

A PRELIMINARY ANALYSIS OF THE EPIDEMIOLOGY OF INFLUENZA A(H1N1)v VIRUS INFECTION IN THAILAND FROM EARLY OUTBREAK DATA, JUNE-JULY 2009

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As the influenza A(H1N1)v pandemic unfolds globally, it is vital to monitor closely for signals of change in the current patterns of transmission. We estimate the basic reproduction ratio for A(H1N1)v virus in Thailand and propose a method to keep track of the actual case count notwithstanding the exponential growth rate.

Introduction

The threat of an influenza pandemic posed by a novel reassortant influenza A virus was identified in late April in Mexico. The influenza A(H1N1)v virus has since spread into five continents infecting at least 134,503 people and causing 816 deaths as reported by World Health Organization (WHO) on 27 July 2009. Further spread of the virus especially within affected countries is considered inevitable at this point. Also, the increasing number of cases in many countries is making it difficult for laboratories to individually test and confirm all suspected cases.

The first two cases of A(H1N1)v in Thailand were reported on 10 May. After a two week lapse and despite intense containment measures, more cases were reported, building up into an exponential growth phase in early June. The basic reproduction ratio (R_0), estimated from the daily case reports in the exponential growth phase, is useful in assessing the ultimate course of the epidemic in Thailand. The reproduction ratio as a function of time (R_t) generally drops after the primary exponential phase due to a drop in susceptibles as well as due to control measures, and varies throughout the epidemic until it ultimately drops below 1 long enough to suppress further transmission.

We calculate the intrinsic growth rate (r) during the exponential growth phase from 1 to 12 June and estimate R_0 and the *final size* [1,2] - the proportion of the population that would be ultimately infected assuming 100% susceptibility at the outset and minimal control measures - of the epidemic. Furthermore, we give a rough estimate for the case fatality ratio (CFR) from early fatality counts and use it to extrapolate the number of infected cases at a later date, after laboratory testing of all suspected cases was abandoned (20 June) paving the way for significant underreporting. All reported deaths up to 14 July are analysed to compare the CFR between age groups.

Methods

Our data come from two sources. First, we counted the cases by symptom onset date from the records at the WHO National Influenza Centre, which was used to calculate r , R_0 and CFR. The age distribution of the infected population up to 14 July was inferred from the daily incidence reports from the Bureau of Emerging Infectious Diseases, Department of Disease Control (DDC), Ministry of Public Health in Thailand (http://beid.ddc.moph.go.th/th/index.php?option=com_content&task=view&id=1784902&Itemid=240) while the disease onset dates and age of the deceased were obtained directly from DDC.

Estimate of r , R_0 and final size

The intrinsic growth rate r is estimated by Poisson regression of the epidemic curve over the exponential growth phase, R_0 is derived by $R_0 = 1 + rT_c$ (where is T_c the mean generation interval [GI])

and the final size by a Newton-Raphson numerical solution [1] of $\ln(1 - \chi) + R_0\chi = 0$.

The mean GIs derived in two previous studies ($T_1=2.6$ [2.1-3.0] [3] and $T_2=1.9$ [1.3-2.7] [4]) were used as no information was available for the current epidemic. The equation used to calculate R_0 gives the Laplace transform of the GI distribution assuming it is exponentially distributed, whereas the error for non-exponentially distributed GIs are known to be small [3]. Visual inspection of the epidemic curve revealed significant deviations from the exponential curve toward the latter part of the period of 1-12 June, necessitating the choice of a valid combination of points in order to achieve a realistic goodness of fit. Goodness of fit (or lack of it) of the model was assessed by a combination of the R-squared measure and Pearson's statistic.

