The Effective Reproduction Number of Pandemic Influenza

Prospective Estimation

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Background: Timely estimation of the transmissibility of a novel pandemic influenza virus was a public health priority in 2009.

Methods: We extended methods for prospective estimation of the effective reproduction number (R_t) over time in an emerging epidemic to allow for reporting delays and repeated importations. We estimated R_t based on case notifications and hospitalizations associated with laboratory-confirmed pandemic (H1N1) 2009 virus infections in Hong Kong from June through October 2009.

Results: R_t declined from around 1.4–1.5 at the start of the local epidemic to around 1.1–1.2 later in the summer, suggesting changes in transmissibility perhaps related to school vacations or seasonality. Estimates of R_t based on hospitalizations of confirmed H1N1 cases closely matched estimates based on case notifications.

Conclusion: Real-time monitoring of the effective reproduction number is feasible and can provide useful information to public health authorities for situational awareness and calibration of mitigation strategies.

When pandemic (H1N1) 2009 virus emerged, an urgent priority for international and national public health authorities was to establish the transmissibility and virulence of the pandemic strain. The effective reproduction number, R (defined as the average number of secondary cases that 1 index case generates over the course of its infectious period), is a useful measure of transmissibility and can be estimated over time (ie, R_t) through the course of an epidemic.[1] Cauchemez et al[2] developed methodology to permit prospective estimation of R_t. In this paper, we extend the method for prospective estimation to account for repeated importations and reporting delays. We apply the method to prospective surveillance of laboratory-confirmed pandemic H1N1 notifications and pandemic H1N1-associated hospitalizations in Hong Kong.

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METHODS

We obtained individual patient data on all laboratory-confirmed pandemic H1N1 cases reported between 1 May and 15 November 2009 and collected by the Hong Kong Hospital Authority and Centre for Health Protection (the "e-flu" database). The database includes demographic information on age and sex, clinical information including illness-onset date, laboratory-confirmation date and hospital-admission date, and an indicator for recent overseas travel to an affected area (collected until 16 June 2009). In Hong Kong, pandemic H1N1 infection was a reportable disease throughout our study period.

We estimated delays between illness onset and case notification, and for the subset that were hospitalized, the joint distribution of delays from illness onset and hospitalization to notification. We extended the methodology proposed by Cauchemez et al[2] to allow for these reporting delays. Cases classified as imported infections were incorporated into the analysis as infectors but not infectees, to avoid overestimation of R_t. Illness-onset dates were not available for some confirmed cases, and we used multiple imputation to incorporate these in the analysis.[3] We estimated R_t assuming that the serial interval followed a Weibull distribution with mean 3.2 days and standard deviation 1.3 days.[4] In a sensitivity analysis, we used serial intervals with mean 2.6 days[5–7] and 3.6 days.[8] All statistical analyses were conducted in R version 2.9.2 (R Development Core Team, Vienna, Austria). Further technical details of the statistical methods used and R syntax are given in the eAppendix (http://links.lww.com/EDE/A419).

RESULTS

Following the World Health Organization global alert on 27 April 2009, Hong Kong implemented "containment phase" protocols that included entry screening at airports, ports, and border crossings, and enhanced surveillance of outpatients and inpatients with influenza-like illness. Laboratory-confirmed pandemic H1N1 cases were medically isolated and usually prescribed oseltamivir treatment. Their close contacts were quarantined for 7 days and usually prescribed oseltamivir chemoprophylaxis. Imported pandemic H1N1 cases were sporadically identified from late April to June. On 11 June 2009, following identification of the first untraceable local pandemic H1N1 case, the Hong Kong government initiated a "mitigation phase" and announced immediate class dismissal in primary schools, kindergartens and childcare centers for 14 days starting from 12 June 2009. The school closures were subsequently extended to summer vacation in early July. Some containment phase policies, such as medical isolation of confirmed cases and contact tracing of airplane passengers, continued through June. On 13 June 2009, 8 public outpatient clinics were converted to designated flu clinics across the territory to provide low-cost high-throughput outpatient medical consultation, free laboratory testing for pandemic H1N1, and antiviral treatment. These public outpatient clinics resumed some chronic disease services in mid-August.

Figure 1A shows the epidemic curve of notified pandemic H1N1 cases and associated hospitalizations from May through October 2009. Under containment-phase protocols, all laboratory-confirmed cases until 28 June were medically isolated in hospitals, and recorded as hospitalizations in the e-flu database. We therefore analyzed only the 5553 hospital admissions from 29 June to 31 October. The cumulative proportion of laboratory-confirmed cases that were hospitalized fluctuated around 15% during the early stages of the epidemic (Fig. 1B). After the designated flu clinics resumed chronic disease services and laboratory testing was focused on more severe cases, the cumulative proportion of cases hospitalized gradually increased to around 18% by the end of the study period.

