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SPECIAL ARTICLE

Containing Pandemic Influenza with Antiviral Agents

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For the first wave of pandemic influenza or a bioterrorist influenza attack, antiviral agents would be one of the few options to contain the epidemic in the United States until adequate supplies of vaccine were available. The authors use stochastic epidemic simulations to investigate the effectiveness of targeted antiviral prophylaxis to contain influenza. In this strategy, close contacts of suspected index influenza cases take antiviral agents prophylactically. The authors compare targeted antiviral prophylaxis with vaccination strategies. They model an influenza pandemic or bioterrorist attack for an agent similar to influenza A virus (H2N2) that caused the Asian influenza pandemic of 1957–1958. In the absence of intervention, the model predicts an influenza illness attack rate of 33% of the population (95% confidence interval (CI): 30, 37) and an influenza death rate of 0.58 deaths/1,000 persons (95% CI: 0.4, 0.8). With the use of targeted antiviral prophylaxis, if 80% of the exposed persons maintained prophylaxis for up to 8 weeks, the epidemic would be contained, and the model predicts a reduction to an illness attack rate of 2% (95% CI: 0.2, 16) and a death rate of 0.04 deaths/1,000 persons (95% CI: 0.0003, 0.25). Such antiviral prophylaxis is nearly as effective as vaccinating 80% of the population. Vaccinating 80% of the children aged less than 19 years is almost as effective as vaccinating 80% of the population. Targeted antiviral prophylaxis has potential as an effective measure for containing influenza until adequate quantities of vaccine are available.

antiviral agents; bioterrorism; computer simulation; disease outbreaks; influenza; influenza A virus; influenza vaccine; Monte Carlo method

Abbreviations: AVE, antiviral efficacy; AVE_D, antiviral efficacy for symptomatic disease given infection; AVE_I, antiviral efficacy for infectiousness; AVE_S, antiviral efficacy for susceptibility to infection; AVE_{SD}, antiviral efficacy for symptomatic disease; CI, confidence interval; R, reproductive number; R_0, basic reproductive number; VE_I, vaccine efficacy for infectiousness; VE_S, vaccine efficacy for susceptibility; VE_{III}, overall effectiveness.

Influenza is an annual major public health threat. In the United States, influenza epidemics usually occur during the winter months between November and April and are responsible for an average of 36,000 excess deaths per year (1). These annual epidemics are generally due to genetically drifting strains of influenza that differ slightly from previous strains (2). Each year, influenza vaccine is targeted against the strains (usually from the past year) that are expected to circulate in the next season. However, when a major antigenic shift occurs, time is insufficient to manufacture

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vaccine for the first wave of the ensuing pandemic. Three major pandemics were caused by antigenic shifts in the 20th century. The 1918–1919 "Spanish flu" is believed to have caused more than 500,000 deaths in the United States and more than 20 million deaths worldwide. The 1957–1958 "Asian flu" A (H2N2) is estimated to have caused 70,000 deaths in the United States, and the 1968–1969 "Hong Kong flu" A (H3N2) is estimated to have caused 34,000 deaths in the United States. Since the Hong Kong flu, there were the "swine flu" scare of 1976 and the return of the Russian flu A (H1N1) in 1977, which has caused relatively mild epidemics since then. Starting in 1997, avian influenza A (H5N1) has caused large outbreaks in chickens in various countries in east Asia, with several countries affected as of January 2004. This virus is highly virulent in humans who have been infected directly from chickens, but, fortunately, the virus has not achieved person-to-person transmission. Should a new pandemic strain capable of person-to-person transmission appear, large-scale use of influenza antiviral agents could be an attractive first line of defense until an adequate supply of vaccine is available. Hayden (3), as well as others (4, 5), suggests that stockpiling influenza antiviral agents, coupled with an effective rapid distribution strategy, is essential for dealing with future pandemic influenza. Moreover, influenza is classified by the National Institute of Allergy and Infectious Diseases as a category C (i.e., emerging infectious disease threat) potential bioterrorist weapon (6). To deal with the threat of bioterrorist influenza, Madjid et al. (7) suggest stockpiling antiviral agents and increasing the capacity to develop and produce influenza vaccine rapidly. Vaccine development and production for novel and emerging influenza strains could be greatly speeded up through the use of plasmid-based reverse genetic systems to construct influenza virions and vaccines (5).

In this paper, we explore the most effective strategies for the use of influenza antiviral agents for the first wave of pandemic influenza or for a bioterrorist attack of a novel strain of influenza. We compare the effectiveness of such a strategy with that of vaccination, if vaccine were available.

