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# The Transmissibility and Control of Pandemic Influenza A (H1N1) Virus

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Pandemic influenza A (H1N1) 2009 (pandemic H1N1) is spreading throughout the planet. It has become the dominant strain in the Southern Hemisphere, where the influenza season has now ended. Here, on the basis of reported case clusters in the United States, we estimated the household secondary attack rate for pandemic H1N1 to be 27.3% [95% confidence interval (CI) from 12.2% to 50.5%]. From a school outbreak, we estimated that a typical schoolchild infects 2.4 (95% CI from 1.8 to 3.2) other children within the school. We estimated the basic reproductive number,  $R_0$ , to range from 1.3 to 1.7 and the generation interval to range from 2.6 to 3.2 days. We used a simulation model to evaluate the effectiveness of vaccination strategies in the United States for fall 2009. If a vaccine were available soon enough, vaccination of children, followed by adults, reaching 70% overall coverage, in addition to high-risk and essential workforce groups, could mitigate a severe epidemic.

**P**andemic H1N1, which first emerged in Mexico in April 2009, had spread worldwide, resulting in more than 130,000 laboratory-confirmed cases and 800 deaths in over 100 countries, by mid-July (1). The global distribution of this novel strain prompted the

World Health Organization to declare the first influenza pandemic of the 21st century in June 2009 (2). Initially, most cases were clustered in households (3–6) and schools (7), with over 50% of the reported cases in schoolchildren in the 5- to 18-year-old age range. A recent anal-

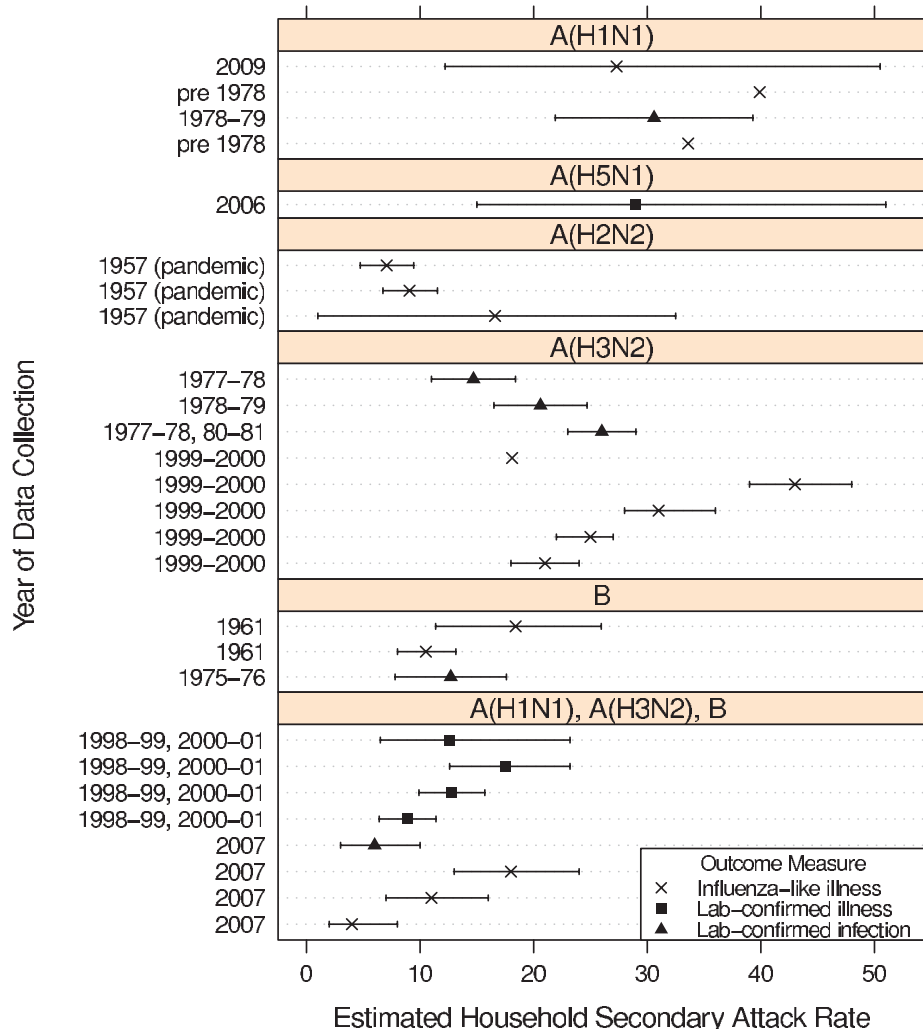
ysis of data from the United States, Canada, the United Kingdom, and the European Union suggests upper bounds on case fatality ratios ranging from 0.20% to 0.68% in these regions and a possibly higher case fatality ratio in Mexico of 1.23% [95% confidence interval (CI) from 1.03% to 1.47%] (8).