Estimate of CFR and present case count

We estimated the CFR for cases with symptom onset on or before 18 June using our daily onset data for that period and the number of fatalities subsequently arising from these cases until 15 July. This rough estimate was used to extrapolate the number of infected cases from the number of deaths on later dates. The normalised age-specific CFR was calculated by dividing the age distribution of all deceased patients as of 14 July against the age distribution

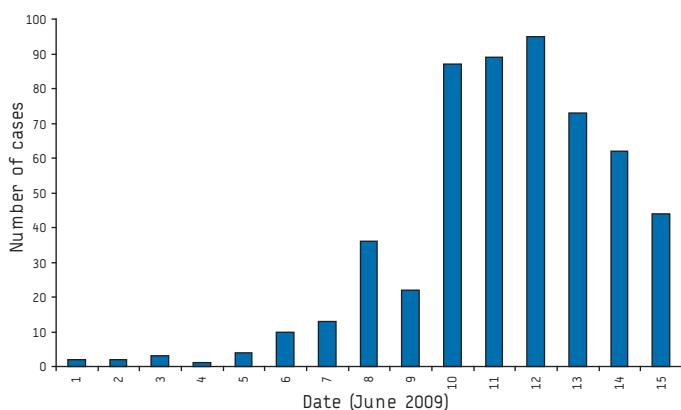
of all reported cases as of 7 July, and further dividing each value by the overall CFR for the total population. Since the seven-day gap is not sufficient to account for the delay from onset to death, there are two implicit assumptions made here: the age distribution of the infected population is constant over time, and the time from onset to death is independent of the patient's age. Underreporting bias is effectively eliminated by normalising, provided the rate of underreporting was similar across all age groups.

Results

The epidemic curve for the period 1-12 June minus the counts for 8, 10, and 11 June (Figure 1 and Table) yielded the best fit for exponential growth ($R_2 = 0.9802$), giving $r=0.41$ [95%CI: 0.35-0.47]. The corresponding R_0 were 2.07[1.92-2.22] for T_1 and 1.78[1.67-1.89] for T_2 . The final-size were 81.5[77.4-84.8]% for T_1 and 72.5[67.7-76.4]% for T_2 .

FIGURE 1

Epidemic curve for influenza A(H1N1)v in Thailand by date of onset, 1-15 June 2009 (n=543)



TABLE

Epidemic growth rates estimated for the exponential growth phase (1-12 June) of A(H1N1)v in Thailand and corresponding basic reproduction ratio and final-size estimates for two different generation intervals

Period (dates removed)	R^2	Pearson	r	SD	95% CI	T=2.6						T=1.9						
						R_0	95% CI	final size	95% CI	R_0	95% CI	final size	95% CI					
8, 10, 11 June	0.9802	0.6485	0.41	0.029	0.35	0.47	2.07	1.92	2.22	81.5%	77.4%	84.8%	1.78	1.67	1.89	72.5%	67.7%	76.4%
9, 11, 12 June	0.9695	0.3018	0.54	0.041	0.46	0.62	2.40	2.19	2.61	87.9%	84.2%	90.6%	2.02	1.87	2.18	80.3%	75.8%	83.9%
8, 12 June	0.968	0.1264	0.43	0.028	0.37	0.48	2.11	1.97	2.25	82.4%	78.7%	85.3%	1.81	1.71	1.91	73.6%	69.4%	77.1%
8, 10, 12 June	0.9644	0.2452	0.47	0.036	0.40	0.54	2.22	2.03	2.40	84.7%	80.5%	87.9%	1.89	1.75	2.02	76.3%	71.5%	80.3%
10 June	0.9454	0.0082	0.40	0.025	0.35	0.45	2.05	1.92	2.17	80.9%	77.3%	83.8%	1.76	1.67	1.86	71.8%	67.8%	75.4%
9 June	0.928	0.001	0.39	0.023	0.35	0.44	2.02	1.90	2.13	80.1%	76.7%	83.0%	1.74	1.66	1.83	71.0%	67.2%	74.4%
12 June	0.9258	0.001	0.47	0.031	0.41	0.53	2.22	2.06	2.38	84.7%	81.1%	87.5%	1.89	1.77	2.00	76.3%	72.1%	79.8%
8 June	0.9244	0	0.42	0.026	0.37	0.47	2.08	1.95	2.21	81.8%	78.4%	84.7%	1.79	1.70	1.89	72.9%	69.0%	76.3%
None	0.9131	0	0.40	0.024	0.35	0.45	2.04	1.92	2.16	80.8%	77.4%	83.6%	1.76	1.67	1.85	71.7%	67.9%	75.1%
11 June	0.8972	0	0.39	0.024	0.35	0.44	2.03	1.90	2.15	80.4%	76.8%	83.3%	1.75	1.66	1.84	71.3%	67.2%	74.8%

Note: All plausible combinations of dates that may yield a better fit were tested.

