Infection attack rates during the epidemic of swine influenza A by tracking temporal changes in age-specific seroprevalence rates

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KEY MESSAGE

Serial cross-sectional serological data are a valuable addition to future surveillance of pandemic influenza and other emerging infectious diseases.

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Introduction

During the epidemic of swine influenza A/H1N1 (pdmH1N1) in Hong Kong in 2009, two large-scale serological surveys were conducted to track temporal changes in population-level seroprevalence of pdmH1N1 antibodies.[1] The serological data from our pdmH1N1 serosurveys were combined with daily hospitalisation data from clinical surveillance from e-flu database (managed by the Hospital Authority) to characterise the transmission dynamics, infection attack rates (IARs), and severity of pdmH1N1 during the first wave.

This study aimed to: (1) obtain weekly estimates of age-specific IARs among hospital outpatients; (2) construct a representative description of the epidemic by combining the above results with serological data from daily samples of blood donations at the Hong Kong Red Cross Blood Transfusion Service between June 2009 and January 2010 for serum antibodies specific to this virus; and (3) estimate the reproductive number of the H1N1 virus over the course of the epidemic and the effectiveness of community-wide interventions (eg school closure, vaccination) in reducing the reproductive number.

Methods

Subjects

Serum specimens were collected from three groups of subjects. The first group comprised 13 328 blood donors aged 16 to 60 years from the four largest blood donation centres (Mongkok, Causeway Bay, Kwun Tong, and Tsuen Wan) of the Hong Kong Red Cross Blood Transfusion Service between 12 June and 31 December 2009. The second group comprised 3613 outpatients aged <16 years and >60 years with suboptimal health conditions from the paediatric and adolescent medicine outpatient clinic and the medicine outpatient clinic at the Queen Mary Hospital between 2 September 2009 and 30 April 2010. The third group comprised 151 children aged 5 to 14 years (between November and December 2008) and 766 children aged 5 to 14 years (between September and December 2009) who participated in an independent cohort study of paediatric seasonal influenza vaccination and household transmission of influenza. All subjects were bled once only.

Epidemiological surveillance data

Age-stratified data on virologically confirmed outpatient consultations, hospitalisations, intensive care unit admissions, and deaths associated with pdmH1N1 from 29 April 2009 to 15 November 2009 were provided by the Hospital Authority (the e-flu database). Since May 2009, patients admitted with acute respiratory illnesses routinely underwent laboratory testing for pdmH1N1 virus by molecular methods.

Laboratory methods

Sera were tested for antibody responses to A/California/4/2009 by viral microneutralisation (MN). Each serum sample was tested for MN titre ≥1:20 and ≥1:40. Seroprevalence at a given MN titre cutoff (1:20 or 1:40) was defined as the proportion of individuals whose titres were at or above that cutoff.

Estimation of age-specific incidence

The e-flu hospitalisation data suggested that incidences between 30 June and 15 November 2009 were generated mostly by local transmission, whereas