Both pandemic and seasonal influenza cause sustained epidemics in the upper Northern Hemisphere (above latitude ~20°N) and lower Southern Hemisphere (below latitude ~20°S) during the respective late fall to early spring months, with epidemics in the more tropical regions (between latitudes ~20°S and 20°N) occurring spor-

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**Fig. 1.** Estimated influenza illness and infection household secondary attack rates from this study and a PubMed literature search. Detailed information on the search references is given in section 2 of (15) and table S8. The household illness secondary attack rate has its basis in the onset date of an influenza-like illness. Lab-confirmed illness is confirmed through a virus-positive nasopharyngeal or throat swab taken at the time of the influenza-like illness. The household infection secondary attack rate has its basis in paired sera bracketing the usual influenza season, where an infection is defined as a substantial rise in hemagglutination-inhibition titer comparing the preinfluenza season sample to the postinfluenza season sample. The 95% CIs are taken from the referenced paper or calculated by the authors if sufficient information was presented. Estimates from pandemic strains include the current estimate and those from Asian influenza A (H2N2) in 1957. The influenza A (H1N1) strain of 1978–1979 reemerged after being absent since 1957. The influenza A (H5N1) strain in 2006 was an avian strain that did not spread beyond the initial family clusters.



radically, but sometimes corresponding to the rainy season. The last influenza pandemic was the Hong Kong influenza A (H3N2) 1968–1969 pandemic. At that time, the first large epidemic was in Hong Kong in July 1968, followed by epidemics in Southeast Asia in August to September 1968, in the upper Northern Hemisphere between September 1968 and April 1969 (peaking in late December 1968 and early January 1969), and in the lower Southern Hemisphere between June and September 1969 (9). In the United States and the upper Northern Hemisphere, shifted (i.e., pandemic) or drifted strains of influenza tend to have a relatively small spring “herald wave” before returning in the fall (10). In the upper Northern Hemisphere, the 1918–1919 influenza A (H1N1) pandemic had a mild spring 1918 herald wave, followed by a severe second wave in the fall of 1918. Pandemic Asian influenza A (H2N2), 1957–1958, caused mid-summer 1957 outbreaks in Louisiana schools that were open in the summer because of the need for children helping with the spring harvest (11). However, there was no extensive community-wide spread of influenza A (H2N2) in the United States until the fall of 1957, with the national level epidemic rising in September and peaking in October. Pandemic H1N1 will probably spread in a spatiotemporal pattern similar to those of previous pandemics but accelerated because of increased air travel (12).

