Early transmission characteristics of influenza A(H1N1)v in Australia: Victorian state, 16 May – 3 June 2009

E S McBryde (Emma.McBryde@mh.org.au)[1,2,3], I Bergeri[4], C van Gemert[4,5], J Rotty[3], E J Headley[3], K Simpson[3], R A Lester[3], M Hellard[4], J E Fielding[3]

1. Victorian Infectious Diseases Service, Royal Melbourne Hospital, Melbourne, Victoria, Australia
2. Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia
3. Victorian Department of Health, Melbourne, Victoria, Australia
4. Burnet Institute, Melbourne, Victoria, Australia
5. National Centre for Epidemiology and Public Health, ANU College of Medicine and Health Sciences, Australian National University, Australia

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Australia was one of the first countries of the southern hemisphere to experience influenza A(H1N1)v with community transmission apparent in Victoria, Australia, by 22 May 2009. With few identified imported cases, the epidemic spread through schools and communities leading to 897 confirmed cases by 3 June 2009. The estimated reproduction ratio up to 31 May 2009 was 2.4 (95% credible interval (CI): 2.1-2.6). Methods designed to account for undetected transmission reduce this estimate to 1.6 (95% CI: 1.5-1.8). Time varying reproduction ratio estimates show a steady decline in observed transmission over the first 14 days of the epidemic. This could be accounted for by ascertainment bias or a true impact of interventions including antiviral prophylaxis, treatment and school closure. Most cases (78%) in the first 19 days in Victoria were under the age of 20 years-old. Estimates suggest that the average youth primary case infected at least two other youths in the early growth phase, which was sufficient to drive the epidemic.

Introduction

Pandemic H1N1 influenza was first identified in Mexico in mid-March 2009, and by the end of April, cases had been reported throughout North America [1]. On 25 April 2009, the World Health Organization (WHO) declared the situation to be a public health emergency of international concern [2] and raised the level of influenza pandemic alert to level 3 and then level 4 within one week of the declaration [3]. The virus spread rapidly around the globe and by 12 May cases were reported in 30 countries including Australia's first imported case in the state of Queensland. Victoria, a state of Australia with a population of 5.4 million, subsequently reported rapid community spread.

The first confirmed case of pandemic H1N1 influenza in Victoria was on 20 May in a traveller who had returned to Victoria from the United States of America on 19 May (symptom onset 17 May). In the following two days, this case's two siblings and a Mexican on holiday in Australia were also notified in Victoria. After further case ascertainment, the first onset date of pandemic H1N1 influenza for a Victorian was found to be 16 May. This case was locally acquired. At that time, Victoria was in the *Delay* phase of the pandemic (as classified by the Australian government [4]) during which time the testing algorithm for influenza A(H1N1)v was dependent on a travel history to an affected country. The identification of locally acquired cases resulted in the pandemic phase being upgraded to *Contain*, and from 22 May, anyone with influenza-like symptoms was encouraged to seek testing from their doctor. By 3 June 2009, 897 cases had been notified in the state of Victoria, many from school outbreaks. Modified Sustain phase then commenced and testing was recommended for high risk people only [5]. During the *Contain* phase all notified cases were followed up for information about illness, exposure and contacts in order to decide on the necessity of quarantine (including school closures) and antiviral treatment of cases and prophylaxis for contacts of cases.

Important public health priorities in a new pandemic are to identify the transmission characteristics of the new infection, to determine its severity and to assess the impact of mitigation strategies [6]. Early reports indicated that there were regional differences in the transmission characteristics of influenza A(H1N1)v, with the suggestion that the transmission varied depending on the season. For this reason, particular attention has been paid to the countries of the southern hemisphere to determine the transmissibility during winter.