A total of 690 confirmed cases with disease onset on or before 18 June gave rise to four deaths (as of 15 July) yielding a CFR of 0.58%. The reported number of deaths arising from patients with disease onset on or before 30 June was 16 (as of 15 July), hence the expected value for the actual number of cases at the same date is 2,760 assuming a constant CFR, which is 87% higher than the number of confirmed cases (1,473) reported on 1 July. The normalised age distribution of the CFR (overall CFR=1) is shown in Figure 2.

Discussion

The basic reproduction ratio gives us a fairly good idea about the infectiousness of the virus within a particular demographical area and the potential effect it would have on the community if no public health intervention or changes in social habits take place. Generally, the reproduction ratio decreases after the initial exponential phase due to intervention and a reduction of the number of susceptibles. Thus, R_0 gives us a reasonable upper bound for the reproduction ratio as well.

Making an estimate of R_0 is not trivial due to various limitations in the information we have about an epidemic at the beginning. Firstly, it is highly dependent on the generation time interval [5] which is not easy to estimate when the transmission network is not known. We use mean T_c values estimated elsewhere: T_1 from a comprehensive analysis of household transmission data [3] found to be consistent with viral shedding data from experimental studies; and T_2 from an independent estimate of the influenza A(H1N1)v outbreak in Mexico [4].

Another limitation is the difficulty of fitting the real-life epidemic curve to an exponential growth model. Human errors in reporting as well as stochastic errors arising from the relatively small numbers involved required an arbitrary decision on which data points displayed exponential growth.

Underreporting at the beginning of an epidemic is also usually a confounding factor [6], but we believe the effect of this was minimal in our data due to a highly vigilant healthcare department which sprang into action just after the first few cases were reported in North America.

Our estimate of R_0 for A(H1N1)v in Thailand is higher than one estimate for the Mexican outbreak which used T_2 as the GI [4], but it is lower than another estimate for the same outbreak [6]. The results should be interpreted with caution due to the many uncertainties described above. Nevertheless, they may be used to compare the epidemiological factors of the A(H1N1)v outbreak in Thailand with those from other countries, provided the assumptions behind the calculations are kept in mind.

The final size is a good indicator of the potential magnitude of the epidemic, which may be used by public health officials to estimate the level of damage the epidemic would have on the society should there be no control measures. The case fatality ratio is another vital indicator of the effect of the epidemic on society in general and needs to be continually kept track of until the epidemic is over.

Nevertheless, significant underreporting of infected cases expected after the first few weeks of the infection may result in a CFR estimate significantly higher than the actual value, given that fatalities will not be overlooked as easily even in the middle of the epidemic. Thus, it is imperative to estimate the CFR with data from the initial phase. We used this rate to extrapolate the case counts for later dates after the reporting rate has decreased. Also, our normalised CFR for each age group clearly shows a marked increase in fatality risk with age. However, relatively few infections were seen in the elderly, possibly compensating, at least partly, for the higher fatality rate.

Our rough estimate for the CFR in Thailand, though highly prone to stochastic errors considering the low number of deaths, is not so different from the CFR for Mexico estimated previously [4], but a more recent study [7] showed much lower CFRs for developed countries. Their multiplier method essentially assumes 10-30 unreported cases for each diagnosed case, and incorporating this into the calculation brings down the CFR estimate from a value which would have been in the same order as ours into something drastically lower. Considering the largely undefined nature of asymptomatic or mildly symptomatic infections, we refrain from assigning a number to these cases as that may bring some

confusion in the interpretation and comparison of CFR estimates from different countries or regions. Nevertheless, this issue is undoubtedly valid for Thailand as well, more so after the initial growth phase. Another reason for this comparatively higher CFR may be attributed to differences in the healthcare infrastructure and awareness levels of the public in general.

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FIGURE 2

Normalised case fatality ratio (CFR) by age group, influenza A(H1N1)v in Thailand, June 2009 (n=23 deaths)

