Pandemic influenza H1N1 2009 in Thailand

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**Background:** Developing a quantitative understanding of pandemic influenza dynamics in South-East Asia is important for informing future pandemic planning. Hence, transmission dynamics of influenza A/H1N1 were determined across space and time in Thailand.

**Methods:** Dates of symptom onset were obtained for all daily laboratory-confirmed cases of influenza A/H1N1pdm in Thailand from 3 May 2009 to 26 December 2010 for four different geographic regions (Central, North, North-East, and South). These data were analysed using a probabilistic epidemic reconstruction, and estimates of the effective reproduction number, \( R(t) \), were derived by region and over time.

**Results:** Estimated \( R(t) \) values for the first wave peaked at 1.54 (95% CI: 1.42-1.71) in the Central region and 1.64 (95% CI: 1.38-1.92) in the North, whilst the corresponding values in the North-East and the South were 1.30 (95% CI: 1.17-1.46) and 1.39 (95% CI: 1.32-1.45) respectively. As the \( R(t) \) in the Central region fell below one, the value of \( R(t) \) in the rest of Thailand increased above one. \( R(t) \) was above one for 30 days continuously through the first wave in all regions of Thailand. During the second wave \( R(t) \) was only marginally above one in all regions except the South.

**Conclusions:** In Thailand, the value of \( R(t) \) varied by region in the two pandemic waves. Higher \( R(t) \) estimates were found in Central and Northern regions in the first wave. Knowledge of regional variation in transmission potential is needed for predicting the course of future pandemics and for analysing the potential impact of control measures.

**Key words:** Reproduction number, pandemic, influenza, H1N1, Thailand.

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**Introduction**

Not long after the influenza A/H1N1pdm virus was identified from Mexico in April 2009, many countries in the World Health Organization’s (WHO) South-East Asia Region including India, Nepal, Indonesia and Thailand, experienced epidemics with the same strain. Those countries which submitted data to the WHO surveillance system, FluNet (www.who.int/flunet) - Bangladesh, India, Indonesia, Sri Lanka and Thailand - all

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reported polymerase chain reaction (PCR)-confirmed cases. However, quantitative analyses of the epidemic dynamics in this region have been limited. Although estimates of the initial reproduction number have been reported for Thailand and India, estimates of how reproduction numbers varied by epidemic wave and region are lacking. Quantifying such variation is important for evaluating the value of potential interventions such as school closure, vaccination and antiviral use at different time points in the epidemic, and for planning for future influenza pandemics in the region.

Reproduction numbers are a basic measure of epidemicity; they represent the average number of secondary cases generated by one typical primary case. A distinction is usually made between the basic reproduction number, \( R_0 \), which measures the mean number of secondary cases per case in an idealised population where prior immunity is entirely lacking and in the absence of control measures. The effective reproduction number, \( R(t) \), measures the number of secondary cases per case in a population at time \( t \) where immunity and control measures may be present. Because immunity, interventions and contact patterns all change over time, so does \( R(t) \). When \( R(t) \) is greater than one, i.e. when one infectious case on average produces more than one infected case, the epidemic will be increasing. The epidemic can be said to be under control when \( R(t) \) is less than one, i.e. it will either be decreasing or failing to take off despite the introduction of new cases. A higher value of \( R(t) \) indicates an epidemic where more effort might be needed to bring it under control if it is above one. Also a higher value of \( R_0 \) will be associated with a higher cumulative incidence of infection. When \( R(t) \) is below one prior to an epidemic, monitoring its value can be useful for assessing the risk of a major epidemic. However, even without interventions, \( R(t) \) will fall during an influenza epidemic as immunity increases in the population. \( R(t) \) may also vary spatially and temporally due to different contact patterns, variations in pre-existing immunity, and different atmospheric conditions.