MATERIALS AND METHODS

Influenza antiviral agents considered and targeting

Two classes of antiviral agents could be used: the adamantanes, for example, amantadine and rimantadine, and the neuraminidase inhibitors, for example, zanamivir and oseltamivir. All of these drugs have different efficacies, are licensed for different age groups, and can lead to different levels of transmission of resistant virus. Viral resistance is often associated with the use of the adamantanes (8) but is rarely found with neuraminidase inhibitors (9–11). Resistance to the adamantanes is more commonly associated with therapeutic than with prophylactic use (8). Accordingly, the best use of these antiviral agents would be prophylactic, rather than therapeutic, in settings where persons are most exposed to infection and during the period of highest transmission risk. We will refer to this strategy as "targeted antiviral prophylaxis." We assess targeted antiviral prophylaxis for varying levels of coverage and duration.

Antiviral agent efficacy

Influenza antiviral agents can be used prophylactically to prevent infection given exposure, to reduce the probability of clinical illness given infection, and to reduce the probability of transmission to others given infection. In addition, they can be used therapeutically to achieve the latter two effects. To quantify these effects, we follow our previous work on vaccine efficacy and effectiveness (12) to define the following antiviral efficacy (AVE) measures: 1) the antiviral efficacy for susceptibility to infection (AVE_S) measures how much an antiviral agent will reduce the probability that an uninfected person will be infected, when exposed to infection, compared with an uninfected person not using an antiviral agent; 2) the antiviral efficacy for symptomatic disease given infection (AVE_D) is how much an antiviral agent will reduce the probability that an infected person will develop influenza symptoms compared with an infected person who is not using an antiviral agent; and the antiviral efficacy for symptomatic disease (AVE_{SD}) is how much an antiviral agent will reduce the probability that a person will develop influenza symptoms, given exposure to infection, as compared with an uninfected person who is not using an antiviral agent. The AVE_{SD} is a function of both the AVE_S and the AVE_D, since for a person to have influenza symptoms he/she must first be infected and then develop disease symptoms. This yields the relation, $AVE_{SD} = 1 - (1 - AVE_S)(1 - AVE_D)$. The antiviral efficacy for infectiousness (AVE_I) is how much an antiviral agent will reduce the probability that an infected person will transmit influenza to others compared with an infected person who is not using an antiviral agent. The further definitions of these measures depend on when and how long antiviral agents are used and the definition of influenza symptoms.

There are no direct estimates of the AVE_S, AVE_D, and AVE_{SD} parameters, but values can be inferred from household studies of influenza antiviral agents (8–11, 13). On the basis of these studies, we set the influenza antiviral efficacy measures at $AVE_S = 0.3$, $AVE_D = 0.6$, and $AVE_{SD} = 1 - (0.7)(0.4) = 0.72$. An estimate of the AVE_I for oseltamivir was found to be 0.79 (95 percent confidence interval (CI): 0.60, 0.98), based on family data (11) using maximum likelihood methods (14). Thus, we assume that the $AVE_I = 0.80$. Some evidence suggests that amantadine could be less effective against a pandemic strain than against an interpandemic strain of influenza (3, 13, 15). For the 1968 pandemic strain of influenza A (H3N2), the estimates of the AVE_S varied from 0.28 to 0.52 and of the AVE_{SD} varied from 0.59 to 1.00. For the 1977 pandemic strain of influenza A (H1N1), the estimates of the AVE_S varied from 0.18 to 0.39 and of the AVE_{SD} varied from 0.31 to 0.71 (3). In addition, we assume that an antiviral agent will reduce the length of the illness period by 1 day. In randomized trials with influenza antiviral agents, from 2 to 10 percent of participants stopped taking these agents over the course of the trial (9–11). For our analysis, we assume that 5 percent of persons who start taking influenza antiviral agents will stop taking them after 1 day of treatment. We also assume that those infected persons taking antiviral agents will stop taking the treatment upon recovery. In addition, we assume that all persons taking antiviral

