Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings

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A novel influenza A (H1N1) virus has spread rapidly across the globe. Judging its pandemic potential is difficult with limited data, but nevertheless essential to inform appropriate health responses. By analyzing the outbreak in Mexico, early data on international spread, and viral genetic diversity, we make an early assessment of transmissibility and severity. Our estimates suggest that 23,000 (range 6000 to 32,000) individuals were infected in Mexico by late April, giving an estimated case fatality ratio (CFR) of 0.4% (range: 0.3 to 1.8%) based on confirmed and suspected deaths reported to that time. In a community outbreak in the small community of La Gloria, Veracruz, no deaths were attributed to infection, giving an upper 95% bound on CFR of 0.6%. Thus, although substantial uncertainty remains, clinical severity appears less than that seen in the 1918 influenza pandemic but comparable with that seen in the 1957 pandemic. Clinical attack rates in children in La Gloria were twice that in adults (<15 years of age: 61%; ≥15 years: 29%). Three different epidemiological analyses gave basic reproduction number (R₀) estimates in the range of 1.4 to 1.6, whereas a genetic analysis gave a central estimate of 1.2. This range of values is consistent with 14 to 73 generations of human-to-human transmission having occurred in Mexico to late April. Transmissibility is therefore substantially higher than that of seasonal flu, and comparable with lower estimates of R₀ obtained from previous influenza pandemics.

On 29 April 2009, the World Health Organization (WHO) announced that the rapid global spread of a strain of influenza A (H1N1) virus detected in the previous week warranted moving the global pandemic alert level to phase 5 (www.who.int/csr/disease/swineflu/). Phase 5 indicates sustained human-to-human transmission of a novel influenza strain of animal origin in one WHO region of the world, and exported cases detected in other regions. In this outbreak, the earliest affected country may have been Mexico, with many cases in other nations associated with travels from that country. There are uncertainties about all aspects of this outbreak, including the virulence, transmissibility, and origin of the virus, and this in turn results in uncertainty in judging the pandemic potential of the virus and when effective public health responses, such as recommendations to stay at home or to close schools, should be implemented in individual countries. Here we report findings of key early investigations into the outbreak that could aid such policy decisions.

The presence of fatalities (29 confirmed plus 88 suspected deaths in Mexico as of 4 May 2009 (1), 1 confirmed in the United States as of 5 May 2009 (2)) is not necessarily indicative of the virulence of the infection. The interpretation of these statistics depends on the total number of infections, including those with mild infection or who are asymptomatic, which is currently unknown, given the absence of a specific serological test for the new H1N1 influenza strain and associated population-level screening. As of 4 May 2009, 11,356 suspected and 822 laboratory-confirmed cases have been reported in Mexico (1), but these may represent an underestimate of true case numbers as surveillance has understandably focused on severe cases. Furthermore, severe cases in older individuals will be more difficult to identify because of the higher rate of respiratory illness in those over 60 years of age (3), and this could result in an underestimate of overall morbidity. Right censoring of mortality data, which occurs when additional deaths subsequently arise among cases already included in surveillance data, can also bias estimates of the true case fatality ratio (4). Finally, suspected deaths may not all have been caused by infection with the novel virus. These uncertainties necessarily affect any estimate of the case fatality ratio (CFR).

On the basis of international travel patterns, we would expect a proportion of cases of any infection spreading widely in Mexico to be exported by travelers (5). Owing to intense surveillance for influenza-like illness in those returning from Mexico, ascertainment of early cases in newly affected countries was almost certainly more complete and rapid than local surveillance of mild cases in Mexico. Airline passenger flow out of Mexico shows a significant correlation with the frequency of detected confirmed cases worldwide (Spearman correlation coefficient: 0.56, P = 0.004) (Fig. 1, A and B). We thus use data on cases among travelers and backcalculation methods to estimate the total number of people infected in Mexico. Key underlying assumptions in this analysis are that population mixing in Mexico is equally likely between Mexican residents and tourists, and tourists and Mexican residents are at equal risk of infection (despite demographic and other differences). If infections are concentrated away from traveler destinations (Fig. 1E presents the spatial distribution, by state, of cases within Mexico by 5 May), the number of people infected in Mexico will be underestimated, and conversely will be overestimated if the epidemic has disproportionately affected geographical zones visited by travelers. Under the assumption that reporting of infections in travelers was complete, we estimated the number of infections that occurred in Mexico by late April from a model of the interval-censored country case counts, which varied between 18,000 and 32,000 (Table 1), depending on the mean duration of stay of tourists assumed, with perhaps the most credible single value (based on journey duration data) being 23,000. An alternative model that assumed at least one case had been confirmed in every country affected by late April gave lower estimates of the number infected in Mexico, in the range of 6000 to 11,000. However, this model may be viewed as a worst case (from the perspective of resulting CFR estimates), and it fitted the observed number of exported cases in key countries (such as the United States and Canada) substantially worse than did the first model. We used 30 April 2009 as the cut-off date for the data analyzed, but the case data analyzed are subject to delays (clinical onset, testing, and reporting) of up to 1 week, so these estimates may be more representative of infections up to 23 April. The epidemic has subsequently spread further, although the impact of the nonpharmaceutical interventions introduced in Mexico is not yet known.