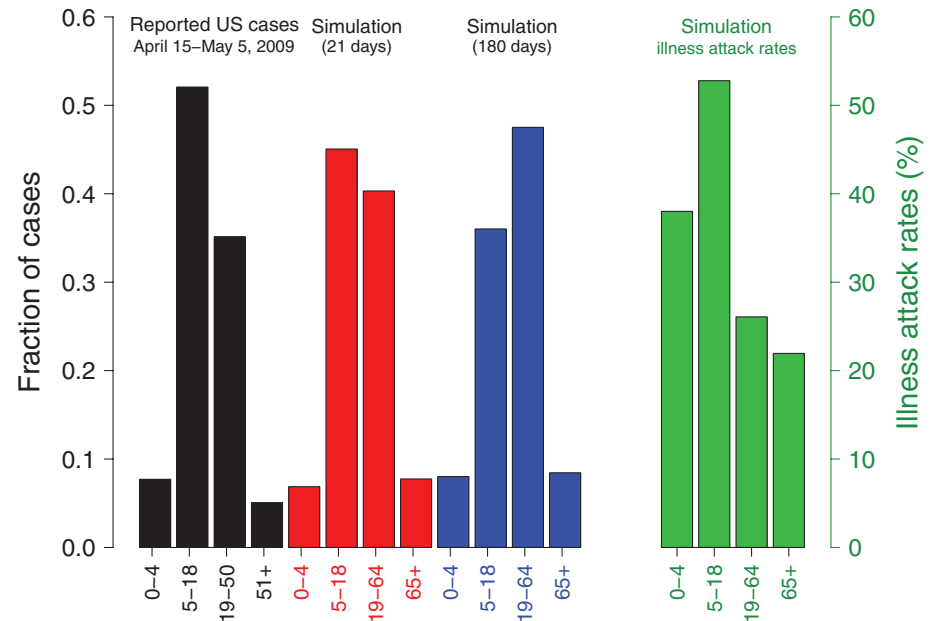
Estimates of the transmissibility of pandemic H1N1 are crucial to devising effective mitigation strategies. Historically, the best characterization of influenza transmissibility has been based on the household secondary attack rate. The household secondary attack rate is the probability (sometimes expressed as a percent) that an infected person in the household will infect another person in the household during the infectious period. We used maximum likelihood methods (13, 14) to estimate the illness secondary attack rate of pandemic H1N1 from reported influenza-like illness onset dates in U.S. households (fig. S1) with confirmed index cases of pandemic H1N1 (15). The best estimate is 27.3% (95% CI from 12.2% to 50.5%) (table S1), which is robust to uncertainty in the assumed incubation and infectious periods and source of secondary infections (15) (tables S1 and S2). Thus, on the basis of early spread of pandemic H1N1 in the United States, each index case has a probability of 0.273 of infecting another household member who becomes ill (table S1). This estimate places pandemic H1N1 in the higher range of transmissibility compared with other influenza viruses for which household secondary attack rates have been estimated (Fig. 1 and table S8). The estimate of the household infection secondary attack rate for the previous influenza A (H1N1) strain from the 1978–1979 epidemic, 30.6% (95% CI from 21.9 to 39.3) (16), was slightly higher than our estimate for pandemic H1N1. The other estimates of the household secondary attack rate for influenza A (H1N1) from 1978–1979 or before (16, 17) are quite similar to our estimate.

After disappearing in 1957, influenza A (H1N1) reappeared during the 1978–1979 influenza season, cocirculated with influenza A (H3N2), and was the dominant strain in the United States (16). There are no estimates of the household secondary attack rate for the 1918–1919 pandemic strain of influenza A (H1N1). Another influenza virus with comparable household transmissibility to pandemic H1N1 was the avian influenza A (H5N1) virus in Indonesia, with an estimated household secondary attack rate of 29% (95% CI from 15 to 51%), that resulted in a small set of family clusters but no further spread (14).

The early spread of influenza A (H1N1) in 1978–1979 was predominately among children, similar to the current pattern of pandemic H1N1 (Fig. 2 and fig. S13). As the epidemic matures, we expect more spread to adults, but with children still experiencing the highest illness attack rate (Fig. 2 and table S10). From the pandemic H1N1 outbreak in the St. Francis Preparatory School in New York (fig. S2), we used maximum likelihood to estimate that the typical schoolchild in-

fectured an average of 2.4 (95% CI from 1.8 to 3.2) other schoolchildren in his or her school (table S3). This estimate is robust to uncertainty in the assumed incubation period and proportion of influenza-like illness cases positive for influenza infection (tables S3 and S4 and figs. S8 and S9). This is a very early estimate of the transmissibility of pandemic influenza in schools.

