Published in final edited form as:
Science. 2009 October 30; 326(5953): 729–733. doi:10.1126/science.1177373.

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

Yang Yang[1], **Jonathan D. Sugimoto**[1,2], **M. Elizabeth Halloran**[1,3], **Nicole E. Basta**[1,2], **Dennis L. Chao**[1], **Laura Matrajt**[4], **Gail Potter**[5], **Eben Kenah**[1,3,6], and **Ira M. Longini Jr.**[1,3,*]

[1]Center for Statistics and Quantitative Infectious Diseases, Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, WA, USA

[2]Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, USA

[3]Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA

[4]Department of Applied Mathematics, University of Washington, Seattle, WA, USA

[5]Department of Statistics, University of Washington, Seattle, WA, USA

[6]Department of Global Health, University of Washington, Seattle, WA, USA

Abstract

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 is underway. Here, based on reported case clusters in the USA, we estimate the household secondary attack rate for pandemic H1N1 to be 27.3% (95% CI: 12.2%–50.5%). From a school outbreak, we estimate a school child infects 2.4 (95% CI: 1.8–3.2) other children within the school. We estimate the basic reproductive number, R_0, to range from 1.3–1.7 and the generation interval to range from 2.6–3.2 days. We use a simulation model to evaluate the effectiveness of vaccination strategies in the USA for the Fall, 2009. If 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.

Pandemic H1N1, which first emerged in Mexico in April, 2009, 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 school children in the 5–18 year old age range. A recent analysis of data from the United States, Canada, the United Kingdom, and the European Union suggests case fatality ratios ranging from 0.20%–0.68% in these regions and a higher case fatality ratio in Mexico of 1.23% (95% CI 1.03%–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 sporadically, but sometimes corresponding to the rainy season. The last influenza pandemic was the Hong Kong A (H3N2)

* To whom correspondence should be addressed. longini@scharp.org .

Supporting Online Material Materials and Methods Figs. S1 to S13 Tables S1 to S14 Movies M1 to M2 References

1968-1969 pandemic. At that time, the first large epidemic was in Hong Kong in July, 1968, followed by epidemics in South East Asia in August-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 USA 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 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 USA until the Fall of 1957, with the national level epidemic rising in September and peaking in October. Pandemic H1N1 will probably spread in a similar spatio-temporal pattern as previous pandemics, but accelerated due to increased air travel (12).

Estimates of the transmissibility of pandemic H1N1are 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 USA households (Fig. S1) with confirmed index cases of pandemic H1N1 (15). The best estimate is 27.3% (95% CI: 12.2%–50.5%) (Table S1), which is robust to uncertainty in the assumed incubation and infectious periods, and source of secondary infections (15)(Tables S1–S2). Thus, based on early spread of pandemic H1N1 in the USA, 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 to 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: 21.9–39.3) (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) re-appeared during the 1978–1979 influenza season and co-circulated with influenza A (H3N2) and was the dominant strain in the USA (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: 15-51%), 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 (Figs. 2 and 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 use maximum likelihood to estimate that the typical school child infected an average of 2.4 (95% CI: 1.8 - 3.2) other school children 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-S4, Figs. S8-S9). To our knowledge, this is the first estimate of the transmissibility of pandemic influenza in schools.

Using household studies and modeling, we estimate that 30–40% 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). Based on this information and the estimated transmission parameters from USA households and the St. Francis Preparatory School, using maximum likelihood methods (15), we estimate 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), using maximum likelihood methods, we estimate the mean generation interval to be 3.2 days (95% CI: 3.0–3.5 days) (Figs. S4–S5) (and R_0 to be 2.3 (95% CI: 2.1–2.5), although the R_0 could be as high as 2.9 (95% CI: 2.6–3.2) (Table S7) for that setting. We define 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: 2.5–2.8 days) (Figs. S6–S7). This estimate is robust to variation in the assumed incubation and infectious periods (Figs. S6-S7). Fig. 3 shows simulated final illness attack rates for the USA and the projected global number of people with influenza illness at different levels of R_0.

Another previous estimate of R_0 in Mexico ranges from 1.4–1.6 (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_0s in the 1.5–1.8 range and were considered to be of moderate transmissibility, while the influenza A (H1N1) of 1918–1919 had an estimated R_0 in the range 1.8–2.4 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 (Tables S11), school, and community transmission given above (Tables S10 and S12). Simulation results for the Los Angeles County, USA, (Figs. 2 and S13) reveal the characteristic pattern of early spread in school children 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 planning to produce novel influenza A (H1N1) vaccines, and human immunogenicity trials are already underway (26,27). In the USA, vaccine could be 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 could be delayed until October, 2009. Though no data are yet available to assess the efficacy of these vaccines, one could assume that the level of protection provided would 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 three weeks between the first and second dose. 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 heterologous matches to the wild type circulating virus. Since 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 USA, we used a stochastic simulation model (*Sec.4* (15)) for both Los Angeles County and the USA, assuming different levels of vaccine match (see Table S9) and coverage prior to and during spread of the virus in the Fall 2009. We assumed that the limited spread of pandemic H1N1 in the USA 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 consider two possible scenarios. First, we consider universal (i.e., all age and risk groups) prevaccination before the spread of the virus in the US. Second, we consider 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 significantly 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), 50-70% coverage would be effective for mitigating epidemics only at an $R_0 \leq 1.7$, although prevaccination would still slow spread considerably (Figs. 4C and 4D). Basta, *et al*. (31) show that prevaccination of 70% of school children could be effective in mitigating pandemic H1N1 in the US 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 (Figs. 4A and 4C). 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 ≤ 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 M1 and M2 show simulated epidemics for the entire USA 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 child 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 child 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 $R_0 \leq 1.6$, with child first and no delay (Table S13).