Figure 1C shows the estimated R_t based on pandemic H1N1 notifications from late May through October. The estimated R_t reached an initial peak of 1.5 on 12 June and fell below 1 between 20 June and 3 July. Subsequently, R_t fluctuated between 0.8 and 1.3 through the school vacations in July and August. R_t briefly increased to around 1.2–1.3 after schools reopened in September until the epidemic peaked in late September, and subsequently fluctuated below 1 as the epidemic declined. The trends in R_t based on H1N1-associated hospitalizations were broadly consistent with the estimates based on case notifications, with wider confidence intervals (Fig. 1D).

The real-time estimates of R_t based on data to the end of July, August, September, and October were consistent with the final estimates for the period (Fig. 2), with some divergence only in the last few days of each analysis. In a sensitivity analysis using alternative serial intervals, real-time estimates of R_t were similar to our main results and slightly closer to 1 with a shorter serial interval (eAppendix, http://links.lww.com/EDE/A419).

DISCUSSION

Situational awareness of the transmissibility and epidemic growth rate of pandemic influenza was a priority for national and international health authorities in 2009. Much early attention focused on counts of laboratory-confirmed cases, but in affected regions laboratory capacity was typically focused on more severe cases, and changes in laboratory testing and notification rates meant that case counts did not necessarily reflect the underlying epidemic.[9] An example of this in our data is the apparent peak in cases in mid-June and the subsequent decline through to the end of June. This pattern was probably an artifact of changes in testing priorities (as Hong Kong switched from containment to mitigation phase) rather than a real decline in epidemic growth.[10] Substantial declines have been seen previously in R_t during SARS outbreaks, in response to implementation of government control measures.[1,11] In contrast, there were no apparent substantial changes in R_t through the first wave of H1N1pdm in Hong Kong, other than the suppression of R_t during school holidays.

A useful alternative to case-based surveillance is surveillance of the subset of severe infections, such as hospital admissions or intensive-care-unit admissions.[9] Our results lend support to this approach, although changes in the hospitalization rate over a shorter time period (as for example occurred in Hong Kong at the end of June 2009) could lead to problems in estimation of R_t based on hospitalizations.

The estimated reproduction number of pandemic H1N1 appeared to be lower in Hong Kong during our study period than in other countries. For example, other studies estimated that R was around 1.5–2.0 in the initial phases of epidemics in the United States,[12] Peru,[13] Australia,[14] and New Zealand.[15] Lower transmissibility may be associated with the summer vacations from July through August[16] or interventions during the mitigation phase such as widespread use of antiviral treatment. Seasonality may also be a factor, because influenza virus does not usually circulate in Hong Kong after July or August.[17] Finally, Hong Kong has an ageing population and some older people may have pre-existing immunity to pandemic H1N1.[18]

Around 20% of notified cases were admitted to hospital during the mitigation phase in Hong Kong. This is a higher hospitalization rate than observed in other countries such as Australia (13%)[19] and Canada (10%).[20] However, among the