A key summary measure of the transmissibility of an emerging contagious disease is the reproduction ratio (R) which is the expected number of secondary cases generated per primary case. This number is highly predictive of the likely impact of interventions on the spread of an emerging infectious disease [6] as well as the ultimate community attack rate [7]. The reproduction ratio for influenza A(H1N1)v has been estimated in several countries with differing results, including Mexico with R estimates of 1.4–1.6 [8] Japan with 2.0–2.6 [9], the Netherlands with 0.5 [10], Thailand with 1.78-2.07 [11], New Zealand with 1.80-2.15 [12] and Peru with 1.2-1.7 [13]. The differences in transmission rates

could be due to ascertainment biases from under-reporting early in the epidemics, real differences due to season or social mixing patterns or to the mitigation strategies used, or else reflect the sub-populations in which influenza was introduced. Mitigation strategies varied from country to country, with respect to the use of school closure, cancellation of mass gatherings, other social distancing measures [14], home quarantine and antiviral prophylaxis.

In this paper we assessed the transmissibility of influenza A(H1N1)v using the onset times of cases in Victoria, Australia. Victorian onset times have not been available in the public domain to date. We estimated the generation interval using linked cases. The reproduction ratio is examined, with summary, time-varying and age-specific estimates. A method that leads to a more robust estimate of *R* in this setting is presented, reducing ascertainment bias by imputing undetected transmission. Additionally, we considered the sensitivity of estimates to differences in generation interval.

Methods

Exponential growth rate

During the exponential growth phase of an epidemic, the relationship between past daily incidence $I(t-\tau)$ and current daily incidence $I(t)$ of symptom onset can be expressed as $I(t)=I(t-\tau)e^{r\tau}$, where r is the exponential growth rate, and τ is the time difference. The exponential growth rate was estimated from the daily incidence curve, using Poisson regression.

Estimation of the generation interval

Of the initial 897 cases in the Victorian influenza A(H1N1) pandemic 2009, 750 had data on contacts and 37 had an identified primary contact, with source case and contact case onset dates known. The generation interval was defined as the time between the onset of symptoms in case A to the onset of symptoms in case B, given that case A infected case B. The generation interval was parameterised to a *Gamma (alpha, beta)* distribution, using the *gammfit* function in Matlab™.

Estimation of the reproduction ratio

Method A

We estimated the reproduction ratio (R) using the exponential growth rate (r) and the gamma distribution fitted to the generation interval. It has been shown previously [15] that R can be estimated from r, using the relationship

$$R = \frac{1}{M(-r)}$$

where M is the moment generating function of the generation interval. For the gamma distribution this leads to

We estimated R using the onset date of the influenza

$$R = (1 + \beta r)^{\alpha}$$

A(H1N1)v cases in Victoria from 16 May 2009 (earliest known onset date) until the end of the exponential growth phase. Estimates of R are sensitive to the choice of end-date of this phase, so three different time intervals were examined 16-27 May, 16-29 May and 16-31 May 2009.

Method B

To estimate R in a time-varying manner, we adapted the generation interval-informed method of White *et al.* [16], using the formula

Eq(1)

$$L(R_z, \mathbf{p}) = \prod_{t=T_{z-1}+1}^{T_z} \frac{e^{-\mu_t} \mu_t^{A_t}}{A_t!},$$

where

$$\mu_t = \sum_{j=1}^{\min(t,k)} R_z^{I(t-j>T_z)} R_{z-1}^{I(t-j<T_z)} N_{t-j} p_j$$

and P_j is the probability function for the generation interval on day j. R_z is the estimated R over time period, z, bounded by $T_{z-1}+1$ to T_z. I is the indicator function, and is equal to one if the statement in parentheses is true and zero otherwise. N_t is the total number of cases on day t, and A_t is the number of autochthonous cases. Estimates were made using Bayesian inference, with uninformative conjugate gamma (10^{-3}, 10^{3}) prior distribution for R and a Poisson likelihood function from equation 1.

Sensitivity to generation interval

Sensitivity analysis of generation interval on estimates of the reproduction ratio was conducted. Using method B, we repeated the estimated of R using generation intervals of 1.5, 2, 2.5, 3 and 3.5 days.

Age specific transmission

Method C

The next generation matrix is an estimate of the type-specific reproduction ratios. We divided the population into youth (under 20 years-old) and adult (20 years-old or older). The epidemic curve was then divided into discrete generations from 16 to 27 May, based on onset date. We examined the sensitivity to generation time by investigating generation time of two days for six generations and three days for four generations.

The expected number of cases of youths (Y) and adults (A), respectively, in generation T is given by

where a is the youth → youth, b is the youth → adult, c is the adult → youth, and d is the adult → adult type-specific reproduction ratio.