All the vaccination strategies explored here with coverage of 70% have a significant mitigating effect. Clearly, 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 USA. A drifted version of that virus has co-circulated with influenza A (H3N2) and B until the present. By mid-July 2009 in the US, 99% of all sub-typed influenza A isolates were pandemic H1N1 (33). Similarly,

by the end of May 2009, in Chile, in the southern hemisphere where the influenza season is currently underway, 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 USA and most parts of the upper northern hemisphere, pandemic H1N1 has caused outbreaks in close contact groups of children in schools or camps and has spread readily in households when introduced, but does not appear to be community-wide. Our preliminary estimate of R_0 from 1.3–1.7 is consistent with pandemic spread causing illness in 25%–39% of the world's population over a one 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 US 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 USA 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, child-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 US 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was partially supported by the National Institute of General Medical Sciences MI-DAS grant U01-GM070749 and the National Institute of Allergy and Infectious Diseases grant R01-AI32042.

References

1. World Health Organization. Novel Influenza A (H1N1) - Update 59. [accessed July 28, 2009]. Jul 272009 http://www.who.int/csr/don/2009_07_27/en/index.html
2. Chan, M. World now at start of 2009 influenza pandemic. statement to the press by WHO director-general. [accessed July 28, 2009]. Jun 112009 http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en
3. Centers for Disease Control and Prevention. Swine Influenza A (H1N1) infection in two children–Southern California, March-April 2009. 2009. http://www.cdc.gov/mmwr/PDF/wk/mm5815.pdf
4. Center for Diseases Control and Prevention. Update: swine influenza A (H1N1) infections–California and Texas, April 2009. 2009. http://www.cdc.gov/mmwr/PDF/wk/mm5816.pdf
5. Kansas Department of Health and Environment. Swine influenza news conference. [accessed April 29, 2009]. Apr 292009 http://www.dhe.state.ks.us/SwineFlu/swineflunewsconf.wmv
6. Kansas Department of Health and Environment. KDHE Reports 2 Cases of Swine Flu in Kansas. http://www.kdheks.gov/news/web_archives/2009/04252009.htm
7. New York City Department of Health and Mental Hygiene. St. Francis Prep Update: Swine Flu Outbreak. [accesed July 28, 2009]. Apr 302009 http://www.nyc.gov/html/doh/downloads/pdf/cd/h1n1_stfrancis_survey.pdf
8. Garske T, et al. BMJ 2009;339:b2840. [PubMed: 19602714]

9. Rvachev LA, Longini IM Jr. Mathematical Biosciences 1985;75:3.
10. Glezen W, Couch R, Six H. Am J Epidemiol 1982;116:589. [PubMed: 7137146]
11. Dunn F, Carey D, Cohen A, Martin J. Am J Hyg 1959;70:351. [PubMed: 13818677]
12. Grais R, Ellis J, Kress A, Glass G. Health Care Manag Sci 2004;7:127. [PubMed: 15152977]
13. Yang Y, Longini IM Jr. Halloran ME. Computational Statistics and Data Analysis 2007;51:6582. [PubMed: 18704156]
14. Yang Y, Halloran ME, Sugimoto JD, Longini IM Jr. Emerg Infect Dis 2007;13:1348. [PubMed: 18252106]
15. Materials and methods are available as supporting material on Science Online.
16. Longini IM Jr. Koopman JS, Monto AS, Fox J. Biometrics 1982;115:736.
17. Longini IM Jr. Koopman JS. Biometrics 1982;38:115. [PubMed: 7082755]
18. Halloran ME, et al. Proc Natl Acad Sci U S A 2008;105:4639. [PubMed: 18332436]
19. Fraser C, et al. Science 2009;324:1557. [PubMed: 19433588]
20. Longini IM Jr. Mathematical Biosciences 1986;82:19.
21. Chowell G, Ammon CE, Hengartner NW, Hyman JM. Math Biosci 2007;4:457.
22. Chowell G, Miller M, Viboud C. Epidemiol Infect 2008;136:852. [PubMed: 17634159]
23. Mills C, Robins J, Lipsitch M. Nature 2006;432:904. [PubMed: 15602562]
24. Germann TC, Kadau K, Longini IM Jr. Macken CA. Proc Natl Acad Sci U S A 2006;103:5935. [PubMed: 16585506]
25. Sander B, et al. Value in Health 2009;12:226.
26. National Institute of Allergy andInfectious Diseases. Clinical trials of 2009 H1N1 influenza vaccines conducted by NIAID-supported vaccine treatment and evaluation units. [accessed July 28, 2009]. Jul 222009 www3.niaid.nih.gov/news/QA/vteuH1N1qa.htm
27. World Health Organization. Production and availability of pandemic influenza a H1N1 vaccines. [accessed July 28, 2009]. Jul 122009 www.who.int/csr/disease/swineflu/frequently_asked_questions/vaccine_preparedness/production_availability/en/index.html
28. Robinson R. H1N1 vaccine products and production. Advisory Committee on Immunization Practices (ACIP) July 2009 meeting. July 31;2009 http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-jul09-flu/05-Flu-Robinson.pdf.
29. Basta NE, Halloran ME, Matrajt L, Longini IM Jr. Am J Epidemiol 2008;168:1343. [PubMed: 18974084]
30. Centers for Disease Control and Prevention. FluView: 2008-2009 Influenza Season Week 20 ending May 23, 2009, FluView: 2008-2009 Influenza Season Week 20 ending May 23, 2009. 2009. http://www.cdc.gov/flu/weekly
31. Basta NE, Chao DL, Halloran ME, Matrajt L, Longini IM Jr. Am J Epidemiol. August 13;2009 http://aje.oxfordjournals.org/cgi/reprint/kwp237v1.
32. Longini IM Jr. et al. Science 2005;309:1083. [PubMed: 16079251]
33. Centers for Disease Control and Prevention. FluView. 2008-2009 Influenza Season Week 28 Ending July 18, 2009. [accessed July 28, 2009]. Jul 242009 http://www.cdc.gov/flu/weekly/weeklyarchives2008-2009/weekly28.htm
34. Briand, S. Epidemiology and illness severity of pandemic (H1N1) 09 virus. World Health Organization Extraordinary Strategic Advisory Group of Experts on Immunization Meeting. [accessed July 28, 2009]. Jul 102009 http://www.who.int/immunization/sage/1.Briand_epi_7th_July_2009_(rev_6July_09).pdf
35. Garten R, et al. Science 2009;325:197. [PubMed: 19465683]
36. Centers for Disease Control and Prevention. Press release: CDC Advisors Make Recommendations for Use of Vaccine Against novel H1N1. [accessed August 5, 2009]. Jul 292009 http://www.cdc.gov/media/pressrel/2009/r090729b.htm
37. Longini IM Jr. Ackerman E, Elveback LR. Mathematical Biosciences 1978;38:141.
38. Halloran ME, Longini IM Jr. Science 2006;311:615. [PubMed: 16456066]