By using household studies and modeling, we estimate that 30 to 40% of influenza transmissions occur in households, about 20% in schools, and the remainder in other settings such as workplaces and the general community [see Halloran *et al.* (18) and table S12]. On the basis of this information and the estimated transmission parameters using maximum likelihood methods from U.S. households and the St. Francis Preparatory School (15), we estimated the lower bound on the  $R_0$  to be from 1.3 to 1.7 and an upper bound as high as 2.1 (table S5). From the epidemic in Mexico (figs. S3 and S10), with use of maximum likelihood methods, we estimated the mean generation interval to be 3.2 days (95% CI from 3.0



**Fig. 2.** Observed and simulated age-specific fraction of influenza cases and illness attack rates, with  $R_0 = 1.6$ . The black bars show the observed proportion of reported pandemic H1N1 cases by age group in the United States during the early days of the reported U.S. epidemic. The red and blue bars show the simulated proportion at different times after introduction of cases into the Los Angeles County area. The age distribution of cases at 21 days of the simulated epidemic is similar to that of the early observed epidemic. As reflected in the later epidemic, older age groups would become more involved as the infections spreads beyond schools and households. The green bars show the simulated age-specific illness attack rates by the end of an epidemic that runs to completion in the Los Angeles County area. This final age-specific attack rate pattern is similar to that observed for the 1957–1958 Asian A (H2N2) pandemic (37).

	Pandemic transmissibility											
	low			moderate			high					
$R_0$	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4
Illness attack rate (%)	21	26	29	32	35	38	40	42	44	46	48	49
Global cases (billions)	1.4	1.7	2.0	2.2	2.4	2.6	2.7	2.9	3.0	3.1	3.2	3.3

**Fig. 3.** Simulated illness attack rate for the United States and projected total number of global cases for 1 year of pandemic influenza at different values of  $R_0$ . The projections were obtained by multiplying the simulated illness attack rates by the world population of 6.8 billion.

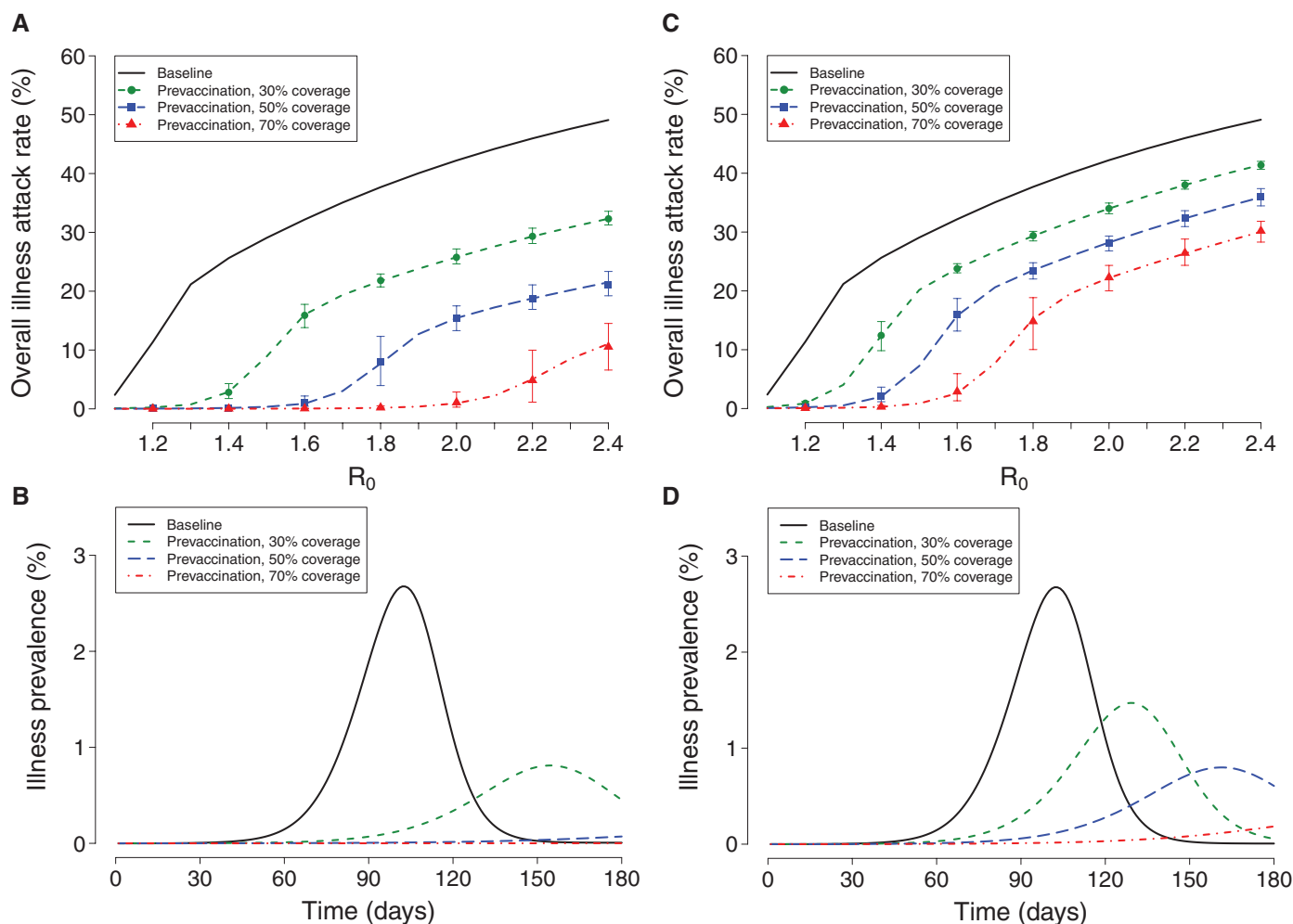
to 3.5 days) (figs. S4 and S5) and  $R_0$  to be 2.3 (95% CI from 2.1 to 2.5), although the  $R_0$  could be as high as 2.9 (95% CI from 2.6 to 3.2) (table S7) for that setting. We defined the generation interval as the time between illness onsets of the index case and someone he or she infects. The mean generation interval could be as low as 2.6 days (95% CI from 2.5 to 2.8 days) (figs. S6 and S7). This estimate is robust to variation in the assumed incubation and infectious periods (figs. S6 and S7). Figure 3 shows simulated final illness attack rates for the United States and the projected global number of people with influenza illness at different values of  $R_0$ .