On the basis of the 9 confirmed and 92 suspected deaths that were reported by 30 April 2009...
(6) and assuming similar times from infection to confirmation and from infection to death, we estimated CFRs in the range of 0.3 to 0.6% from the interval-censored case count model, based on confirmed and suspected deaths combined, or 0.03 to 0.05% for confirmed deaths only. Using the alternative, more pessimistic, country presence/absence model, we estimated CFRs of 0.9 to 1.8% based on suspected and confirmed deaths, and 0.08 to 0.16% from the confirmed deaths alone. These estimates have already changed somewhat as a result of data available after 30 April, but we deliberately report the earlier analysis because it formed part of the evidence base used by WHO to move to phase 5.

Another source of information on severity comes from the large outbreak of respiratory disease seen in the small, isolated community of La Gloria in Veracruz province, one case of which has been confirmed to have been caused by the novel H1N1 strain. It is possible that other viruses were circulating at the same time as the outbreak, but the overall attack rate is substantially larger than would be expected for a seasonal influenza outbreak. No fatalities among 616 cases have been attributed to infection during the full period of surveillance of that outbreak (Fig. 3A), giving a 95% confidence interval (CI) of 0 to 0.60%.

Data on the magnitude of the current outbreak in Mexico can also be used to estimate the transmissibility of the virus if the start date of the outbreak is known or can be estimated. Epidemiological investigations into the emergence of the virus in Mexico have focused on the La Gloria outbreak, where the first case in that outbreak is thought to have occurred around 15 February 2009 (Fig. 3A).

An alternative approach to estimating the start date of the outbreak is to look at the diversity in the genetic sequences of viral samples collected from confirmed cases, assuming that diversity accumulates according to a molecular clock model. Twenty-three complete publicly available hemagglutinin (HA) gene sequences from cases not linked in epidemiological clusters were analyzed with a Bayesian coalescent method that gives an estimate of exponential growth of the viral population (7). This yielded an estimate of the time of most recent common ancestor (TMRCA) of 12 January 2009 [95% credible interval (CrI): 3 November 2008 to 2 March 2009]. The genetic model also gave an estimate of the doubling time of the epidemic of 10 days (95% CrI: 4.5 to 37.5 days) (Fig. 2). Assuming exponential growth, the TMRCA is a reasonable estimate of the start of the outbreak, although it is formally an upper bound due to incomplete sampling of the epidemic and the effects of the exponential model prior to distribution. These findings from a population genetic analysis are consistent with the epidemiological investigation of both the start and magnitude of the current epidemic in Mexico. Figure 2 also shows a preliminary version of this analysis based on the first 11 sequences, which gave similar estimates highlighting the power of these methods. [See (8) for further sensitivity analysis and methods.]

The reproduction number, defined as the number of cases one case generates on average over the course of their infectious period, is a key measure of transmissibility and can be estimated in a number of ways from the data currently available.

First, by assuming exponential growth, the growth rate of the epidemic (r) can be inferred from estimates of the current cumulative number of infections (Yt) and estimated start date and size for the outbreak (t0 and Y0, respectively). The basic reproduction number (R0) can be estimated from the exponential growth rate if one also assumes that the generation time distribution for the new H1N1 strain is similar to that of other strains of seasonal and pandemic viruses (9, 10) [Table 1 and (8)]. Using the date of 15 February as the first case of the La Gloria outbreak (8) gives reproduction number estimates of between 1.31 and 1.42, depending on which variant of the geographical backcalculation model is used. Extending a more sophisticated Bayesian estimation method (11) that allows for stochastic variability intrinsic to epidemic dynamics and parameter uncertainty gave similar but slightly higher estimates for R0 with wider ranges; posterior median = 1.40; 95% CrI: 1.15 to 1.90 (Fig. 1C).