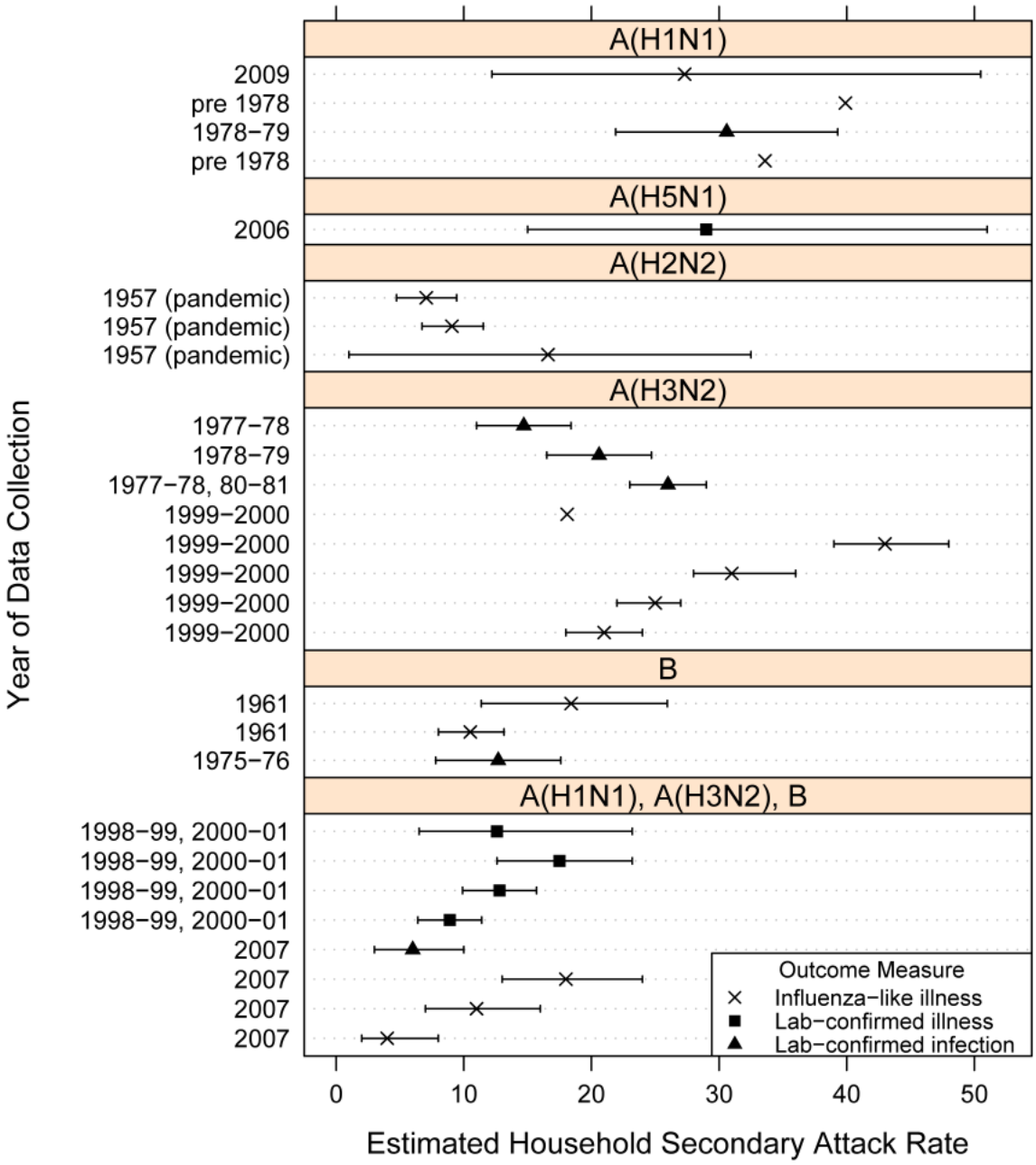


Fig. 1.