Another previous estimate of  $R_0$  in Mexico ranged from 1.4 to 1.6 (19), a lower range than our estimates from Mexico. The influenza Asian A (H2N2) pandemic of 1957–1958 and Hong Kong A (H3N2) of 1968–1969 had estimated  $R_0$  values in the 1.5 to 1.8 range and were considered to be of moderate transmissibility, whereas the influenza A (H1N1) of 1918–1919 had an esti-

ated  $R_0$  in the range of 1.8 to 2.4 and was considered to be highly transmissible (9, 20–23).

To evaluate the early transmission of pandemic H1N1 and the potential for control of the virus with pandemic vaccines, we used a previously developed simulation model (18, 24) calibrated to the household (table S11), school, and community transmission given above (tables S10 and S12). Simulation results for Los Angeles County (Fig. 2 and fig. S13) reveal the characteristic pattern of early spread in schoolchildren with eventual spread of infection to other age groups. Although social distancing and the use of antiviral agents can be partially effective at slowing spread, vaccination remains the most effective means of pandemic influenza control (24). The primary means for early control of pandemic H1N1 has been to close schools and other social gathering places, but cost-effectiveness analysis reveals that school closure is the least cost-effective measure and that vaccination is the most cost effective for pandemic influenza control (25).

Currently, more than 20 manufacturers are in various stages of production for pandemic H1N1 vaccines (26, 27). In the United States, vaccine could have been delivered, starting in September 2009, over several months with enough vaccine for up to 20% of the population per month (28). However, the start of delivery was delayed until October 2009. Early analysis of phase I and II immunogenicity data indicates that the level of protection provided should be similar to that of the seasonal influenza A (H1N1) vaccines presently in use. We assume that two doses of vaccine would be needed, with at least 3 weeks between first and second doses. However, one dose for people over 9 years old may prove to be sufficient. We assume that immunity will build over time according to the pattern shown in fig. S11. The final modeled efficacies of seasonal inactivated influenza vaccine based on human challenge studies, vaccine trials, and observational studies are given in table S9 (29). Estimates are given for both homologous and