The parameters, a, b, c and d were estimated assuming a Poisson relationship between E(A) and E(Y) and their respective observed values.

$$E(Y_T) = a\ Y_{T-1} + b\ A_{T-1}$$
$$E(A_T) = c\ Y_{T-1} + d\ A_{T-1},$$

Sensitivity to ascertainment bias from unobserved transmission

Method D

For this analysis, unobserved transmissions were imputed, and R was estimated from this augmented dataset, rather than the observed data. We assumed that incident cases were incompletely observed during the *Delay* phase of the pandemic, which lasted from the time of the WHO alert, 24 April [17], until 22 May 2009. We assumed the observed data from 22 May until 30 May were accurate. The incidence data were partitioned into generations of three days, with the observed data starting on 22 May.

Let the vector ***G*** represent the augmented dataset, being the incidence by generation. ***G*** consists of observed incidence for the final three generations (22-24, 25-27 and 28-30 May) and imputed incidence for all generations preceding 22 May. The imputed cases are generated from the relationship

Eq(2)

$$G_A(n+1) \sim Poisson(R(G_A(n)+\varepsilon(n)))$$

where $G_A(n)$ is the number of autochthonous cases in the nth generation and $\varepsilon(n)$ is a small, generation-dependent number to account for importations. Exponential growth was assumed for $\varepsilon(n)$, reflecting a global incidence of influenza A(H1N1)v (that is $\varepsilon(n+1) = R\ \varepsilon(n)$). For the fully observed generations, it was assumed that importations were fully observed as Poisson realisations of $\varepsilon(n)$.

The likelihood of R is given by

$$L(R) = \prod_{n=1}^{\max(n)} Poisson(G_A(n), R(G_A(n-1)+\varepsilon(n-1))).$$

Using Bayesian tools of Metropolis-Hastings updates, R was estimated concurrently with the number of generations that preceded the *Contain* phase. The number of preceding generations was estimated by beginning with the first generation of the *Contain* phase and working backwards, using Gibbs updates. When $G_A(n+1)$ was two or more, $G_A(n)$ was estimated with the sampling distribution determined by Eq(2), that is

$$\Pr(G_A(n) = X \mid G_A(n+1)) = \frac{\Pr(G_A(n+1) \mid G_A(n) = X)\Pr(G_A = X)}{\sum_{i=1}^{\infty} (G_A(n+1) \mid G_A(n) = i)\Pr(G_A = i)}$$

where $\Pr(G_A(n+1) \mid GT(n) = X)$ is given by Eq(2). In practice, this formula was implemented by putting an upper limit on the value of X, so that X could only take the values {0, max(40, $2G_A(n+1)$}.

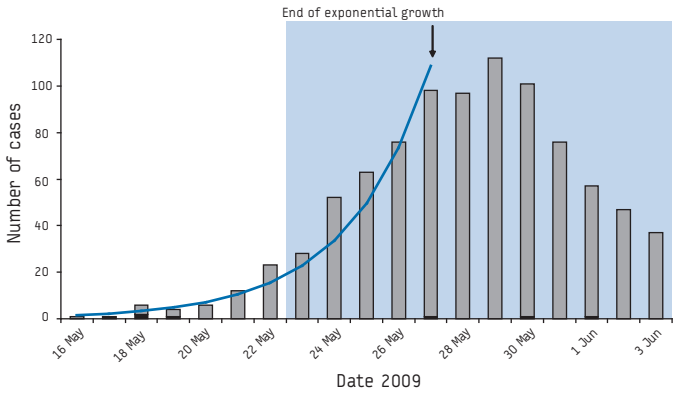
Uniform discrete priors were used for the $\Pr(G_A=X)$, simplifying the sampling distribution of G_A to

$$\Pr(G_A(n) = X \mid G_A(n+1)) = \frac{\Pr(G_A(n+1) \mid G_A(n) = X)\Pr(G_A = X)}{\sum_{i=1}^{\max(40,2n)} \Pr(G_A(n+1) \mid G_A(n) = i)}.$$

If $G_A(n)$ was <2, the algorithm was terminated. The process was iterated until convergence was achieved for both R and the number of preceding generations. No adjustment was made for the change in model complexity as each successive generation was added.