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 (*Sec*. 2 (15) and Table S8). The household illness secondary attack rate is based on 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 is based on paired sera bracketing the usual influenza season, where an infection is defined as a significant rise in hemagglutination-inhibition titer comparing the pre-influenza season sample to the post-influenza season sample. The 95% confidence intervals 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 re-emerged 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.

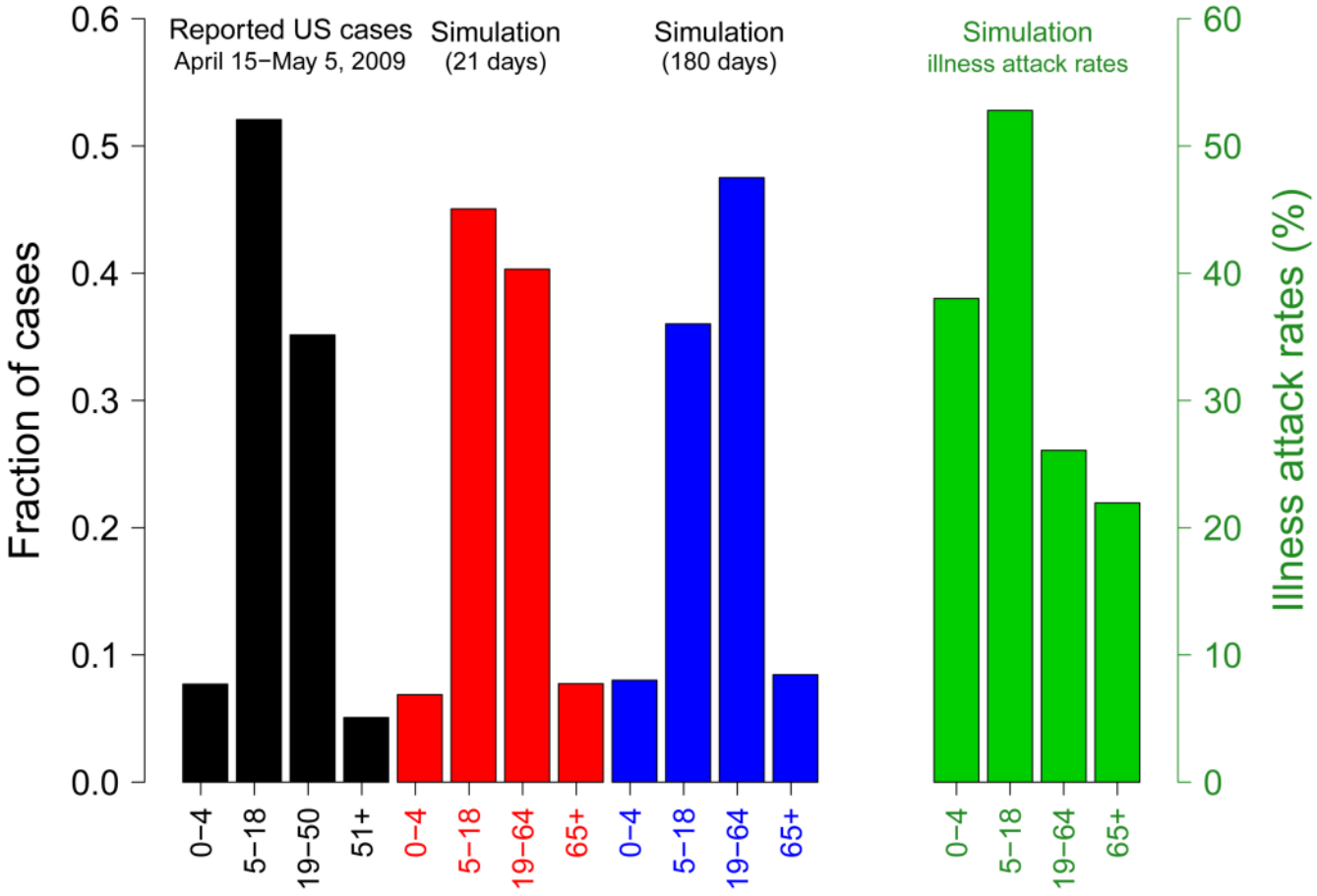
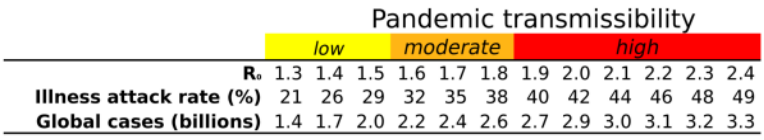


Fig. 2.