Second, by assuming a prior distribution on the generation time distribution informed by previous estimates of influenza, the Bayesian coa-
lescent population genetic analysis yielded a second set of estimates for $R_0$: posterior median = 1.22; 95% CrI: 1.05 to 1.60 (Fig. 2C).

Third, $R_0$ can also be estimated from analysis of the dynamics of the epidemic within defined settings. Detailed data collected by the Mexican authorities investigating the La Gloria outbreak indicate that 616 individuals from a resident population of 1575 had acute respiratory infection between 15 February and 14 April 2009 (Fig. 3A). Data on the age distribution of cases and the dates of disease onset were used in our analysis. Figure 3B shows that the clinical attack rate varied markedly as a function of age, with 61% of individuals under 15 years old affected, dropping to 29% of people over that age. The corresponding relative risk is 2.13, with a 95% CI of 1.89 to 2.39. Based on all confirmed cases in Mexico as reported on 5 May 2009 (1), the corresponding relative risk is 1.52 (95% CI: 1.33 to 1.73). The overall community attack rates seen in La Gloria are comparable to (or higher than) those seen in previous pandemics (12).

Fitting alternative epidemic models to the La Gloria data (8) demonstrated that a model with heterogeneous mixing by age plus age-dependent susceptibility to infection was required to adequately fit the data with plausible parameter estimates. The resulting maximum-likelihood estimate of $R_0$ was 1.58 with a 95% CI of 1.34 to 2.04 (Table 2). This analysis also provided the only independent estimate of the mean generation time, $T_g$ (1.91 days; 95% CI: 1.30 to 2.71 days) (Table 2), shorter than earlier estimates for influenza (9, 10), though not significantly so. It is biologically plausible that $R_0$ and $T_g$ could be correlated, because both are linked to the underlying replicative fitness of the virus. More data are needed. Owing to parameter identifiability issues, it was not possible to estimate age-dependent infectiousness, as well as age-dependent mixing, from these data. Although these estimates are informative, it should be emphasized that some uncertainties remain regarding the denominator population and that a range of other models may fit the data as well as the model choice shown here. Household data would be particularly useful in reducing remaining uncertainty.

Fourth, the time-dependent reproduction number ($R_t$) can be estimated from the time series of reported disease onsets among confirmed cases in Mexico (Fig. 4). These data are subject to much uncertainty because of marked changes in surveillance over the reporting interval, plus the nonspecificity of symptoms that are similar to existing and perhaps simultaneously circulating strains of influenza. However, we developed methods for analyzing such data (8) that account for substantial underreporting, with a change in the underreporting rate from 17 April when surveillance within Mexico was intensified. The average value of $R_t$ estimated for Mexico up until the end of April was 1.37 (95% CrI: 1.24 to 1.59) for a model with Poisson case counts, and 1.47 (95% CrI: 1.21 to 1.88) for a perhaps more plausible negative binomial model allowing daily case counts to be overdispersed (8).

Given estimates of $R_0$ and the current epidemic size $x$, we can estimate the number of generations $N_t$ of transmission of the virus among humans that is necessary to explain the current epidemic. Assuming a simple branching process with reproduction number $R_0$, the mean number of generations of transmission is given by $N_t = -\ln(x)/\ln(R_0)$, assuming the epidemic was started by $x_0$ humans being infected from animal sources. Assuming $x_0 = 1$ gives estimates of $N_t$ between 14 and 73. But even if we assume that 5% of cases were infected directly from animal sources, we obtain an estimated 5 to 22 generations of transmission, indicating sustained human-to-human transmission in Mexico.

All of the $R_0$ estimates are comparable with, but perhaps on the low end of, $R_0$ estimates...
Mexican residents by late April 2009, along with corresponding estimates of the cumulative number of influenza A (H1N1) infections in Mexico among Mexican residents relates to the cumulative number of infections up to 23 April 2009 (i.e., 1 week before the data were reported). Table 1.