**Influenza control measures in Thailand**

During the early stages of the pandemic, Thailand had very limited stocks of effective influenza-specific antiviral drugs, hence, these were used in a highly selective manner. Instead, school closure, masks, and hand hygiene were the main control measures used in an attempt to reduce transmission. By July 2009, as the pandemic progressed, 435 public schools in the Bangkok Metropolitan Administration (BMA) had been closed (without formal direction from the Ministry of Public Health). Overall, schools were closed for five days, from 15 to 19 July 2009. The BMA later established a comprehensive school screening programme in order to detect outbreaks of respiratory infection illnesses in the schools, and to provide information rapidly to relevant organizations to aid in the development of a control plan. For the other regions, the school closure policy was applied only to schools that had an epidemic. There was widespread use of surgical masks. Hand hygiene was promoted in schools and other public places around the end of June 2009. Health promotion materials such as leaflets, posters and billboards were distributed to all levels of the community across all regions. Self-isolation of cases at home, delays of mass gathering, hand washing and mask use were promoted. In early 2010, approximately 2 million doses of monovalent pandemic H1N1 vaccine were imported and administered to healthcare workers, pregnant women, citizens aged over 65 years of age, obese people, and
patients with high risk chronic diseases (e.g. asthma, heart diseases, mental disability). In June 2010, 2 million doses of the seasonal trivalent influenza vaccine were purchased for the same target populations,\(^\text{11}\) enough to cover only 3.14% of the Thai population.

Given the limited understanding of the spread of influenza A/H1N1pdm and its temporal and spatial heterogeneity in the South-East Asian Region, we conducted this study to address the question of how the effective reproduction number of influenza in Thailand varied with space and time over two epidemic waves.

**Methods**

We used as input data for the estimation procedure the dates of symptom onset of daily laboratory-confirmed cases of influenza A/H1N1pdm in Thailand from 3 May 2009 to 26 December 2010 by region - Central, North, North-East, and South (Figure 1). The total mid-year population for 2010 in Thailand was 63 701 703 people: 21 534 318 in the Central region, 11 779 330 in the North, 21 534 582 in the North-East, and 8 853 473 in the South.\(^\text{12}\)

The laboratory-confirmed cases were positive for influenza A/H1N1pdm 2009 viral culture by real-time PCR. The data were systematically reported through the national disease surveillance centre operated by the Bureau of Epidemiology, Thai Ministry of Public Health (MoPH).

We used the method of Wallinga and Teunis to calculate the effective reproduction number, \(R(t)\).\(^\text{13}\) This required as input data the number of people with an onset of symptoms on each day in each region and the probability distribution of the serial interval (the time from onset of symptoms in one case to onset of symptoms in secondary cases resulting from this case). The method uses these data to probabilistically reconstruct the epidemic tree. This is done using a likelihood-based estimation procedure to derive a matrix with elements representing probabilities that each pair of cases are linked by a transmission event. These probabilities in turn enable the estimation of the average number of secondary cases caused by an individual with onset at time \(t\) \((R(t))\). Weekly estimates of the effective reproduction number are then obtained by averaging over corresponding daily estimates. The serial interval distribution was assumed to
follow a gamma distribution with shape 4.17 and scale 0.33, corresponding to a mean of 2.51 days and standard deviation of 1.55 days. This distribution was derived from a contact-tracing study.\textsuperscript{14} Confidence intervals were calculated using a bootstrap procedure that assigned the source of each non-index case by sampling from a multinomial distribution with probabilities taken from the probability matrix. Using this procedure 1000 possible epidemic trees were constructed and used to calculate a distribution of the number of secondary cases per case for each onset date. Quantiles of this distribution were used to calculate associated 95% and 80% confidence intervals for $R(t)$.