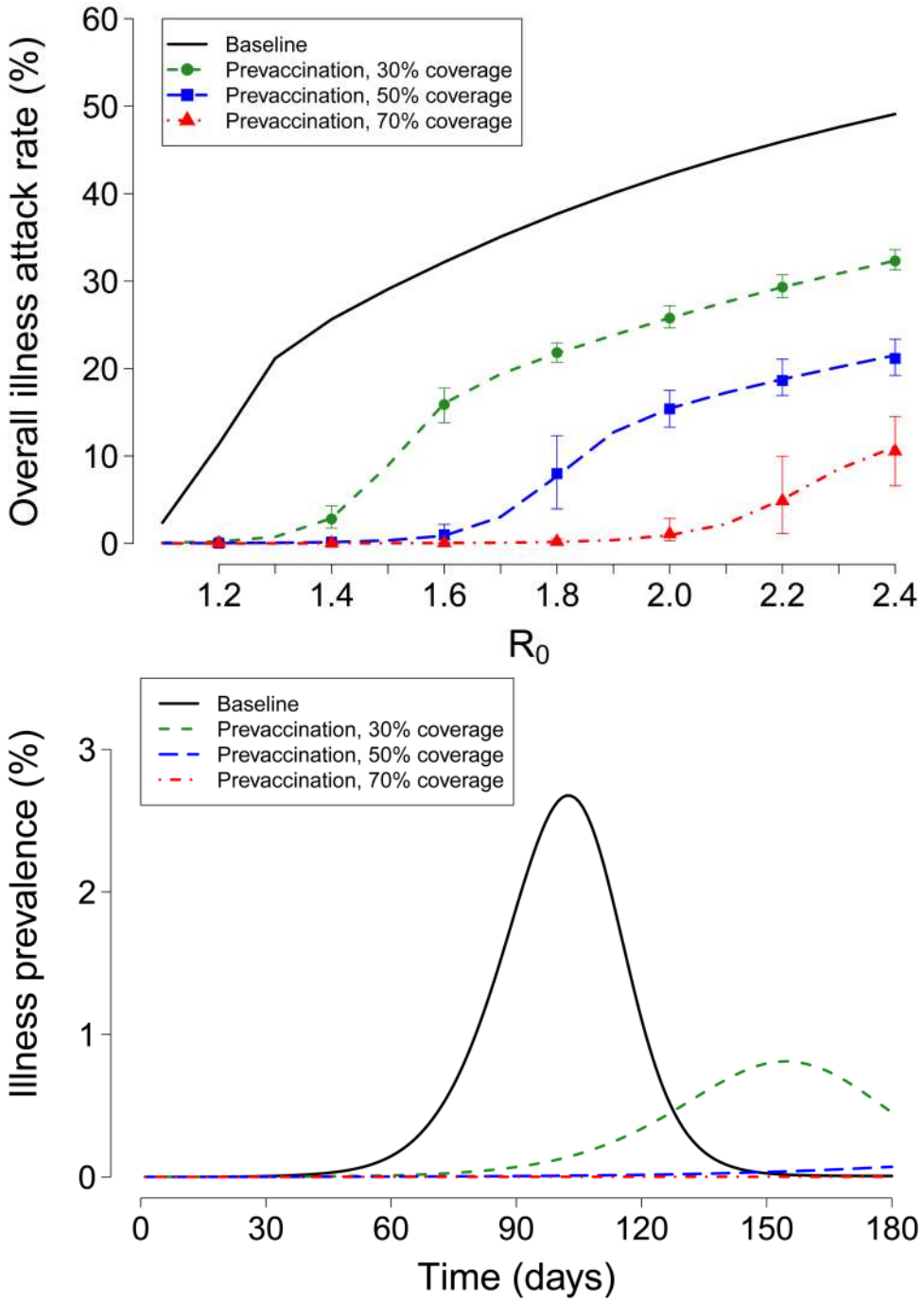
Observed and simulated age-specific fraction of influenza cases and illness attack rates, with $R_0 = 1.6$. The left plot shows the observed proportion of reported pandemic H1N1 cases by age group in the USA during the early days of the reported USA epidemic. The next two plots show the simulated proportion 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 laterepidemic, older age groups would become more involved as the infections spreads beyond schools and households. The final plot shows 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).



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 USA and projected total number of global cases for one year of pandemic influenza at different levels of R_0. The projections are obtained by multiplying the simulated illness attack rates by the world population of 6.8 billion.