Figure 1

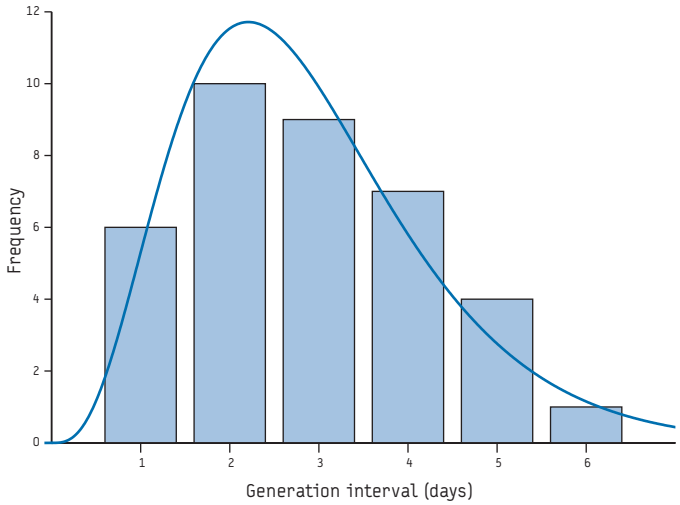
Epidemic curve by date of symptom onset of laboratory-confirmed cases of influenza A(H1N1)v, 16 May – 3 June 2009 Victoria, Australia (n= 897)



Light blue background: *Contain* phase; arrow : the end of the exponential growth phase, from which estimates were made; black bars: imported cases; gray bars: autochthonous cases; dark blue line: fitted exponential growth curve.

Figure 2

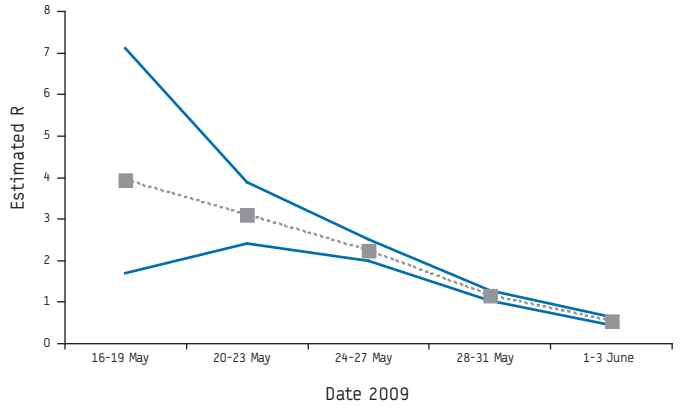
Histogram of the frequency of the known linked cases by generation interval, influenza A(H1N1)v, 16 May – 3 June 2009 Victoria, Australia



The dark blue curve is the fitted gamma distribution.

Figure 3

Time-varying reproduction ratio *R*(t), influenza A(H1N1)v, 16 May - 3 June 2009, Victoria, Australia



Dark blue lines represent the 95% credible interval, under the assumptions of the model.

Final size

We can estimate the expected number of people who developed infection by the end of the epidemic using the relationship between R and final size, given by the numeric solution to the transcendental equation

$$\log(s_\infty) = R_0(s_\infty - 1)$$

where s_∞ is the proportion of the population who remain susceptible, hence $1\text{-}s_\infty$ is the proportion infected by the end of the epidemic, referred to as the final size of the epidemic [7]. This assumes that the population is fully susceptible initially, that there are no effective mitigation measures and that homogenous mixing of the population takes place.

Results

Exponential growth rate

In the state of Victoria, Australia, following the first known imported cases, the number of incident cases of notified laboratory-confirmed influenza A(H1N1)v was growing exponentially. There were eight imported cases and 889 autochthonous cases during the period from 16 May to 3 June 2009. Figure 1 shows the temporal distribution of confirmed influenza A(H1N1)v cases in Victoria. Exponential growth of the epidemic lasted approximately 12 days (16 to 27 May inclusive). The epidemic growth rate during this period is estimated to have been 0.40 (95% CI: 0.39-0.41) per day, giving a doubling time for the epidemic of 1.7 days.