<table>
<thead>
<tr>
<th>Assumed average duration of stay for visitors arriving by flights</th>
<th>Estimated number of infections among Mexican residents</th>
<th>Case fatality ratio*</th>
<th>Estimated reproduction number ( R_0 )‡</th>
<th>Estimated exponential growth rate‡ (doubling time in days‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 days</td>
<td>32,000</td>
<td>0.03%</td>
<td>1.42</td>
<td>0.123</td>
</tr>
<tr>
<td>9 days (23)</td>
<td>(26,000, 39,000)</td>
<td>(0.02%, 0.03%)</td>
<td>(0.26%, 0.39%)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>12 days</td>
<td>23,000</td>
<td>0.04%</td>
<td>1.40</td>
<td>0.118</td>
</tr>
<tr>
<td>12 days</td>
<td>(20,000, 280,00)</td>
<td>(0.03%, 0.05%)</td>
<td>(0.37%, 0.52%)</td>
<td>(5.9)</td>
</tr>
<tr>
<td>12 days</td>
<td>180,00</td>
<td>0.05%</td>
<td>1.39</td>
<td>0.114</td>
</tr>
<tr>
<td>12 days</td>
<td>(150,00, 220,00)</td>
<td>(0.04%, 0.06%)</td>
<td>(0.46%, 0.66%)</td>
<td>(6.1)</td>
</tr>
</tbody>
</table>

*This is a simple estimate of the CFR (4). The numbers of deaths and the data on cases in countries were both obtained as reported on 30 April. Although censoring is important to consider when estimating the CFR (due to the time interval between case report and death), in these data we have both the time between clinical onset and death within Mexico and the time between clinical onset and case confirmation in other countries to consider. Given uncertainty surrounding both of these distributions, we have made the simplifying assumption that these time intervals are similar and thus that the CFR can be estimated by the deaths within Mexico attributed to the novel influenza A (H1N1) divided by the estimated number of infections among Mexican residents on data reported up to 30 April. §Based on 9 confirmed and 92 suspected deaths (101 total) that were reported by 30 April 2009 (6). ‡These estimates assume that the estimated cumulative number of influenza A (H1N1) infections in Mexico among Mexican residents relates to the cumulative number of infections up to 23 April 2009 (i.e., 1 week before the data were reported).

Table 2. Epidemiological parameters estimated by fitting an age-stratified mathematical model to the outbreak in the village of La Gloria (Fig. 3). For sensitivity analysis and model selection, we tested several reduced model variants. None fitted significantly worse, but several produced implausible estimates of the generation time. The respective best-fit values are as follows: 1. No asymptomatics and no misreporting, no assortative mixing: \( p_{symb} = 1 \), \( \theta = 0 \), \( R_0 = 1.37 \), \( T_g = 1.39 \), and \( R_{child} = 2.80 \). 2. No asymptomatics and no misreporting: \( p_{symb} = 1 \), \( R_0 = 1.41 \), \( T_g = 1.53 \) days, \( \theta = 0.31 \), and \( R_{child} = 2.22 \). 3. No assortative mixing: same, as variant 1. 4. Model with long generation time consistent with previous estimates from influenza (also shown in Fig. 3), \( T_g = 2.60 \) days, \( R_0 = 1.97 \), \( R_{child} = 2.52 \), \( \theta = 0.51 \), and \( p_{symb} = 0.72 \). (The symbol *“* denotes parameters defined to take fixed values.)

<table>
<thead>
<tr>
<th>Best estimate</th>
<th>95% confidence interval</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_0 )</td>
<td>1.58</td>
<td>1.34–2.04</td>
</tr>
<tr>
<td>( T_g )</td>
<td>1.91</td>
<td>1.30–2.71</td>
</tr>
<tr>
<td>( p_{symb} )</td>
<td>86%</td>
<td>69–100%</td>
</tr>
<tr>
<td>( R_{child} )</td>
<td>2.06</td>
<td>1.60–3.31</td>
</tr>
<tr>
<td>( \theta )</td>
<td>0.50</td>
<td>0.00–0.72</td>
</tr>
</tbody>
</table>

Assumed value

<table>
<thead>
<tr>
<th>( f_c )</th>
<th>1/3</th>
<th>Assumed</th>
<th>Fraction of the generation time that is latent (uninfectious)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \phi_{child} )</td>
<td>1</td>
<td>Assumed</td>
<td>Infectiousness of children relative to adults</td>
</tr>
</tbody>
</table>

As the situation develops, a key issue is to optimize study designs and surveillance protocols to be most informative in estimating some of these unknown factors, thus potentially informing and refining the public health response. Clearly, detailed investigations of transmission in households and schools will be useful, as would be the consistent collection and dissemination of electronic patient records, which could be used to detect cofactors in the severity of infection.