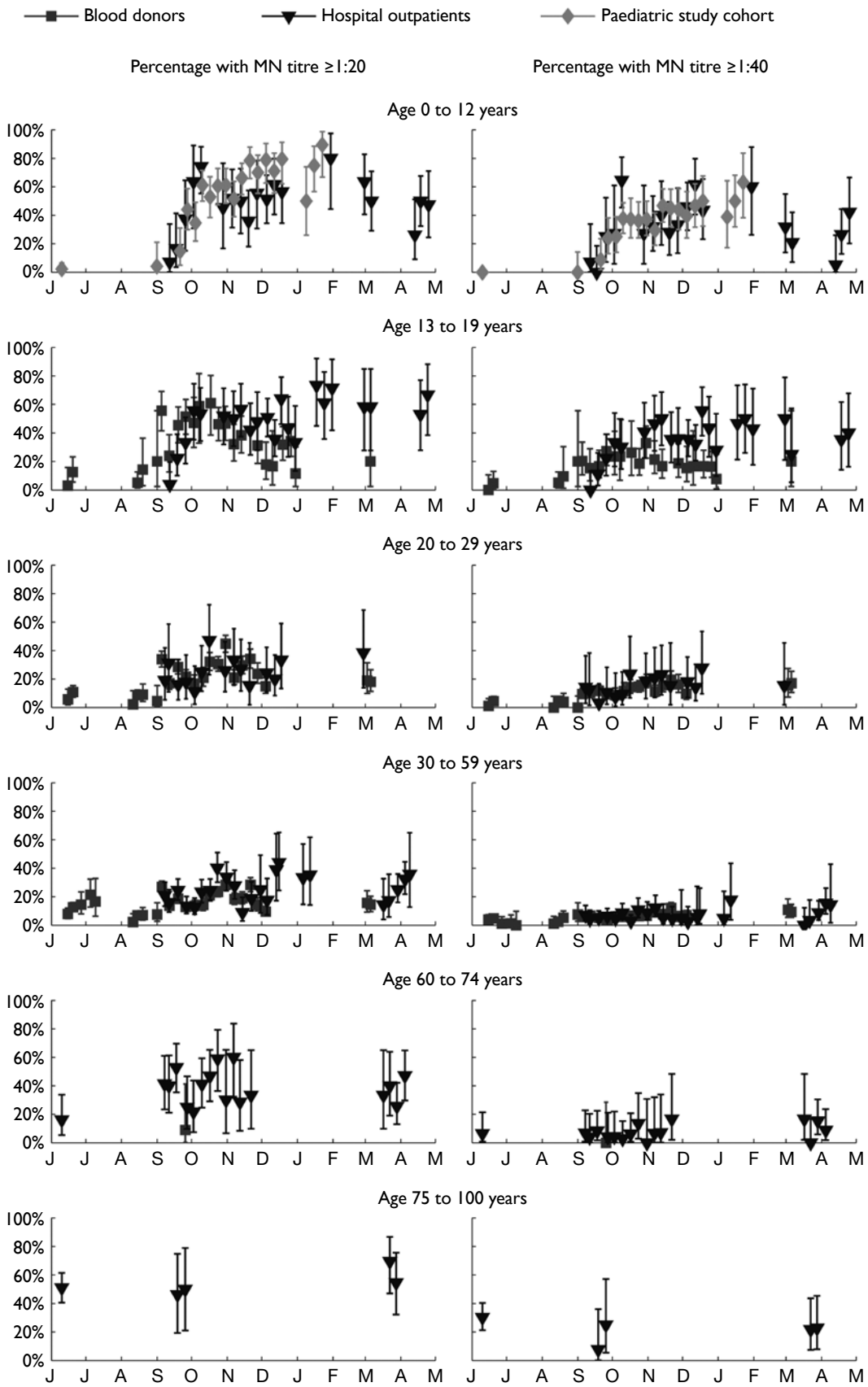

FIG 1. Percentages of age-specific individuals with antibody titres ≥1:20 and ≥1:40 by viral microneutralisation (MN) in Hong Kong between 1 June 2009 and 30 April 2010. Weekly averages and 95% confidence intervals are estimated by the exact binomial method. Data points with a sample size of <10 are not shown. Each tick on the X-axis indicates the first day of month.

incidences from 15 November 2009 onwards were driven mostly by exogenous importation (ie the reproductive number from 15 November onwards was <1). As such, a two-step procedure was used to estimate age-specific incidence from our serological and hospitalisation data: (1) transmission parameters and incidence between 10 June and 15 November 2009 were estimated using an age-structured susceptible-infectious-recovered (SIR) model; and (2) incidences from 15 November 2009 onwards were estimated by dividing daily hospitalisation by the Centre for Health Protection estimated in step 1.