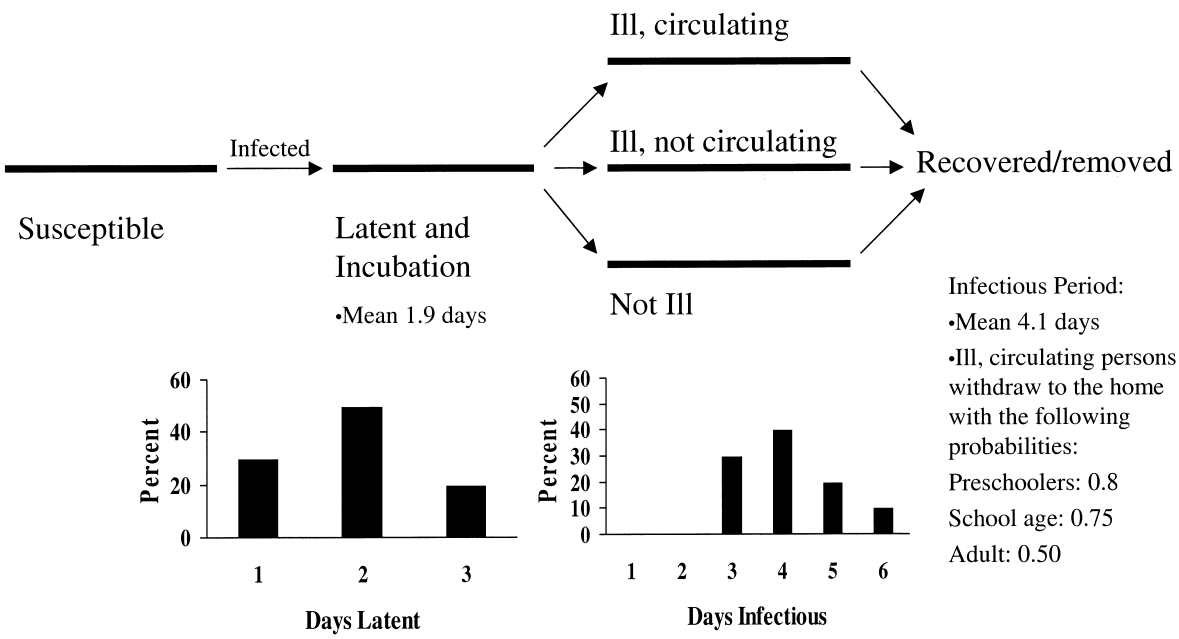

FIGURE 1. Natural history of influenza. Newly infected persons pass through the latent and infectious states after which they recover with immunity or die. The probability that a person will be symptomatic given that person has been infected is 0.67. An asymptomatic infection is assumed to be 50% as infectious as a symptomatic infection. Additionally, this model allows for persons to withdraw from all of their mixing groups except the family unit if they become infected.

agents at the termination of the epidemic will stop taking them at that point.

Vaccine efficacy

For comparison with the effectiveness of antiviral efficacy, we analogously define vaccine efficacy for susceptibility (VE_S) and infectiousness (VE_I) (12). We assume that either killed or live, cold-adapted influenza virus vaccine would be used. We assume that vaccination takes place early enough before the influenza season such that vaccinated persons can develop immunity, and that one dose is given. We assume that the vaccine efficacy for susceptibility is $VE_S = 0.70$ and that the vaccine efficacy for infectiousness is $VE_I = 0.80$ (16–19).

The simulation model

We used a discrete-time, stochastic simulation model of influenza spread within a structured population to compare the effectiveness of various intervention strategies. The model simulates stochastic spread of influenza in populations of persons interacting in known contact groups (19, 20). A similar model has been applied to smallpox (21). The model represents the number of close and casual contacts that a typical person makes in the course of a day and, thus, it represents a cross-section of a typical American community. For each simulation, the contact structure of 2,000 persons is stochastically generated based on the age distribution and approximate household sizes from the 2000 US Census (22). Each population has four neighborhoods, one high school, one middle school, and two elementary schools. Preschool children attend either small playgroups or larger day-care centers. Households have 1–7 persons per family (mean, 2.3), with 33 percent of the households being single adults. Person-to-person transmission probabilities are highest in households; lower in the day-care centers, playgroups, and schools; and even lower in the neighborhoods and population at large (appendix table 1). Each day, for each susceptible, the probability of becoming infected was calculated on the basis of that person's antiviral or vaccination status, who was infectious in his contact groups and their antiviral or vaccination status, and the group-specific transmission probabilities. Influenza was introduced by randomly assigning 12 initial infective persons. The initial infective persons were omitted in the analysis.

People infected with influenza first pass through a latent and incubation period when they are not infectious and do not have influenza symptoms. The lengths of the latent and infectious periods follow empirical probability distributions as shown in figure 1, with mean lengths of 1.9 and 4.1 days, respectively. We assume that the latent period and the incubation period have the same length. This is followed by the infectious period during which persons may develop influenza symptoms (2, 19, 20). In the model, persons with symptoms withdraw with some probability to the home, exposing only the other members of their household. We calibrate the baseline epidemic to have age-specific illness attack rates similar to those of the 1957–1958 influenza A (H2N2) Asian influenza pandemic in the United States (20, 23, 24).