For each region, we also calculated the predicted percentage of people infected during the first wave ($\zeta$). Because this quantity includes both clinical and subclinical cases, it is not directly comparable with the cumulative number of laboratory confirmed cases which we expect to represent only a small fraction of true cases. If sampling is similar in all regions, however, $\zeta$ should approximately scale with the reported cumulative cases. Calculating $\zeta$ required solving $\zeta R_0 = \ln\left(\frac{1}{1-\zeta}\right)$, assuming the entire population is initially susceptible (see equation 6.22 from Bailey, 1975).\textsuperscript{15} We took $R_0$ to be the maximum regional value of $R(t)$ during the first wave.

**Results**

**Epidemic curves of all regions**

In Thailand, of the first 12 cases of laboratory-confirmed Influenza A/H1N1pdm virus, eleven cases (seven students aged 17-20 years and four businessmen aged 21-52 years) imported the virus from the North American continent into Thailand, mainly Bangkok and provinces in the Central region of Thailand, between 3 May and 9 June 2009.\textsuperscript{11} The resulting epidemic had two main waves: the first wave peaked in mid-July 2009 and lasted until October 2009; and the second wave started in November 2009 and peaked in early January 2010. Cases occurring between 3 May 2009 and 31 October 2009 were considered as belonging to the first wave, while cases with onset between 1 November 2009 and 30 April 2010 belong to the second wave.\textsuperscript{11}

All four regions in Thailand experienced a large first wave. During the first wave, there were 28 432 confirmed cases: 11 791 cases in the Central region, 6653 cases in the North, 6062 cases in the North-East, and 3926 cases in the South. There were 7052 confirmed cases during the second wave: 4959 cases in the Central region, 1050 cases in the North, 880 cases in the North-East, and 163 cases in the South.

In the first wave, there were 44.6 laboratory-confirmed cases per 100 000 people for the whole period. The highest peak was in the Central region (which reached 1.8 cases per 100 000 people per day on 1 July 2009) followed by the North and South (1.2 cases per 100 000 people per day in both regions, peaking on 15 July 2009 in the North and 7 July 2009 in the South) and the North-East (0.5 cases per 100 000 people per day, on 7 October 2009) (Figure 2). The Central and North regions had the steepest epidemic curves, followed by the South region. The epidemic curve in the North-East was notably flatter. It is clear that the first wave of the epidemic did not start at the same time in all regions (Figure 2), and from the timing of the epidemic curves and the peaks it appears that the epidemic started in the Central region then spread to the other three regions within a period of about 20 days, first in the North followed by the North-East and then the South. The first epidemic wave lasted for about 100 days in all regions.
The second wave was considerably smaller than the first in all regions. There were only 11.1 confirmed cases per 100,000 people for the whole country. The timing of the second wave was similar for the Central and the North regions (January to March 2010). The North-East and the South regions were hardly affected by the second wave.

The normal first semester school break in Thailand (which lasts about one month) was between the end of the first wave and the beginning of the second wave. This break was
some time after the first peak of the pandemic in all regions and also preceded the second wave. There was a public holiday that lasted for five days (4 to 8 July 2009) which was close to the peak of the epidemic for the Central region, but was before the epidemic peaks in the other three regions. The school closure in the BMA occurred around one week after the peak in the Central region (Figure 2).

**Regional weekly effective reproduction number, R(t)**

The earliest estimates of $R(t)$ for all regions were unstable because of the small number of laboratory-confirmed cases and the importance of stochastic effects. Thus only the weekly estimated $R(t)$ from 17 May 2009 onwards in the Central region (where the epidemic first took off) and from 3 June 2009 in the other regions are reported. At some time points we could not calculate the confidence intervals due to a lack of sufficient laboratory-confirmed cases. Point estimates for $R(t)$ at these points are not reliable because of the small numbers.