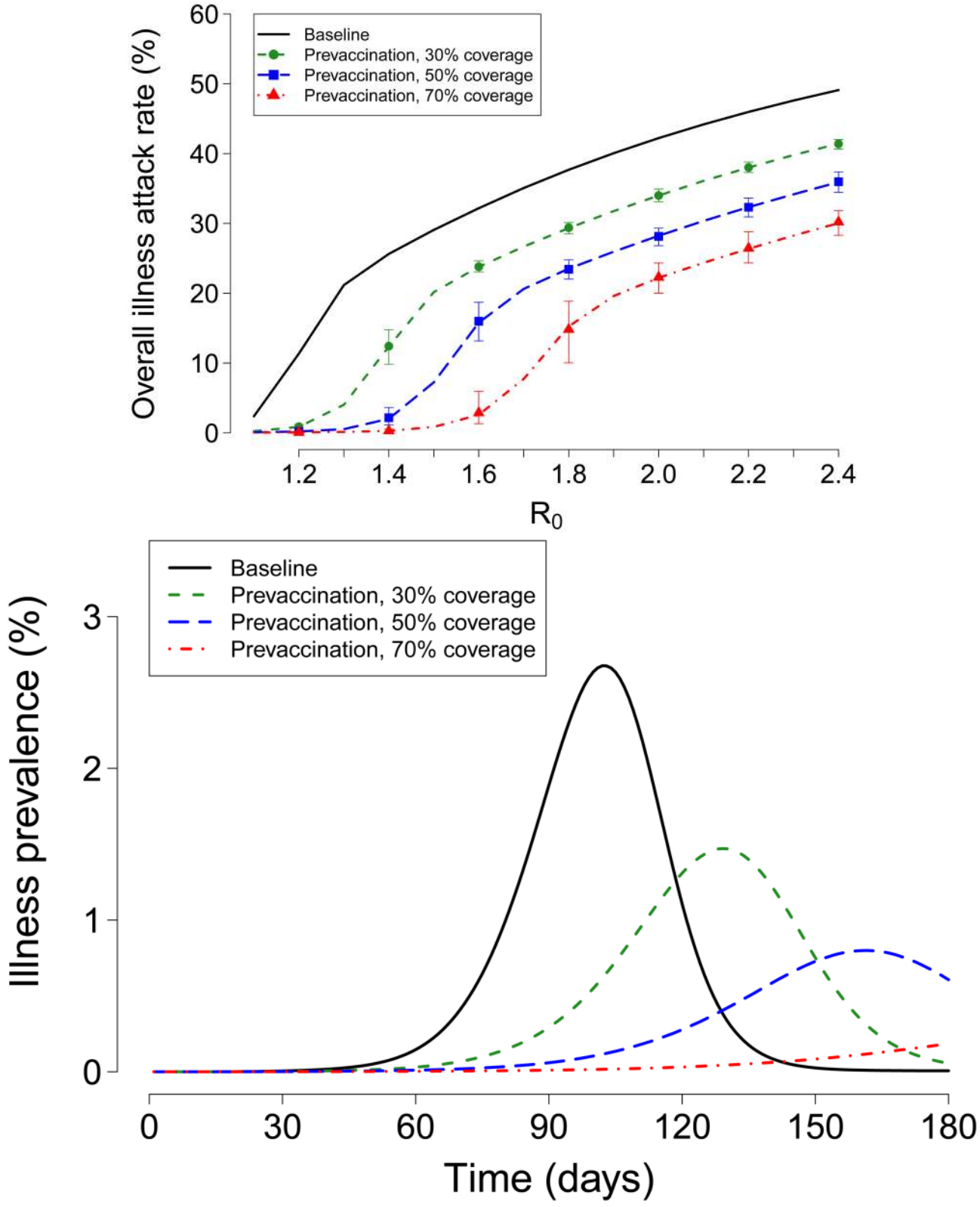
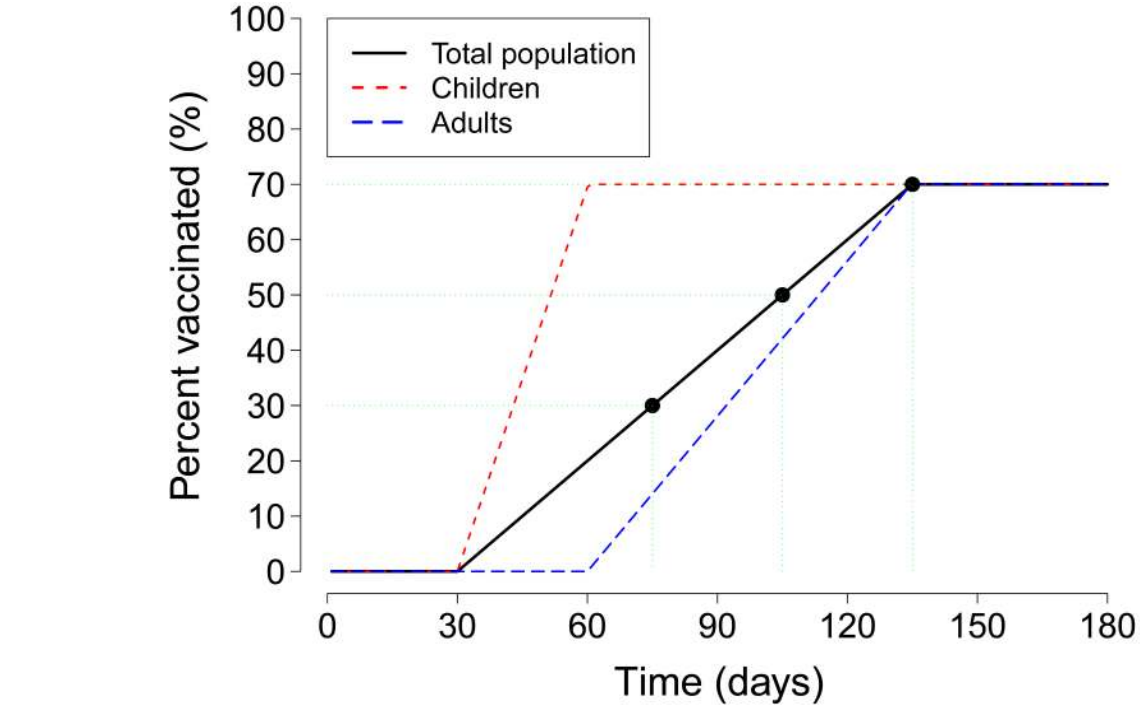