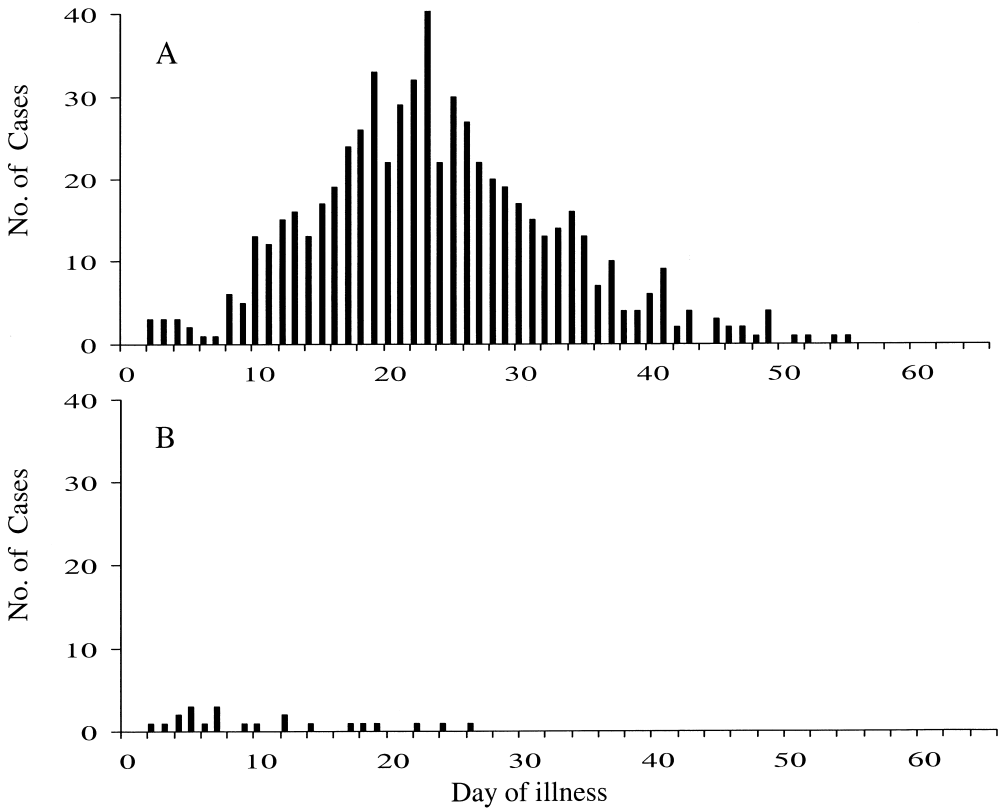

FIGURE 2. A typical stochastically simulated influenza epidemic. A, baseline with no intervention; B, intervention with 80% targeted antiviral prophylaxis for up to 8 weeks per person. The simulated epidemics without intervention last on average about 57 days.

Since influenza antiviral agents are expensive and probably would be in relatively short supply, we consider the targeted antiviral prophylaxis strategy for treating only identified index cases and offering prophylaxis only to the contacts of these index cases in predefined mixing groups. The mixing groups considered are households, day-care centers, playgroups, and schools. Prophylaxis of group members occurs the day after the first symptomatic illness, that is, the index case, occurs in the mixing group. In the next section, we explore varying duration of prophylaxis from 1 to 8 weeks. Each mixing group receives prophylaxis only once over the course of an epidemic. In general, we assume that the antiviral agents would be available from the start of the epidemic. We assumed that up to 80 percent of the index cases in households could be ascertained and that all of the other household members would receive prophylaxis. If the ascertained index case is also in a day-care center or playgroup, we ascertain up to 80 percent of these groups, and then the entire day-care center or playgroup would receive prophylaxis. If the index case is in a school, then 80 percent of the children in the school would receive prophylaxis. We also consider levels of less than 80 percent. In the model, 33 percent of unmodified influenza infections are asymptomatic. If the first infection in a mixing group is asymptomatic, then the prophylactic use of antiviral agents would not be triggered unless and until a later case in the mixing group were symptomatic.

Intervention effectiveness

The two measures of intervention effectiveness that we use are the average overall effectiveness (VE_{III}) (12) and the epidemic prevention potential (19). The VE_{III} is 1 minus the average attack rate in the intervention populations divided by the average attack rate in the nonintervention populations. The epidemic prevention potential is 1 minus the relative probability of an epidemic's occurring in the intervention populations compared with that in the nonintervention populations. We define an epidemic to be an influenza outbreak for which the overall attack rate is greater than 2.5 percent.

RESULTS

The simulator reproduces the typical epidemic curve observed for an influenza epidemic in a single population (figure 2). Table 1 gives the mean attack rates and 95 percent confidence intervals for the baseline epidemic for 200 stochastic simulations. Children have the highest attack rates, and the overall illness attack rate averages 33 percent (95 percent CI: 30, 37). We empirically calculated the basic reproductive number (R_0, the average number of new infec-

TABLE 1. Simulated baseline illness attack rates*

Age group (years)	Average illness attack rate	
	%	95% CI†
Children		
0–4	36	28, 46
5–18	62	57, 67
Adults		
19–64	25	21, 28
≥65	21	15, 27
Overall	33	30, 37

* Based on 200 simulations.
† CI, confidence interval.

tive persons that one infective person will produce in a particular completely susceptible population) (25, 26) (figure 3; Appendix). In our model, the empirical $R_0 = 1.7$ with a range of secondary cases from zero to 17.