**Fig. 4.** Simulated effect of prevaccination with a homologously and a heterologously matched pandemic influenza vaccine at different values of  $R_0$  and coverage for the United States. **(A)** Overall illness attack rates for homologous vaccine. Lines indicate the average illness attack rate over five simulations of Los Angeles County for each value of  $R_0$  with the vaccine efficacies summarized in table S9. The 95% error bars indicate the empirical confidence intervals for

100 simulations where the vaccine efficacy parameters are chosen randomly within 15% of their estimated values. **(B)** Epidemic curves at  $R_0 = 1.6$  with homologous vaccine. **(C)** Overall illness attack rates with a heterologous vaccine and 95% error bars indicating the empirical confidence intervals when varying the vaccine efficacy parameters. **(D)** Epidemic curves at  $R_0 = 1.6$  with heterologous vaccine.

heterologous matches to the wild-type circulating virus. Because we do not know how well-matched a pandemic vaccine will be, we evaluate both scenarios.

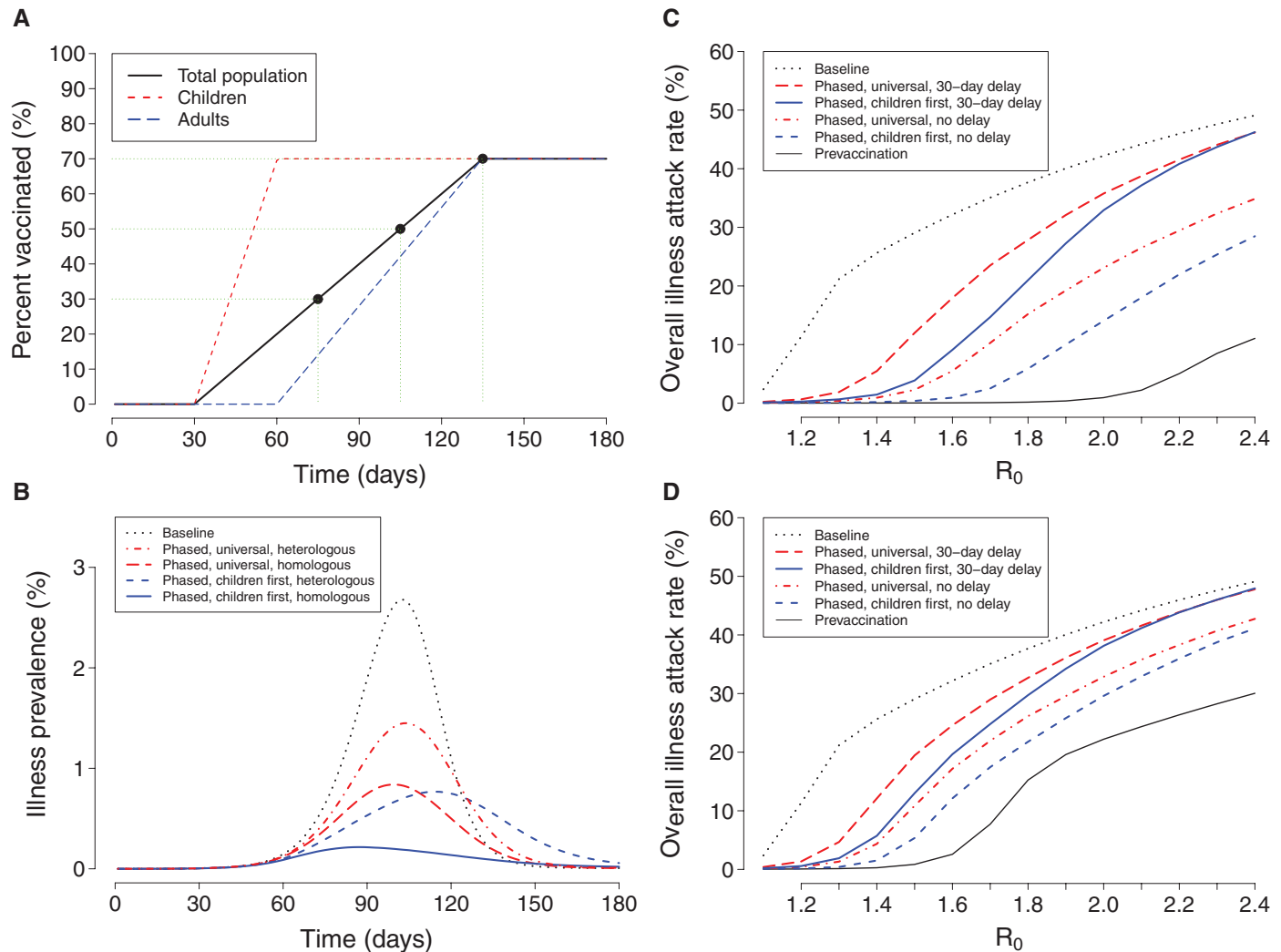
To evaluate the effectiveness of pandemic vaccine use in the United States, we used a stochastic simulation model [section 4 of (15)] for both Los Angeles County and the United States, assuming different levels of vaccine match (table S9) and coverage before and during spread of the virus in the fall 2009. We assumed that the limited spread of pandemic H1N1 in the United States during the spring and summer of 2009 (30) will result in very limited population-level immunity in the fall 2009.