In conclusion, while the emerging data from Mexico and other countries have enabled important insights into the origin, extent, transmissibility, and severity of the unfolding pandemic (including detailed epidemiological analysis of data from the U.S. outbreak recently published (22)), many uncertainties remain and should not be underestimated. The incubation and infectious periods have not yet been reliably ascertained, leaving uncertainty in estimates of the generation time. Much remains to be done to estimate clinical severity of infection, to understand regional variations seen so far (or indeed, whether they exist). As the epidemic spreads further, it is likely that severity will vary from country to country depending on health care resources and the public health measures adopted to mitigate impact. The existence of any cross-immunity (perhaps not mediated via HA-specific antibodies) from past exposure to prior influenza A subtypes is unknown, but the strong age dependence in clinical attack rates seen in La Gloria is intriguing. Cross-immunity would imply that \( R_0 \) could be higher in fully susceptible populations than estimated here.

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The future evolution of the transmissibility, antigenicity, virulence, and antiviral resistance profile of this or any influenza virus is difficult to predict. It is also unclear whether this strain will displace existing influenza A subtypes from the human population, as occurred in the past three pandemics. The extent to which seasonal damping of transmission in North America and Europe is responsible for the moderate transmissibility seen to date is uncertain; the progress of transmission in the Southern Hemisphere (which is just entering its influenza season) needs to be carefully monitored in the next few months. To reduce all these uncertainties, it is essential that public health agencies around the world continue to collect high-quality epidemiological data in a focused, resource-efficient manner despite the expected increases in case numbers in coming weeks. Epidemiological analysis and modeling are useful tools for guiding such efforts and interpreting the resulting data.

Note added in proof: We cited two sources (1, 6) for confirmed and suspected deaths in Mexico, reported by 4 May 2009 and 30 April 2009, respectively. These sources are not publicly available: The Mexican government, Mexico, reported by 4 May 2009 and 30 April 2009, respectively. These sources are not public-situation report ([www.salud.gob.mx/sites/salud/descargas/pdf/informes/3May2009/IN%2020090501.pdf](http://www.salud.gob.mx/sites/salud/descargas/pdf/informes/3May2009/IN%2020090501.pdf)). We cited two sources (1, 6) for confirmed and suspected deaths in Mexico, reported by 4 May 2009 and 30 April 2009, respectively. These sources are not public-situation report ([www.salud.gob.mx/sites/salud/descargas/pdf/informes/3May2009/IN%2020090501.pdf](http://www.salud.gob.mx/sites/salud/descargas/pdf/informes/3May2009/IN%2020090501.pdf)).

Rapid and Accurate Large-Scale Coestimation of Sequence Alignments and Phylogenetic Trees

Kevin Liu,1 Sindhu Raghavan,1 Serita Nelesen,2 C. Randall Linder,2 Tandy Warnow2*

Inferring an accurate evolutionary tree of life requires high-quality alignments of molecular sequence data sets from large numbers of species. However, this task is often difficult, slow, and idiosyncratic, especially when the sequences are highly diverged or include high rates of insertions and deletions (collectively known as indels). We present SATé (simultaneous alignment and tree estimation), an automated method to quickly and accurately estimate both DNA alignments and trees with the maximum likelihood criterion. In our study, it improved tree and alignment accuracy compared to the best two-phase methods currently available for data sets of up to 1000 sequences, showing that coestimation can be both rapid and accurate in phylogenetic studies.

Phylogeny estimation from molecular sequences typically has two phases: An alignment is estimated, and then a tree is produced for the alignment. Alignment methods like MAFFT (1), Probcons (2), Probtree (3), Prank (4), and Muscle (5) provide more accurate alignments than earlier methods (3, 4, 6), and maximum likelihood (ML) methods of phylogeny estimation [e.g., RAxML (7, 8), GARLI (9), and Phyml (10)] produce more accurate trees for large data sets than other

References and Notes
8. Additional details on methods, data, and results are in the Supporting Online Material.
Editor's Summary

Swine Flu Benchmark

The World Health Organization (WHO) announced on 29 April 2009, a level-5 pandemic alert for a strain of H1N1 influenza originating in pigs in Mexico and transmitting from human to human in several countries. Fraser et al. (p. 1557, published online 11 May; see the cover) amassed a team of experts in Mexico and WHO to make an initial assessment of the outbreak with a view to guiding future policy. The outbreak appears to have originated in mid-February in the village of La Gloria, Veracruz, where over half the population suffered acute respiratory illness, affecting more than 61% of children under 15 years old in the community. The basic reproduction number (the number of people infected per patient) is in the range of 1.5—similar or less than that of the pandemics of 1918, 1957, and 1968. There remain significant uncertainties about the severity of this outbreak, which makes it difficult to compare the economic and societal costs of intervention with lives saved and the risks of generating antiviral resistance.