Table 2 gives the intervention results. In the absence of any intervention, the model predicts that there would be 334 cases of influenza per 1,000 persons in the population (95 percent CI: 297, 370) and 0.6 influenza-related deaths per 1,000 persons in the population (95 percent CI: 0.4, 0.8). Targeted antiviral prophylaxis for up to 1 week per exposed person has a low VE_{III} of only 36 percent (95 percent CI: 20, 99) and an epidemic prevention potential of only 6 percent (95 percent CI: 3, 9). However, up to 1 week of targeted antiviral prophylaxis would still prevent an average of 122 cases/1,000 persons and save an average of 0.25 lives/1,000 persons. With up to 4 weeks of prophylaxis per person, the VE_{III} increases to 79 percent (95 percent CI: 38, 99), the epidemic prevention potential increases to 61 percent (95 percent CI: 50, 72), and the death rate would be cut to 0.11 deaths/1,000 persons (95 percent CI: 0.0002, 0.38). If exposed persons maintained prophylaxis for up to 8 weeks, then both the VE_{III} and epidemic prevention potential are quite high, and the death rate would be only 0.04 deaths/1,000 persons (95 percent CI, 0.0003, 0.25). A possible 6 weeks of targeted antiviral prophylaxis is almost as effective as a possible 8 weeks. Table 2 also gives results for vaccination. Targeted antiviral prophylaxis for up to 4 weeks has roughly the same overall effectiveness as vaccinating 50 percent of the entire population, although vaccination at this level has a much lower epidemic prevention potential. Targeted antiviral prophylaxis for up to 8 weeks has nearly as high an overall effectiveness as vaccinating 80 percent of the entire population, although vaccination at this level has a somewhat higher epidemic prevention potential. Vaccinating 80 percent of the children has nearly as high an overall effectiveness as vaccinating 80 percent of the entire population, although vaccinating 80 percent of the entire population has a much higher epidemic prevention potential than vaccinating 80 percent of the children.

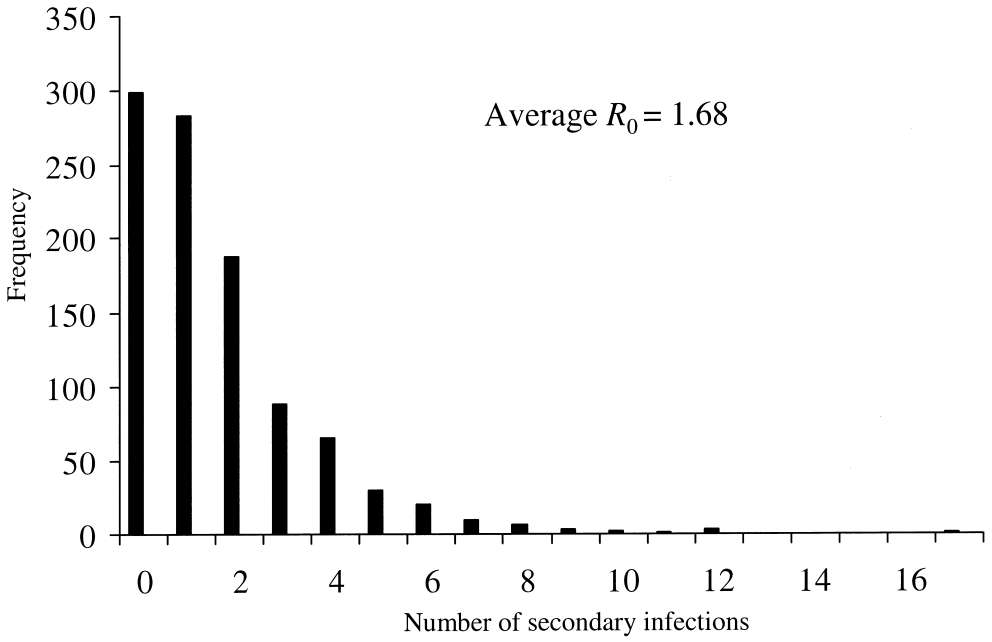

FIGURE 3. The basic reproductive number (R_0) for pandemic influenza. R_0 is defined as the number of secondary infections produced by a random infected person in a fully susceptible population. To calculate R_0, we assumed a scenario in which one randomly chosen, unvaccinated infected person was seeded into a population where everyone else's ability to transmit was 0 and then counted the number of secondary infections. This was repeated 1,000 times. The frequency is the number of times out of 1,000 that the given number of secondary cases occurred; for example, there were 0 secondary cases for 300 of the stochastic replications.

TABLE 2. Simulated influenza case and death rates and effectiveness of interventions*

Intervention	Cases (no./1,000 persons)		Deaths (no./1,000 persons)		VE_{III}† (%)		EPP† (%)	
	Mean	95% CI†	Mean	95% CI	Mean	95% CI	Mean	95% CI
None	334	297, 370	0.58	0.43, 0.75				
80% targeted antiviral prophylaxis								
1 week	212	5, 265	0.33	0.01, 0.48	36	20, 99	6	3, 9
2 weeks	150	3, 238	0.23	0.00, 0.42	55	28, 99	28	20, 35
4 weeks	71	2, 204	0.11	0.00, 0.38	79	38, 99	61	50, 72
6 weeks	36	3, 182	0.06	0.00, 0.31	89	45, 99	75	63, 86
8 weeks	23	2, 162	0.04	0.00, 0.25	93	51, 100	79	67, 91
Vaccination (% of population)								
30	189	148, 231	0.25	0.14, 0.37	43	30, 55	1	0, 1
50	77	3, 134	0.08	0.00, 0.17	77	60, 99	18	12, 23
80	6	1, 20	0.01	0.00, 0.03	98	94, 100	99	85, 100
Vaccination (% of children)								
50	154	8, 227	0.28	0.01, 0.45	53	31, 98	7	3, 10
80	22	4, 62	0.05	0.00, 0.15	93	81, 99	65	54, 76

