which depends on the probability of symptoms, as well as med-

ical care-seeking behavior of the population [3, 12]. Our estimated case-ICU admission rates and case-fatality rates are broadly consistent with severity estimates using “approach 2” of Presanis et al [3] but are ~7–9 times lower than the estimates using their “approach 1.” Our estimates of case-hospitalization rates are 2–10 times higher than their Approach 2 estimates of symptomatic case-hospitalization rate. However, the hospitalization-to-death ratio was 164 (4253/27) as of 15 November in Hong Kong but was 19 (996/53) as of 14 June in New York [3], implying that the clinical threshold for admission in terms of disease severity at presentation may have been lower in Hong Kong.

We estimated that ~0.4 cases per 100,000 infections in school-aged children led to mortality, whereas the risk of ICU admission and death per infection was 9.5 and 66 times higher in older adults aged 50–59 years (Figure 3). The estimates for mortality rates in children are consistent with data from the United Kingdom, where one study estimated a mortality rate of 11 deaths per 100,000 symptomatic cases in children aged 5–14 years [12], while a serologic study suggested that the attack rates had been underestimated by a factor of 10 [8]. Our estimates are lower than early estimates of the case-fatality rate, but the denominators may not have been well estimated in those studies [1, 13, 14]. Previously, a statistical model was used to estimate that the excess number of deaths due to seasonal influenza in Hong Kong was 11.8 deaths (95% CI, 3.8–20.1

deaths) per 100,000 population aged 40–64 years [15]. Assuming an annual IAR of 20%, this estimate would translate into 59 deaths (95% CI, 19–101 deaths) per 100,000 infections, which is slightly larger than our H1N1 influenza case-fatality rate estimate of 18 deaths (95% CI, 9–74 deaths) per 100,000 infections among individuals aged 40–59 years. This supports the prevailing view that H1N1 influenza is not more severe than seasonal influenza in terms of morbidity and mortality.

Simulation studies have suggested that administration of pandemic vaccines to school-aged children provides substantial benefits to the community [16, 17]. However, since 43.4% of school-aged children were infected in the first wave and are likely immune to reinfection, and infections in school-age children are rarely severe (Table 2), there may be less justification to include this age group as a target group for vaccination after the first wave of the pandemic in Hong Kong. Furthermore, given the substantial attack rate in children during the first wave, we speculate that a large second wave may be unlikely to occur unless there is substantial antigenic drift. So far, there has been no evidence of the emergence of antigenically drifted H1N1 influenza viruses [18].

Our study has a number of limitations. First, we have used antibody titers $\geq 1:40$ measured by viral microneutralization as an indicator of recent infection, correcting for baseline (pre-existing) seroprevalence levels, but this may lead to underestimation of the IAR if not all infections led to antibody titers $\geq 1:40$, or if some individuals with baseline titers $\geq 1:40$ were infected. Another study found that $\sim 5\%$ of laboratory-confirmed H1N1 influenza cases did not develop convalescent antibody titers $>1:40$ measured by hemagglutinin inhibition testing [8]. Second, our estimates of the IAR would be biased upward if infection with other circulating influenza viruses led to cross-reactive antibody responses resulting in antibody titers $\geq 1:40$. However, from August through October 2009, 83% of influenza A viruses detected in Hong Kong were H1N1, and only 3% of isolated viruses were seasonal H1N1 viruses, which are more likely to be associated with cross-serological cross reactions with H1N1 virus (Appendix) [10]. Third, a minority of severe illnesses associated with H1N1 influenza infection might not be identified by molecular detection methods—for example, if admission occurred after cessation of viral shedding associated with the primary infection; thus, we may have underestimated the pandemic disease burden. We did not have seroepidemiological data from individuals aged >60 years and consequently cannot comment on attack rates or complication rates in this important age group. Finally, our analyses are primarily based on seroprevalence among blood donors to the Hong Kong Red Cross, who may not be representative of the whole population. We do not have detailed data on donors to compare their risk of infection with the general population, but we did observe very similar seroprevalence rates across the

3 groups of subjects in our study—that is, blood donors, hospital outpatients, and participants in a community cohort (Figure 2 and Figure 2A in the Appendix).

We chose to use microneutralization tests rather than hemagglutination inhibition tests, following preliminary studies that showed that microneutralization was more sensitive than hemagglutination inhibition for detection of antibody responses in H1N1 influenza infection [7, 8]. There is only limited cross-reactivity between pandemic and recent seasonal H1N1 influenza viruses by the microneutralization test (used in this study), but there is some cross-reaction in individuals, increasing with age and particularly noticeable in those aged >65 years [8, 9]. Thus, in a given individual, current serological methods do not conclusively distinguish between antibody resulting from pandemic H1N1 influenza infection from cross-reactive antibody arising from prior infections with seasonal H1N1 influenza, especially in those aged >60 years, which is one reason why we did not address the infection rates or disease severity in elderly individuals. Our study design is based on the difference in age-stratified seroprevalence in the pre-first-wave period versus the post-first-wave period, a time when there was minimal seasonal H1N1 influenza virus circulation in Hong Kong. Thus, our conclusions for individuals aged <60 years are unlikely to be confounded by issues pertaining to serological cross-reactivity. While immune senescence could potentially lead to an underestimation of attack rates in elderly individuals, especially those aged >65 years, this is unlikely to affect our study, which investigated individuals aged <60 years.

In conclusion, $\sim 10.7\%$ of the population aged 5–59 years and half of all school-aged children in Hong Kong were infected during the first wave of pandemic H1N1 influenza. Compared with school children aged 5–14 years, older adults aged 50–59 years, although less likely to acquire infection, had 9.5 and 66 times higher risk of ICU admission and death if infected. Thus, the apparently low morbidity and mortality burden of 2009 pandemic H1N1 influenza, despite an IAR in the first wave similar to that of a seasonal epidemic, appears to be caused by low infection rates in older adults, who faced a much greater risk of severe illness if infected. The reasons why older adults appear relatively resistant to H1N1 influenza infection, even though they appear to lack neutralizing antibody, remain unclear. If antigenic drift or other adaptation of the H1N1 influenza virus allows these older age groups to be infected more efficiently, the morbidity and mortality of subsequent waves of the pandemic could yet become substantial.

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