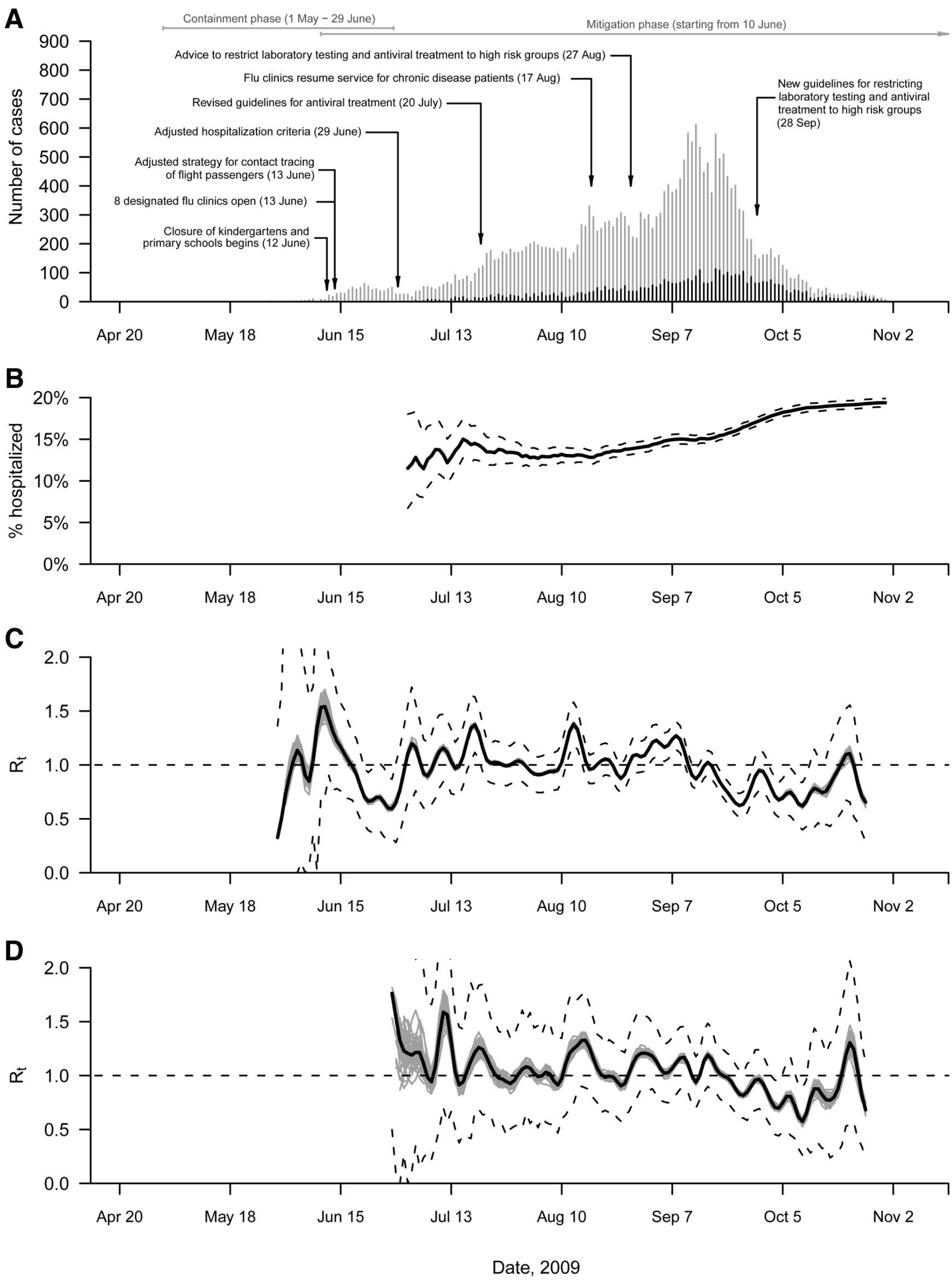

FIGURE 1. A, Number of cases of laboratory-confirmed cases of pandemic influenza A (H1N1) virus infection (gray) and hospitalizations (black) by date of illness onset and dates of important control measures, Hong Kong, from April through October 2009. B, The cumulative proportion of hospitalized cases among all pandemic H1N1 notifications with 95% point-wise confidence intervals. C, Daily estimates of the effective reproduction number R_t based on pandemic H1N1 notifications with 95% confidence intervals, where the dashed line represents the threshold of $R_t = 1$. D, Daily estimates of the effective reproduction number R_t based on pandemic H1N1-associated hospitalizations with 95% confidence intervals, where the dashed line represents the threshold of $R_t = 1$.