* Based on 200 simulations.
† VE_{III}, overall effectiveness; EPP, epidemic prevention potential; CI, confidence interval.

We carried out a number of reduced targeted antiviral prophylaxis strategies. We found that targeting antiviral agents in just schools and preschools or just in families would not be very effective (results not shown here). We also found that much less than 80 percent targeted antiviral prophylaxis would not be very effective but still could result in modest reductions in influenza cases and deaths (results not shown here).

From table 3, we see that targeted prophylaxis for up to 1 week would result in 548/1,000 persons in the population using antiviral agents. However, the rate of persons using antiviral agents would decrease with the duration of prophylaxis. The 8-week strategy would result in a rate of 222/1,000 persons using antiviral agents. In terms of the number of cases prevented per person treated, the treatment efficiency of targeted antiviral prophylaxis increases with the duration of prophylaxis, with 1.4 cases prevented for each person remaining on prophylaxis for up to 8 weeks. Vaccination of children is the most efficient use of vaccine. Vaccinating 80 percent of the entire population would require 796 doses of vaccine per 1,000 persons and would prevent 0.4 cases of influenza per dose of vaccine, while vaccinating 80 percent of just children would require 203 doses of vaccine per 1,000 persons and would prevent 1.5 cases of influenza per dose of vaccine.

In the face of a pandemic or bioterrorist attack, persons would likely be motivated to nearly full compliance. However, we did carry out sensitivity analyses assuming that as many as 20 percent of persons that start antiviral prophylaxis would discontinue after 1 day. In this case, for up to 8 weeks of 80 percent targeted antiviral prophylaxis, the VE_{III} would be 74 percent, and the epidemic prevention potential would be only 26 percent. Thus, even with reduced compliance, targeted antiviral prophylaxis would still be relatively effective at containing influenza spread.

TABLE 3. Simulated rates of persons treated, doses, and cases prevented by intervention*

Intervention	No. treated/ 1,000 persons	No. of doses/ 1,000 persons	No. of cases prevented/ person treated
80% targeted antiviral prophylaxis			
1 week	548	3,672	0.2
2 weeks	444	5,868	0.4
4 weeks	321	7,732	0.8
6 weeks	256	7,754	1.2
8 weeks	222	6,923	1.4
Vaccination (% of population)			
30	299	299	0.5
50	498	498	0.5
80	796	796	0.4
Vaccination (% of children)			
50	128	128	1.4
80	203	203	1.5

* Based on 200 simulations.

TABLE 4. Simulated case and death rates with different levels of delay after the first symptomatic case in a close mixing group, with 80% targeted antiviral prophylaxis and up to 8 weeks of prophylaxis per person

Delay (days)	Cases (no./1,000 persons)		Deaths (no./1,000 persons)		VE_{III}* (%)		EPP* (%)	
	Mean	95% CI*	Mean	95% CI	Mean	95% CI	Mean	95% CI
1	23	2, 162	0.04	0.00, 0.25	93	51, 100	79	67, 91
2	41	6, 204	0.07	0.00, 0.34	88	38, 98	50	40, 59
3	69	10, 225	0.12	0.01, 0.41	79	32, 97	19	13, 24
4	122	45, 256	0.22	0.06, 0.52	63	23, 86	1	0, 1
5	182	91, 251	0.33	0.16, 0.52	45	24, 72	0	0, 0

* VE_{III}, overall effectiveness; EPP, epidemic prevention potential; CI, confidence interval.

In these simulations, we assumed that the initiation of targeted antiviral prophylaxis would begin 1 day after the first symptomatic illness, that is, the index case, in the close mixing groups. However, it may not be practical to get antiviral agents to exposed persons so quickly. We carried out a sensitivity analysis for delays ranging from 2 to 5 days after detection of an index case, with 80 percent targeted antiviral prophylaxis and up to 8 weeks of prophylaxis per person. Table 4 shows that, for a 2-day delay, the VE_{III} would be 88 percent (95 percent CI: 38, 98), and the epidemic prevention potential would be 50 percent (95 percent CI: 40, 59). The mean case and death rates would be 41 cases/1,000 persons (95 percent CI: 6, 204) and 0.07 deaths/1,000 persons (95 percent CI: 0.0022, 0.34), respectively. Thus, there still would be substantial reduction in morbidity and mortality compared with the baseline. The delay could be as great as 4 days while still realizing substantial benefits for targeted antiviral prophylaxis. However, the targeted antiviral prophylaxis strategy would begin to break down for delays of 5 days. The 80 percent targeted antiviral prophylaxis strategy fails to substantially prevent epidemics for 3-day delays (epidemic prevention potential = 19 percent), but it still has good overall effectiveness (VE_{III} = 79 percent).