Generation interval

The generation interval had a mean of 2.9 days and standard deviation of 1.4 days. The optimal gamma distribution fit was the Gamma (4.2, 0.68) distribution. Figure 2 shows the frequency of generation intervals with fitted gamma curve.

Estimates of reproduction ratio

Method A

Using Method A, the reproduction ratio is estimated to be 2.4 for the period 16-31 May 2009.

However, this method is sensitive to the assumed length of the period in which the epidemic was growing exponentially. The table gives the estimates for exponential growth rate and the corresponding estimates of *R* assuming three different dates for the end of exponential growth: 27 May, 29 May and 31 May.

Method B

Using Method B, the estimated reproduction rate from the first case (16 May) to the end of the exponential growth phase (27 May) is 2.4 (95% CI: 2.1-2.6). To assess the sensitivity of results to the observed generation interval of 2.9 days, we examined the estimates assuming generation intervals from 1.5 to 3.5 days. The estimated reproduction ratio for the first 12 days of the epidemic was very sensitive to the generation interval. When the generation interval was 1.5, 2, 2.5, 3 and 3.5 days, *R* was estimated to be 1.6 (95% CI: 1.4-1.7), 1.8 (95% CI: 1.6-1.9), 2.1 (95% CI: 1.9-2.4), 2.5 (95% CI: 2.3-2.7) and 2.8 (95% CI: 2.6-3.1), respectively. These results all assume the reproduction ratio remained constant throughout the period.

Relaxing this assumption produces a time-varying reproduction ratio. Figure 2 shows the time-varying reproduction ratio from 16 May until 3 June. The estimated R begins at 3.9 and falls to less than one by the beginning of June.

Method C

During the *Contain* phase, the overall median age of incident cases was 15 years. The daily median during this period ranged from 13-17 years and there was no trend in age distribution over time.

As shown in the table, the estimated youth to youth transmission was higher than transmission between adults only and between

Table

Reproduction ratio estimates of influenza A(H1N1)v, 16 May - 3 June 2009, Victoria, Australia

Estimation of reproduction ratio			
Conditions of estimation	R (95% Credible interval)	r (95% Credible interval)	
Method A Epidemic growth rate 16-27 May 2009	2.8 (2.70-2.8)	0.40 (0.39-0.41)	
Method A Epidemic growth rate 16-29 May 2009	2.6 (2.5-2.6)	0.37 (0.36-0.37)	
Method A Epidemic growth rate 16-31 May 2009	2.4 (2.3-2.4)	0.33 (0.32-0.33)	
Method D Undetected transmission prior to 22 May 2009	1.6 (1.5-1.8)		
Estimate of age-specific reproduction ratios			
Description of parameter		Generation interval two days	Generation interval three days
Estimated number of secondary cases of youths following each primary youth	Youth to youth	1.8	2.7
Estimated number of secondary cases of youths following each primary adult	Adult to youth	0.5	0.5
Estimated number of secondary cases of adults following each primary youth	Youth to adult	0.5	0.7
Estimated number of secondary cases of adults following each primary adults	Adult to adult	0.2	0.4

youths and adults. The dominant eigenvalue of the next generation matrix, given by

$$\mathbf{M} = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

gives us an estimated R [7] of 2.8, assuming a generation time of three days, and 1.9 assuming a generation time of two days, in keeping with estimates using Methods A and B.

Method D

Allowing for undetected community transmission prior to the start of the *Contain* phase on 22 May 2009, the estimate for R over the exponential growth phase (until 30 May) was 1.6 (95% CI: 1.5-1.8), compared with 2.4 (for the same end date of the epidemic) if detection was assumed to be complete. This corresponds to an estimated final proportion of the population infected (final size) of 64% if we correct for undetected transmission, and of 88% using the uncorrected measure. The estimated number of generations that preceded 22 May, incompletely observed, was 9 (95% CI: 6-13), suggesting that transmission may have been occurring in Victoria from late April, under Method D assumptions. The estimated number of unobserved cases is 170 (95% CI: 120-230), 60% of which occurred between 16 and 21 May 2009.