Vaccination increases population-level immunity and lowers the effective reproductive number, having two main effects: first, slowing the

spread of infection and reducing the height of the epidemic peak, thus, decreasing the surge capacity needed to deal with influenza cases; second, reducing the overall illness attack rate and mortality. The effectiveness of vaccination depends heavily on the rate and timing of vaccine delivery with respect to when substantial transmission begins. We considered two possible scenarios. First, we considered universal (i.e., all age and risk groups) prevaccination before the spread of the virus in the United States. Second, we considered a phased vaccination program where vaccine is either universally delivered over time as the epidemic progresses or vaccine is delivered to children first.

With successful universal prevaccination and a homologous match with the circulating virus (i.e., homologous vaccine), 70% coverage would

be sufficient to successfully mitigate epidemic spread at an  $R_0$  as high as 2.0 (Fig. 4A). We consider an illness attack rate of 15% or less to indicate a well-mitigated epidemic. This would correspond to a relatively mild seasonal influenza epidemic. With 50% universal vaccination, we could mitigate epidemic spread at an  $R_0$  as high as 1.8, whereas 30% coverage would not be effective. At  $R_0 = 1.6$ , prevaccination slows the epidemic considerably (Fig. 4B). Even at the low coverage of 30%, the epidemic peak can be moved from day 94 in the baseline scenario to day 135. If the circulating virus is heterologous to the vaccine (i.e., heterologous vaccine), 50 to 70% coverage would be effective for mitigating epidemics only at an  $R_0 \leq 1.7$ , although prevaccination would still slow spread considerably (Fig. 4, C and D).



**Fig. 5.** Simulated effect of phased pandemic influenza vaccination for homologous and heterologous vaccines at different values of  $R_0$  and coverage for the United States. **(A)** Vaccine coverage over time with a 30-day delay. Vaccine is delivered at a rate of 120 million doses each month or about 20% coverage per month. This is enough vaccine to give 60 million people with two doses, 3 weeks apart per month. Vaccine is delivered uniformly over the month. Day 0 is the beginning of pandemic H1N1 spread in the United States. When there is no delay in vaccine supply, vaccination would start on day 0. The dotted lines show the coverage for a strategy to vac-

inate children first (red) and then adults (blue) starting when coverage reaches 70% in children. **(B)** Epidemic curves when  $R_0 = 1.6$  for homologous and heterologous vaccines, delivered with a 30-day delay. Both universal and the children-first vaccination strategies are shown. **(C)** Overall illness attack rates for homologous vaccine for the universal and children-first vaccination strategies, both with and without the 30-day delay. **(D)** Overall illness attack rates for heterologous vaccine for the universal and children-first vaccination strategies, both with and without the 30-day delay.