To examine the extent to which the value of intervening for children is dependent upon their relative importance in spreading infection, we reduced the child-to-adult transmission probability within households by 50 percent and then recalibrated our model to yield the same target illness attack rates (given in table 1) by increasing the adult-to-adult disease transmission probabilities in the neighborhoods. When we did this, the effectiveness of 80 percent targeted antiviral prophylaxis went down slightly, that is, VE_{III} = 92 percent and epidemic prevention potential = 71 percent, compared with the values in table 2 of VE_{III} = 93 percent and epidemic prevention potential = 79 percent. The number of persons treated with antiviral agents stayed virtually the same. The effectiveness of the vaccination of children went slightly down.

DISCUSSION

Currently, manufacturing and distributing a vaccine to match a newly identified influenza strain would take 6–8 months (27). Thus, vaccine would unlikely be available for the first wave of pandemic influenza in the United States. No vaccine would be available in the case of a bioterrorist influenza attack. We have shown that targeted antiviral prophylaxis could have a significant effect on slowing influenza spread until a vaccine could be deployed for subsequent waves. Although vaccination would be the best means for controlling influenza, 80 percent targeted antiviral prophylaxis for a possible 6–8 weeks is almost as effective as vaccinating 80 percent of the entire population. However, 80 percent targeted antiviral prophylaxis would be somewhat less effective at preventing epidemics than would 80 percent vaccination. In addition, 80 percent targeted antiviral prophylaxis for up to 4 weeks would be almost as effective at containing epidemics as vaccinating 50 percent of the entire population. In the event that limited quantities of vaccine (i.e., fewer than 203 doses/1,000 persons) were available either prior to or during the first wave of a pandemic, it would still be important to carry out targeted antiviral prophylaxis for as many unvaccinated, exposed persons as possible. Even if supplies of antiviral agents were at a level that targeted antiviral prophylaxis could be given for only up to 1 week, millions of influenza cases would be prevented and thousands of lives would be saved.

Recently, surveillance and containment, that is, isolation of identified cases and quarantine of identified close contacts of those cases, were successfully used to contain the spread of severe acute respiratory syndrome (SARS) (28). This was possible because severe acute respiratory syndrome has a relatively long incubation period, with an estimated mean of 6.4 days (29), and it appears that nearly all of the cases were moderately to severely symptomatic and, thus, easy to identify (28). In contrast, influenza has a short incubation period, with a mean of 1.9 days, and with a full spectrum of clinical illness, ranging from asymptomatic to primary viral pneumonia (2). Thus, surveillance and containment would not likely be effective against influenza. However, the targeted antiviral prophylaxis strategy described here has some of the important elements of surveillance and containment, since influenza prophylaxis and treatment are dynamically targeted to where infection transmission is occurring.

We showed through a sensitivity analysis (table 4) that targeted antiviral prophylaxis must be initiated within 3 days of the detected illness of the index cases to be effective in slowing transmission. The effectiveness of targeted antiviral

prophylaxis would also be sensitive to the length of the latent and infectious periods. We have used distributions for the latent and infectious periods with means of 1.9 and 4.1 days, respectively, and with the distributions as shown in figure 1. If the mean latent period were shorter than 1.9 days, then targeted antiviral prophylaxis would be less effective. For example, if the mean were 1 day, then we would get results similar to the 2-day-delay row in table 4. In this case, targeted antiviral prophylaxis would still be quite effective. The pathogenicity of influenza is also important for the success of targeted antiviral prophylaxis since index cases need to be identified. We have assumed that 67 percent of infected persons would have recognizable influenza symptoms. If the pathogenicity were lower than this, then targeted antiviral prophylaxis would be less effective, and if higher, then more effective. Pathogenicity is difficult to define since there are many combinations of symptoms on which to form cutoff points defining an influenza illness. The 67 percent was based on a standard combination of symptoms derived from a number of population-level influenza cohorts from Seattle, Washington (20, 30), Tecumseh, Michigan (31), and Houston, Texas (32), where serologic, virologic, and symptomatic data were collected on the same persons during various influenza seasons.

We chose the epidemiology of 1957–1958 pandemic influenza A virus (H2N2) as the next possible pandemic strain or bioterrorist influenza agent. This was the most severe of the pandemic strains of the 20th century for which we have virologic data. Our model predicts that, if a similar strain of influenza A (H2N2) appeared in the current US population, the number of excess influenza-related deaths would have a mean of 164,000. This number is considerably higher than the 70,000 excess deaths estimated during the 1957–1958 influenza season because of the increased number of older and high-risk persons in the current population.