Disease transmission model and statistical inference

An age-structured SIR model with five age-groups (0-12, 13-19, 20-29, 30-59, and ≥60 years) was used to describe the transmission dynamics of pdmH1N1 in Hong Kong between 10 June and 15 November 2009,[2] assuming that those with pre-pandemic MN titre ≥1:20 were immune to pdmH1N1 and that the mean generation time was 2.5 days.[3] Using the age-structured transmission model, seven parameters were estimated by fitting the age-structured SIR model to our serial cross-sectional serological data and clinical surveillance data: (1) basic reproductive number, (2) susceptibility of each age-group compared to the 20-to-29-year age-group for those who had no immunity, (3) reduction in within-age-group transmission due to school closure, (4) proportion of the age-group that had MN titre at or above the cutoff at the beginning of the pandemic, (5) proportion of infected cases who eventually developed MN titre at or above the cutoff, (6) mean time for MN titre to reach the cutoff after recovery (for those who eventually developed MN titre at or above the cutoff), and (7) case-hospitalisation probability for the age-group. Statistical inference of the parameters was performed using Markov Chain Monte Carlo methods with non-informative priors.

Results

Between 30 June 2009 and 15 November 2009, pdmH1N1 seroprevalence among the three groups of subjects was similar. This implied that IARs were quite similar among blood donors, hospital outpatients, and the vaccination study cohort (Fig 1). As such, the three groups of serological data