Basta *et al.* (31) showed that prevaccination of 70% of schoolchildren could be effective in mitigating pandemic H1N1 in the United States for an  $R_0$  as high as 2.0. Because of uncertainty in the eventual vaccine efficacy, we did a sensitivity analysis by varying the vaccine efficacy parameters within 15% of their estimated values (Fig. 4, A and C). This level of uncertainty does not change our conclusions about the effectiveness of vaccination.

Phased vaccination is started either at the beginning of spread or with a delay of 30 days after spread begins (Fig. 5A). We consider both phased universal vaccination and phased vaccination of children (age  $\leq 18$  years old) first up to 70% coverage before vaccine is delivered to adults (age  $> 18$  years old) (Fig. 5A). Phased vaccination has a potentially large effect on reducing spread but delays the epidemic peak only slightly (Fig. 5B). Movies S1 and S2 show simulated epidemics for the entire United States for  $R_0 = 1.6$ , with phased universal and phased children-first vaccination, respectively, with a 30-day delay. With a 30-day delay, the phased children-first strategy would mitigate epidemic spread for an  $R_0$  up to 1.7 (Fig. 5C). The same is true for the phased, universal, no-delay vaccination strategy. The universal strategy with a 30-day delay would be less effective. For a heterologous vaccine, phased universal vaccination with no delay and children first with a 30-day delay would be effective mitigation strategies at  $R_0 \leq 1.5$  (Fig. 5D). For phased vaccination, we found that 50% final coverage could be effective only for homologous vaccine at  $R_0 < 1.6$  with children first and no delay (table S13).

All the vaccination strategies explored here with coverage of 70% have a substantial mitigating effect. Combining vaccination with other mitigation measures, such as social distancing and targeted use of antiviral agents, could be quite effective (24, 32).

Our current estimates of the transmissibility of pandemic H1N1 indicate the virus is highly transmissible in schools and households, similar to the influenza A (H1N1) that caused high transmission in children during the 1978–1979 influenza season in the United States. A drifted version of that virus has cocirculated with influenza A (H3N2) and B until the present. By mid-July 2009 in the United States, 99% of all subtyped influenza A isolates were pandemic H1N1 (33). Similarly, by the end of May 2009, in the Southern Hemisphere during the influenza season, over 90% of reported influenza isolates are pandemic H1N1 (34). Pandemic H1N1 is antigenically stable with no sign of genetic drift (35). This implies that the vaccine match will be good and that our homologous vaccine scenarios are more likely than the heterologous vaccine scenarios. So far, in the United States and most parts of the upper Northern Hemisphere, pandemic H1N1 has caused outbreaks in close contact groups of children in schools or camps, has spread readily in households when introduced, and now appears to be spreading into the general community. Our preliminary estimate of  $R_0$  from

1.3 to 1.7 is consistent with pandemic spread causing illness in 25% to 39% of the world's population over a 1-year period, similar to the spread of the 1957–1958 Asian influenza A (H2N2) pandemic. Given this situation, making enough pandemic H1N1 vaccine to vaccinate at least 70% of the U.S. population over time is important (Fig. 5A). Because the current pattern of pandemic spread is most likely similar to that of the Asian influenza A (H2N2) in 1957–1958, we expect substantial spread in the United States to begin in early September (around day 60 in Fig. 4B), with the epidemic peaking in October (around day 94 in Fig. 4B). In this case, children-first phased vaccination would need to start as soon as possible and no later than September to be effective in mitigating the epidemic. Should substantial epidemic spread start later in the fall, peaking in late December or early January, then a phased vaccination strategy could be effective for mitigation. The current recommendation of the U.S. Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices is to concentrate early supplies of pandemic H1N1 vaccine in a number of groups (36). In addition to children over 6 months of age, young adults, people at high risk for complications, and health care and emergency services personnel are all included in the list. It would be prudent to cover those listed groups in addition to concentrating vaccine in children (37, 38), but further work will be required to investigate the logistics of doing that with limited supplies of vaccine.

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#### Supporting Online Material

[www.sciencemag.org/cgi/content/full/1177373/DC1](http://www.sciencemag.org/cgi/content/full/1177373/DC1)  
Materials and Methods  
Figs. S1 to S13  
Tables S1 to S14  
Movies S1 and S2  
References

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