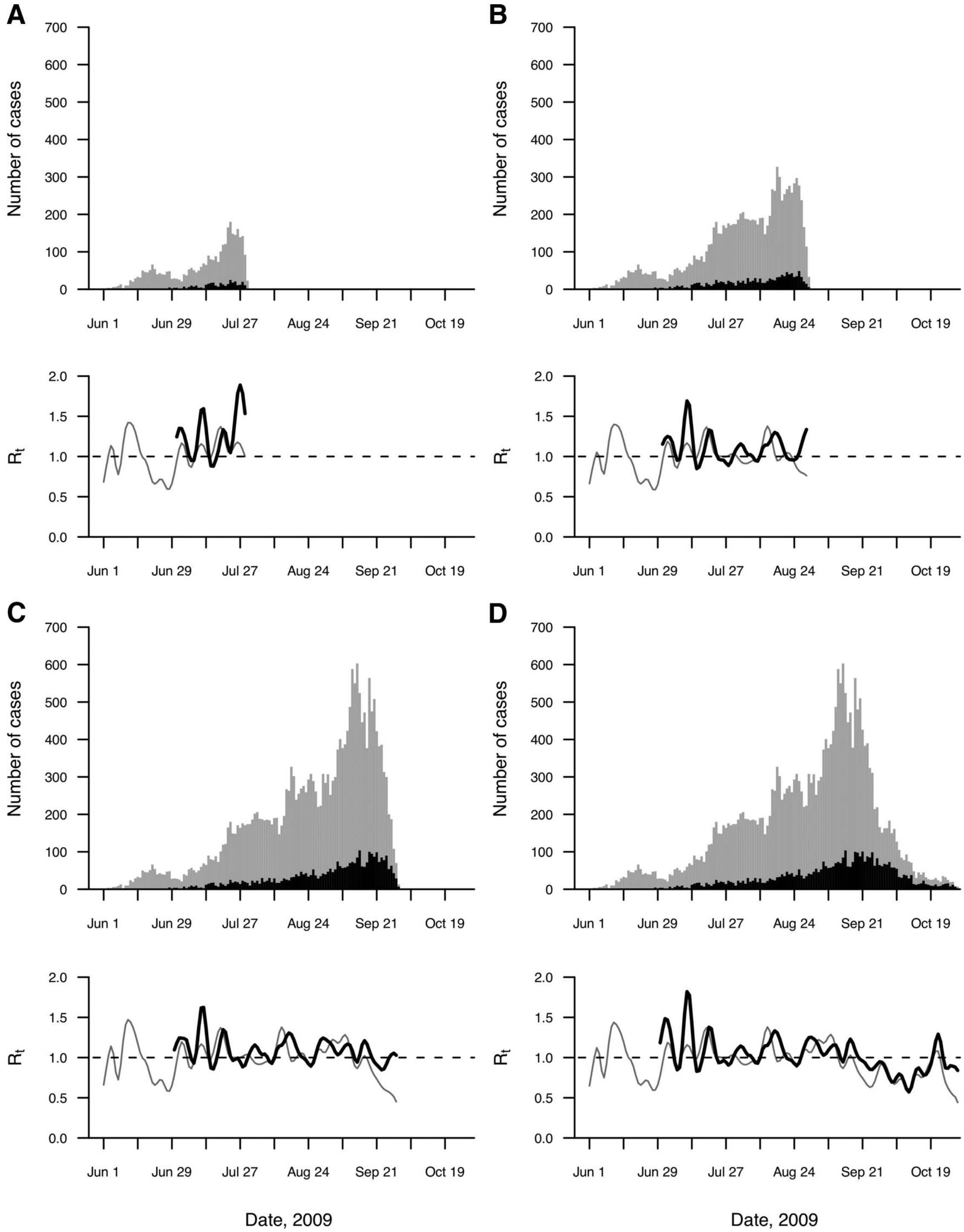

FIGURE 2. The epidemic curves of pandemic H1N1 notifications (gray bars) and pandemic H1N1-associated hospitalizations (black bars) up to different time points and corresponding real-time estimates of R_t (gray lines based on notifications, black lines based on hospitalizations) for the periods. A, up to 31 July; B, up to 31 August; C, up to 30 September 2009; D, up to 31 October 2009.

cases hospitalized in Hong Kong between July and October, only 1.9% were admitted to ICU and only 0.8% died. These rates among hospitalized cases are much lower than in other countries such as Australia (13% admitted to ICU and 4% died),[19] Canada (18% admitted to ICU and 4% died),[20] and California (31% admitted to ICU and 11% died),[21] suggesting that the clinical threshold for hospitalization may have been lower in Hong Kong. The admission rate would also have been higher due to broader admission criteria, with young children and pregnant women routinely admitted for testing and investigation.

In addition to the potential changes in rates of case identification, notification, and hospitalization discussed above, there are other limitations to our work. First, R_t was estimated based on aggregate data and did not take into account variation in transmissibility, for example, due to age. Our estimates of transmissibility provide information about the overall trends in the epidemic, and local data on within- and between-age group contact patterns are limited. Second, while we allowed for imported cases to be infectors but not infectees, we did not allow for cases infected in Hong Kong and exported to other countries; this may have underestimated the total R_t. However, the number of exported cases should be fewer than imported cases during the early stage of the epidemic, and exported cases are less relevant to the local epidemic growth rate. Third, interventions are not the only factors associated with decrease in the effective reproduction number. Particular care must be taken when interpreting estimates of effective reproduction numbers through time since depletion of susceptibles can lead to a decline in the effective reproduction number.[22]

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