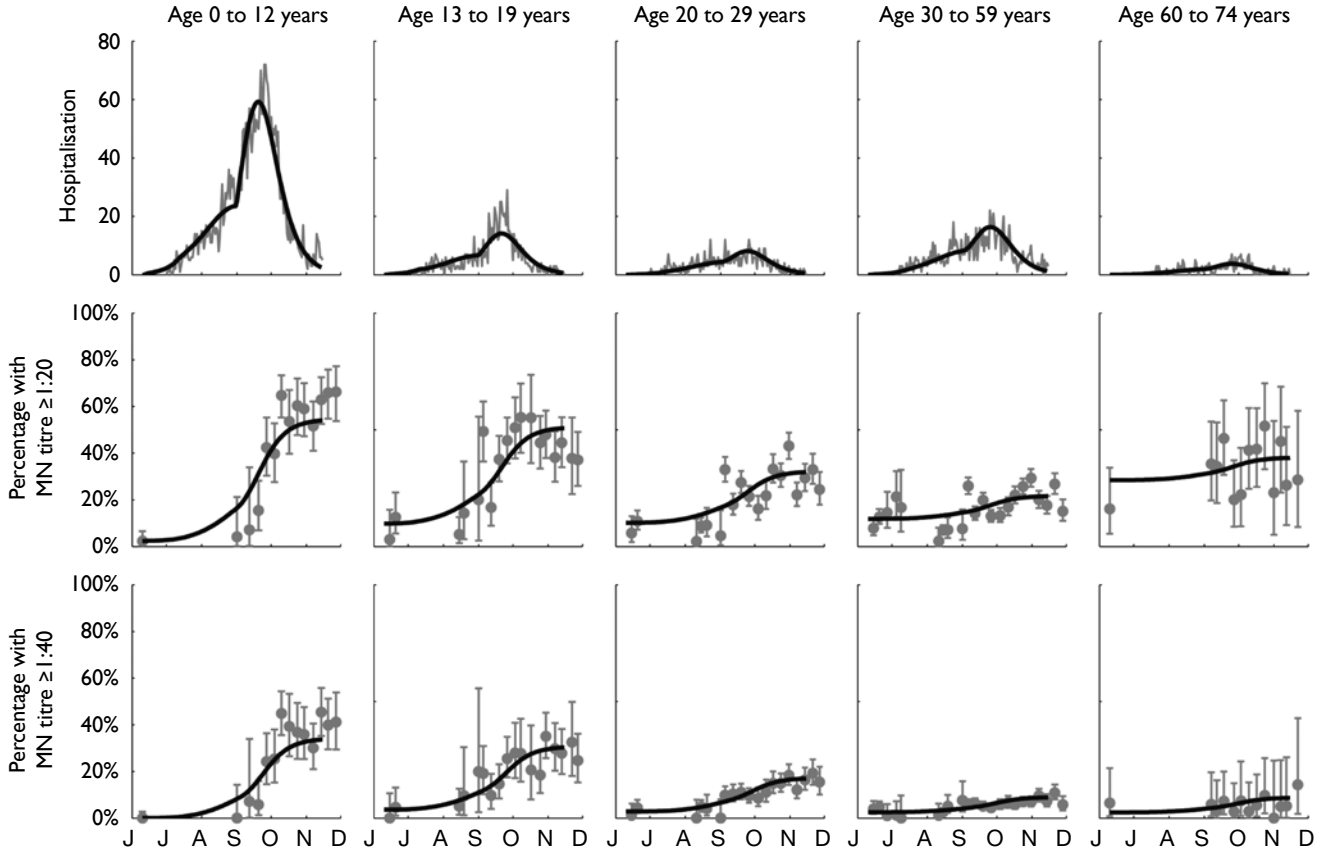

FIG 2. Comparison of the best-fit transmission model with the hospitalisation data and serial cross-sectional serological data: the best-fit hospitalisation and seroprevalence curves are in black colour, whereas the data are in grey colour. Each tick on the X-axis indicates the first day of month.

were aggregated in a transmission modelling analysis, and the estimated IARs thereby were largely applicable to both the general population and hospital outpatients. The best-fit transmission model was reasonably consistent with the serial cross-sectional serological data and hospitalisation data (Fig 2). Regrettably, the proportion of infections that were asymptomatic could not be estimated because most of the subjects did not complete the questionnaire.

Infections were mainly driven by local transmission. The estimated case-hospitalisation probability was 0.23% to 1% for all age-groups. Respectively for the age-groups of 0-12, 13-19, 20-29, 30-59, and 60-74 years, the age-specific IARs were 51% (range, 48-54%), 42% (range, 37-44%), 22% (range, 19-24%), 9.7% (range, 8.5-12.3%), and 10.6% (range, 2.0-17.5%) between 10 June 2009 and 15 November 2009, whereas the estimated age-specific IARs were 13% (range, 12-13%), 5.9% (range, 5.2-6.3%), 6.4% (range, 5.5-7.2%), 4.4% (range, 3.8-5.5%), and 4.7% (range, 0.9-7.7%) between 15 November 2009 and 31 January 2010, assuming that the case-hospitalisation probability was constant over time. The steep drop in IARs with increasing age was consistent with serological studies from other countries.[4,5]

Respectively for the age-groups of 0-12, 13-19, 20-29, 30-59, and 60-74 years, the estimated proportions of individuals who were immune to pdmH1N1 before the endemic were 2.5% (range, 1.0-6.5%), 9.2% (range, 6.4-13.5%), 10% (range, 8.3-12.4%), 11.8% (range, 10.3-12.9%), and 27.2% (range, 21.2-36%), whereas among those who were susceptible to pdmH1N1, the age-groups of 0-12, 13-19, 30-59, and 60-74 years were 2.5 (range, 2.4-2.9), 1.2 (range, 1.1-1.4), 0.5 (range, 0.4-0.6), and 1.4 (range, 0.3-2.1) times more susceptible than the age-group of 20-29 years, respectively.

The estimated basic reproductive number was 1.45 (range, 1.43-1.49), which was consistent with that in earlier studies of pdmH1N1 transmissibility in other populations.[3,6,7] The reproductive number dropped to <1 after mid-September (Fig 3). Among those infected with pdmH1N1, it was estimated that 100% (range, 96-100%) developed MN titre ≥1:20 with a mean delay of 0.4 (range, 0.04-3.7) days after recovery, whereas 64% (range, 53-71%) developed MN titre ≥1:40 with a mean delay of 4.1 (range, 0.5-11.7) days after recovery.