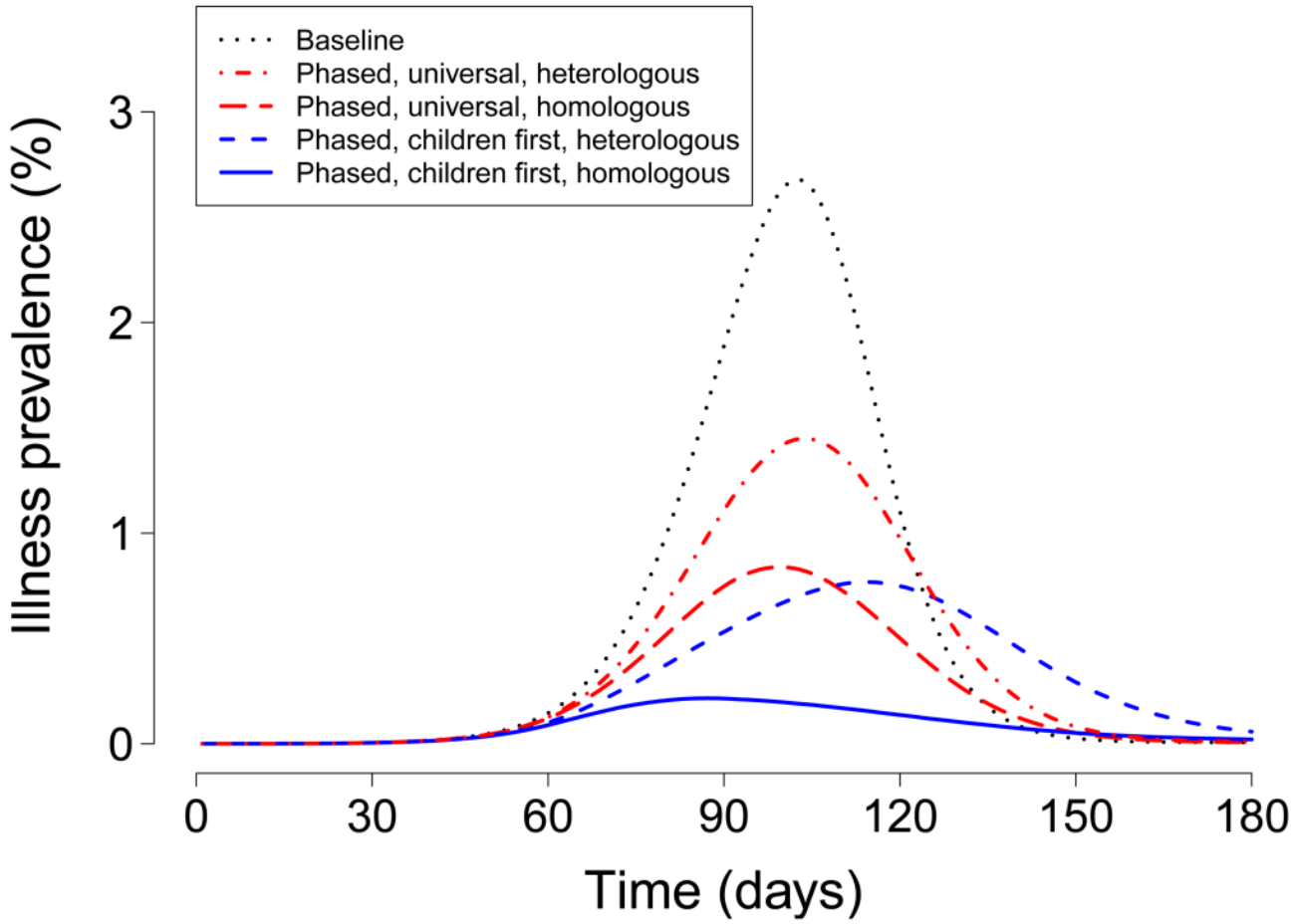
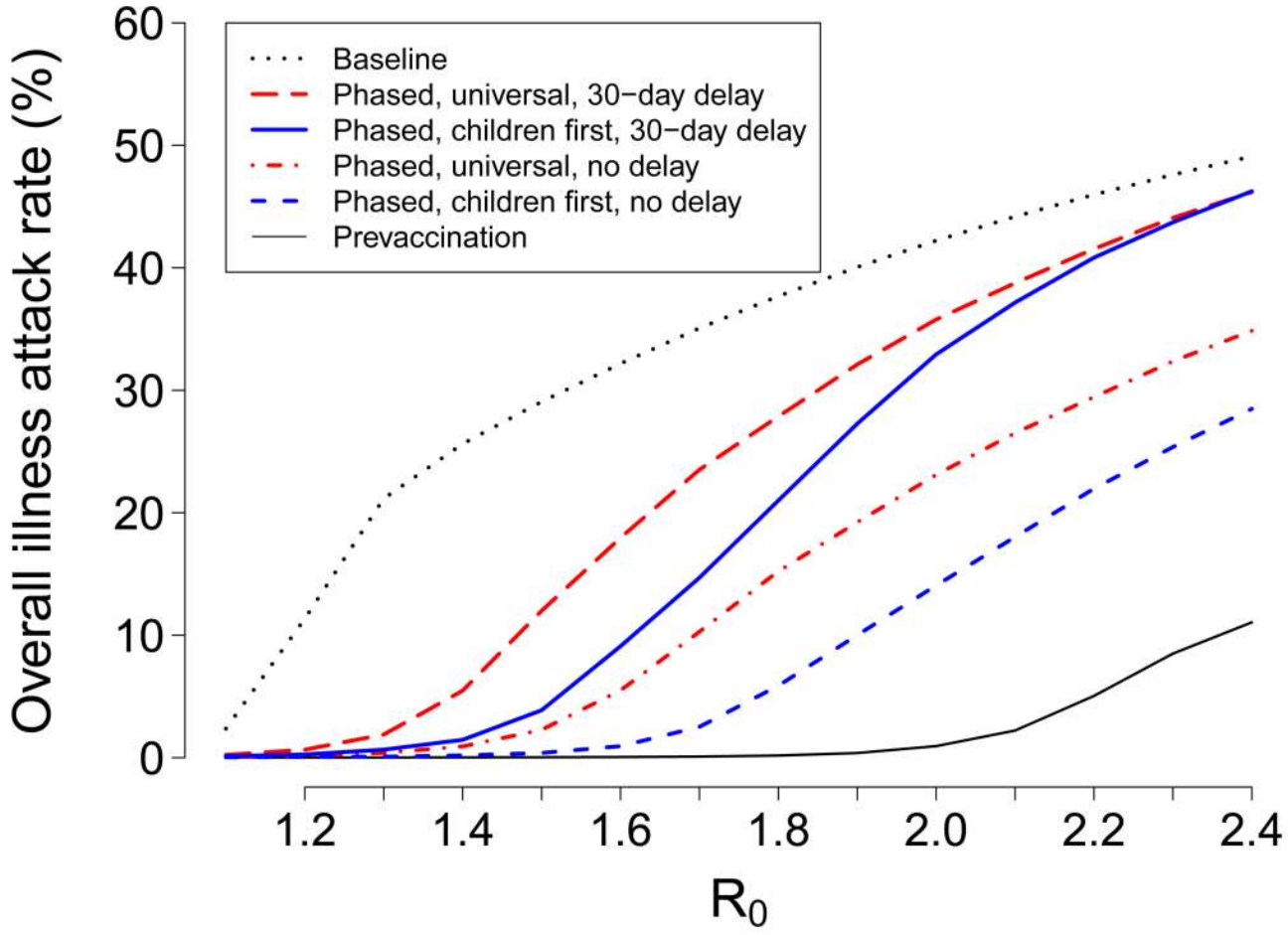