As shown in Figure 3, the $R(t)$ values for the first wave peaked at 1.54 (with 95% CI: 1.42-1.71) in the Central region and 1.64 (95% CI: 1.38-1.92) in the North, whilst the corresponding values in the North-East and the South during the first wave were 1.30 (95% CI: 1.17-1.46) and 1.39 (95% CI: 1.32-1.45) respectively. By the time that the $R(t)$ estimate in the Central region was below one, the value of $R(t)$ in the rest of Thailand started to increase above one. The value of $R(t)$ was estimated to be above one continuously for 30 days in all regions. For the second wave, the $R(t)$ estimates were only marginally above one within the first three months in all regions except the South. There were two spikes when the $R(t)$ value in the South peaked at 4 and at 1.7 in December 2009 and February 2010. However, these estimates were derived from a very small number of cases, and the value went down below one within one week.

The associated 95% (grey band) and 80% (black band) confidence intervals in Figure 3 clearly show that the estimated $R(t)$ values have wide CIs when there are small numbers of laboratory-confirmed cases (which is nearly the whole time period for the second wave in all regions).

**Cumulative first-wave cases by region**

Taking the maximum estimated regional value of $R(t)$ from the first wave as an estimate of the basic reproduction number, $R_0$, and assuming everyone to be initially susceptible leads to wide predicted variation in total numbers infected (clinically or sub-clinically), ranging from two thirds of the population in the North region to approximately 40% in the North-East (Table 1). This predicted variation was found to correspond to the observed variation in the rates of laboratory confirmed cases, which were approximately twice as high in the North as in the North-East region. Moreover, the observed and predicted ordering of cumulative cases by region were identical. This would happen by chance alone with a probability of 0.042.

**Discussion**

The $R(t)$ estimates of influenza A/H1N1pdm in Thailand (apart from a single anomalous week in the Southern region) were substantially lower than the estimates from the early period of the pandemic in Thailand\(^4\) but within the range of those estimated from other countries.\(^1\) The discrepancy probably reflects different assumptions about the serial interval distribution. We found that the estimates of $R(t)$ for the first and the second waves of the influenza A/H1N1pdm epidemic in Thailand varied by region with higher estimates
In the South region (bottom graph) during the third week of December 2009 the estimate of $R(t)$ is 4 (not shown on the graph), but there were insufficient data to calculate confidence intervals. Broken vertical line represents break between Wave 1 and Wave 2. CI= Confidence Interval.

In the WHO South-East Asia Region, India is the only other country to have reported estimates of $R(t)$. In this case, using the onset data for A/H1N1 influenza pandemic during the period 1 June to 30 September 2009, the value of $R(t)$ at the beginning of the first wave reported in Central and Northern regions in the first wave. We also found that the higher the estimated maximum first-wave value of $R(t)$ was, the higher were the number of laboratory confirmed cases per 100 000.
of the epidemic was estimated to be about 1.45 and the regional estimates were in the range 1.34-1.74. These data are in close agreement with our findings. The regional variation in both countries is particularly interesting, and if such findings can be shown to be consistent (for example by replication with seasonal influenza data) it may be worth considering to account for such regional variation in national pandemic preparedness planning. In the Thai context, if the Central region (which includes Bangkok) can be expected to be the first region affected (as was the case in 2009) and has a higher reproduction number leading to a more rapidly-spreading and sharply-peaked epidemic, concentrating initial control efforts (such as vaccination or school closures) on this region could potentially delay the spread of the epidemic to other regions. The value of such regionally-targeted control policies could be worth exploring using spatially-explicit transmission models.

The first wave estimates of $R(t)$ were always larger than the second wave estimates, almost certainly reflecting immunity resulting from sustained and widespread community transmission throughout 2009, before the pandemic vaccine was available in Thailand. Our analysis cannot quantify the impact of the five day school closure policy in the BMA on the epidemic in this region. For this, a more complex analysis with a full transmission model and higher-resolution data would be required; see, for example, Bootsma et al. However, it is interesting to observe the 5-day school closures in this region occurred with close to optimal timing; that is immediately after the epidemic peak, when $R(t)$ was less than one. By delaying school closure until this period the problem of epidemic rebound when schools re-open can be avoided. Previous model-based analysis has shown that closing and reopening schools too early has the potential to reduce the beneficial effects of this intervention or in some cases to actually increase case numbers.