Discussion and conclusions

The epidemic in Victoria had a relatively high estimated transmission rate compared with other countries. The reproduction ratio was estimated to be 2.4 for the epidemic during the second half of May 2009, although it may have started above 3. After accounting for unobserved transmission early in the epidemic (ascertainment bias), this value may be as low as 1.6. Time-varying analysis suggests the reproduction ratio fell during the *Contain* phase.

Age-specific analysis of transmission showed that transmission amongst youth (under the age of 20 years) was sufficient to sustain transmission in its own right, whereas transmission between youth and adults was initially minimal. This is consistent with the view that the early transmission of influenza A(H1N1)v in Victoria in the second half of May 2009 was driven by school age children and occurred in the absence of multiple importations.

These estimated reproduction rates are higher than those in Mexico [8] and Europe [10], but similar to those estimated in Japan [9], Thailand [11] and New Zealand [12]. Japan, which also had a school-fuelled outbreak, had similar age-specific transmission with a sustained transmission in the under 20 year-olds [9].

Even using the more conservative estimate in this study of R=1.6, transmission was relatively high compared, for example, with seasonal influenza in Australia, which from 1972-1997 had a mean of 1.3 (95% CI: 1.2-1.4) [18]. While the increase in transmission measured in the Victorian influenza season 2009 may seem slight, the reproduction ratio has large nonlinear effects on attack rate and efficacy of public health measures. The final proportion of the population predicted to be infected during an epidemic, assuming that no effective mitigation takes place, is 64% for R=1.6 and 42% for R=1.3, if homogenous mixing is assumed. It is probable that the true proportion of people infected with influenza A(H1N1)v in Victoria this year will be smaller than the estimation based on the initial reproduction ratio. This is to be expected, if the effective reproduction ratio declines over time, if a large proportion of the population have prior immunity [19], or if the population mixing patterns lead to substantial groups of the population not being exposed to influenza cases. Serosurveillance studies are awaited to determine the influence of these three factors on the epidemic.

The reproduction ratio also has implications for the potential impact of mitigation strategies that have been considered, such as antiviral treatment and prophylaxis, school closure [20] and vaccination [21]. The falling reproduction ratio observed in Victoria may reflect the impact of mitigation strategies carried out during this time, such as reactive school closure, quarantine, antiviral treatment and prophylaxis, which was offered to all contacts of confirmed cases during *Contain* phase. Voluntary social distancing may also have played a role.

This study is strengthened by the use of case data, particularly symptom onset dates, that were collected from 20 until 31 May 2009, allowing inferences to be made about transmission. Despite this, there are possible inconsistencies of case ascertainment, given that the information is based on surveillance data in a rapidly evolving epidemic. Undetected cases prior to the *Contain* phase could have lead to overestimates in the transmission rates. This study used a method that allowed for hidden transmission in an effort to get more robust estimates of reproduction ratios. However, the assumptions of complete observation from 22-30 May could be false and would lead to an underestimate of the reproduction ratio if the proportion of clinical cases tested decreased over this period. From 3 June, testing was not conducted on cases that were not considered high risk. Given the delay from symptom onset to testing it appears that data based on onset dates are not reliable after 29 May. Active case finding in schools could have led to overestimates of transmission. A lesson from the southern hemisphere experience is that the difficulties in the early analysis of transmissibility could be overcome by consistent measures to ascertain the case incidence which, for the northern hemisphere, could be in place prior to the expected influenza surge in the winter season 2009-10.

Despite the limitations of this study, our results support the value of public health interventions that target the school age population. Governments considering mitigation strategies that involve major social disruption, such as school closure, need to weigh the relative costs and benefits of such action. Results from modelling suggest that school closure is effective if done early and universally, and if it leads to reduced contact [20]. Pre-emptive school closure is predicted to be more effective than reactive school closure. However, the effects of any school closure are estimated to be greater in settings where school transmission is high [22], such as Victoria, where school age children account for the majority of early transmission.

The likely impact of interventions and the cost-benefit profile critically depends on both the severity of disease and its transmissibility. In general, if an infectious disease is highly transmissible, outbreaks are much harder to contain, and interventions have a reduced impact on the final proportion of people infected. The relatively high reproduction ratio may be the reason why the pandemic influenza progressed in Victoria, and other Australian states and territories, despite public health interventions.

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