Fig. 4.

Simulated effect of prevaccination with a homologously and heterologously matched pandemic influenza vaccine at different levels of R_0 and coverage for USA. 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.







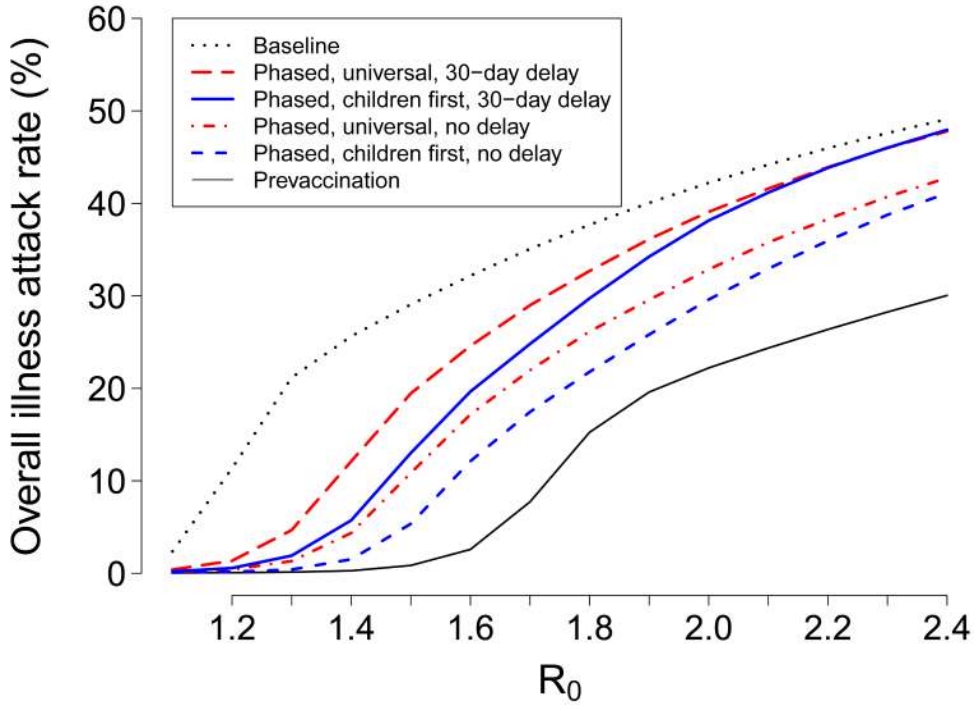


Fig. 5.

Simulated effect of phased pandemic influenza vaccination for homologous and heterologous vaccines at different levels of R_0 and coverage for USA. 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, three weeks apart per month. Vaccine is delivered uniformly over the month. Day 0 is the beginning of pandemic H1N1 spread in the USA. When there is no delay in vaccine supply, vaccination would start on day 0. The dotted lines show the coverage for a strategy to vaccinate children first (red line) and then adults (blue line) 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 child 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.