In the best-fit transmission model, compared to the school period during September to December 2009, school closures reduced within-age-group transmission by 52% (range, 36-56%) among the age-

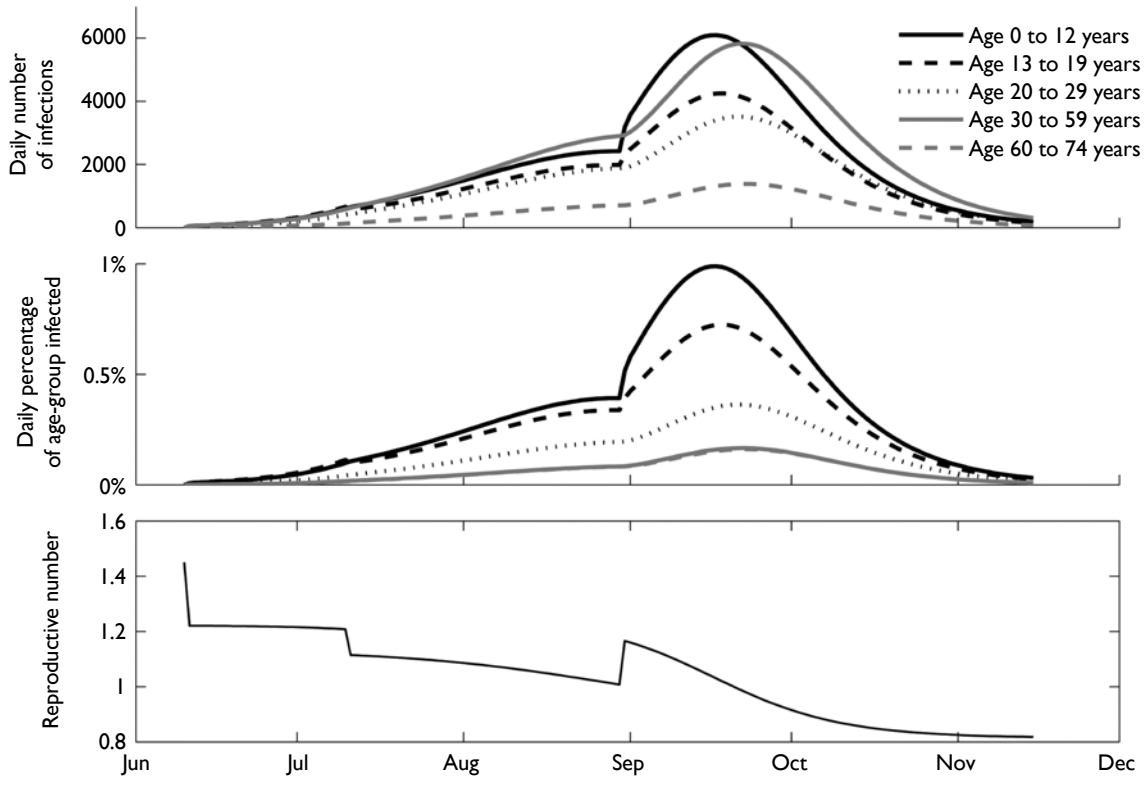

FIG 3. Age-specific incidence and reproductive number as a function of time. Each tick on the X-axis indicates the first day of month.

group of 0-12 years and 26% (range, 18-33%) among the age-group of 13-19 years. Closure of high schools had smaller impact on reducing disease transmission possibly because these teenagers would continue to mix with their peers in other social settings during school closures.

Discussion

It is important to include serological surveys as a component of endemic surveillance. The geographically compact and homogeneously mixed population in the urban environment of Hong Kong enables some degree of confidence in the validity of the estimates of IAR, severity, and transmissibility. The detailed pdmH1N1-reporting system, the wide coverage of the public health care system (that includes >90% of all local inpatient days[8]), and the resource investments since SARS have led to routine laboratory testing for all patients hospitalised with fever or pneumonia. This enables identification of most pdmH1N1 infection–associated hospitalisations. Vaccination did not begin until late December 2009 and therefore had no influence on our estimate of transmissibility, severity, and IAR during the main first wave.

Real-time serial cross-sectional serological data enable accurate estimates of infection attack rates (and from them severity measures) while the endemic is in its nascent stage. These estimates may help public health policymakers to respond to an influenza pandemic, eg assessing the burden that the pandemic would pose on the health care system, and assessing population-level immunity to inform vaccination decisions.

Conclusion

Serial cross-sectional serological data together with hospitalisation data enable accurate estimates of infection attack rate and severity. Serological monitoring should be a key part of updated plans for influenza pandemic preparedness and response.

Acknowledgements

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