Our study has some limitations. We made use of laboratory-confirmed case data. Such data will only represent a small fraction of the true cases, but this is not a major concern as our analytical methods are robust to under-reporting. Biases in our estimates could, however, arise due to temporal variation in the intensity of screening and laboratory testing. We think such temporal variation is unlikely to be significant since guidelines for collecting the samples were implemented throughout the 2009-2010 period. There are other data sources for the influenza A/H1N1pdm epidemic in Thailand including a national sentinel influenza surveillance system, hospital-based influenza like illness (ILI)

Table 1: Regional statistics for the first epidemic wave of Influenza H1N1 2009 in Thailand

<table>
<thead>
<tr>
<th>Region</th>
<th>North</th>
<th>North-East</th>
<th>Central</th>
<th>South</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum $R(t)$</td>
<td>1.64</td>
<td>1.30</td>
<td>1.54</td>
<td>1.39</td>
</tr>
<tr>
<td>Predicted percent infected at end of first wave ($z$)</td>
<td>66%</td>
<td>42%</td>
<td>61%</td>
<td>50%</td>
</tr>
<tr>
<td>Laboratory-confirmed cases observed per 100 000 in the first wave</td>
<td>56.5</td>
<td>28.2</td>
<td>54.7</td>
<td>44.3</td>
</tr>
</tbody>
</table>

The predicted percent infected at the end of the first wave assumes everyone is initially susceptible to infection and takes the basic reproduction number, $R_0$, as the maximum estimated value for $R(t)$. 

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surveillance and suspected case data (which includes cases of acute febrile respiratory illness with onset within seven days of close contact with a confirmed case, or within seven days of travel to a community where there are confirmed cases, or living in a community with one or more confirmed cases). All these different sources of data have indicated the same pattern of pandemic waves in Thailand, providing reassurance that our input data are representative. A further potential limitation is that we based our estimates on aggregated data at the regional level and did not take into account possible age-related variations in transmissibility. Under-reporting of cases can bias estimates of the reproduction numbers if reporting rates are not equal across the different age groups. Another potential source of bias arises from changes in serial interval distribution during the epidemic. While simulation studies have shown that such effects can be important, they also show that biases will be small when reproduction numbers are small, as is the case here. An additional limitation is the relatively coarse spatial resolution in our data. It is possible, for example, that more sharply peaked and shorter first wave epidemic curves in the Central and Southern regions reflect tighter coupling of sub-populations within these regions. The longer and flatter epidemic curves in the North and North-East might reflect reduced movement between subpopulations in these regions resulting in reduced synchronization of local epidemics.

Heterogeneity in population distribution is believed to be a significant factor affecting the spatial spread of directly transmitted pathogens at different scales. However, one study in France concluded that during the initial phase of an influenza epidemic, geographical space and heterogeneities in population distribution were not important factors in the spread of disease; geographical space only becoming relevant to the spread of the influenza epidemic in the few weeks around the epidemic’s peak. Another study has suggested that the regional spread of infection correlates more closely with rates of movement of people to and from their workplaces rather than with geographical distance, enabling influenza to spread rapidly beyond local spatial constraints. Our work suggests, in contrast, that accounting for regional variation in transmission potential (which might arise from differing contact patterns, or atmospheric conditions in different parts of the country) may be important for both predicting the course of future pandemics and for analysing potential control measures for future pandemics.

Acknowledgements

This research project was supported by the National Science and Technology Development Agency (NSTDA), Thailand. The authors would like to thank Dr Orapin Singhadej, Secretary-General Network for WHO-Collaborating Centers and National Centers of Expertise in Thailand, for helpful comments on this paper, and an anonymous reviewer for suggestions that led to improvements in this work. Ben Cooper acknowledges support from the Oak Foundation.

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