We calculated the basic reproductive number of $R_0 = 1.68$ for our baseline influenza A (H2N2) epidemic. We are not aware of any estimates of R_0 for the first wave of pandemic Asian influenza A (H2N2) in 1957, but statistical estimates of the reproductive number (R) from England and Wales (1958–1973), for a mixture of influenza types and subtypes, ranged from 1.4 to 2.6 (table 2 in the article by Longini (33)). In this case, the reproductive number is defined as the average number of infective persons that one infective person will produce in a particular partially susceptible population. Rvachev and Longini (34) estimated $\hat{R}_0 = 1.89$ from influenza case incidence data for the first wave of pandemic influenza A (H3N2) starting in July 1968 in Hong Kong. Given adjustments for smaller families and an older current US population, our modeled R_0 is consistent with past estimates.

The possible mass use of influenza antiviral agents raises concern about the emergence and spread of drug-resistant influenza viruses. As mentioned above, the frequency of resistance is much lower for prophylactic than for therapeutic use of these agents. In addition, the frequency of resistance is lower for the prophylactic use of rimantadine or neuraminidase inhibitors than for amantadine (3). Mathematical modeling has shown that prophylactic use of antiviral agents with the properties of neuraminidase inhibitors would probably lead to minimal community spread of resistant strains (35, 36). Thus, the neuraminidase inhibitors would be better to stockpile, followed by the less expensive rimantadine.

The community on which we based our simulations consists of 2,000 persons. The population is constructed to represent a cross-section of a typical American community. It represents the social connections that are responsible for the transmission of influenza, and it is not meant to be taken literally as a disconnected population. Since the influenza season generally lasts for about 4 months, usually between December and April of each year, actual epidemics occur in subpopulations and regions of the country at different times (31, 37). We have not attempted to model this pattern for the whole country (34, 38). If we assume that the epidemics spread to virtually the whole country with relative uniformity by the end of the season, then we can scale up our results to the US population of 281 million persons. This provides a rough guide to what quantities of influenza vaccine and antiviral agents could be needed. By scaling up the results in table 2, we calculate that there could be 93 million cases and 164,000 deaths due to the first wave of pandemic influenza in the United States. Given that vaccine were available, vaccination of 80 percent of the children in the entire country would require 57 million doses of vaccine (from table 3), but this would reduce the epidemic to just 6 million total cases and 15,000 total deaths in the country. Up to 8 weeks of targeted antiviral prophylaxis would be equally effective as vaccinating 80 percent of the children, but this would require 1.9 billion doses of antiviral agent.

Our results show that mass vaccination of 80 percent of the children could be 93 percent effective in containing pandemic influenza and 65 percent effective in preventing a pandemic, if an appropriate vaccine were available. This result is consistent with previous modeling results for pandemic Asian influenza A (H2N2) (20, 24). Vaccinating other age groups simply adds to the effectiveness of vaccinating children and should be carried out, but vaccination of children should be a high public health priority.

We have shown that intensive targeted antiviral prophylaxis on a large scale could effectively contain the first wave of pandemic or bioterrorist influenza until vaccine would be available for subsequent waves. In the above paragraph, we calculated the number of persons treated and the number of doses of antiviral agent that would be needed in the worst case scenario, where the entire country would uniformly experience substantial influenza transmission. However, targeted antiviral prophylaxis would be used only in those locations where influenza is found to be circulating. Thus, our totals represent an upper bound on the worst case scenario. Up to 8 weeks of prophylaxis per exposed person would require stockpiling a maximum of 1.9 billion doses of antiviral agents. Even if such quantities of stockpiling are unrealistically large, the use of a targeted antiviral prophylaxis strategy with whatever stocks were available would save many lives and constitute the most prudent use of influenza antiviral agents. We have not considered the costs of doing this (39), and a cost-effectiveness study is a subject of further research. A successful targeted antiviral prophylaxis strategy would require the identification of the index influenza cases in households, preschools, schools, and possibly other institutional

settings where targeted antiviral prophylaxis could be useful, such as nursing homes and the workplace. In addition, targeted antiviral prophylaxis would be an effective strategy for health care personnel, those with vital jobs, and first responders. Once suspected index cases were identified, the means for rapid delivery of antiviral agents would be required. Given that the logistic and financial details could be worked out, the targeted use of antiviral agents would be an important intervention tool for pandemic or bioterrorist influenza.

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APPENDIX

Simulation Model

The population

Populations of 2,000 persons are stochastically generated by the age distribution and approximate household size published by the US Census Bureau (19, 21, 22). A family is a group of up to seven persons living together with one or two adults. Each person in the population is assigned to a family within one of four neighborhoods, an age, an initial disease status indicator, and a vaccination status indicator. Preschool-aged children are assigned to either small playgroups or large day-care centers within their neighborhoods. Small playgroups have four children each, and there are between four and six small playgroups per neighborhood. Large day-care centers have, on average, 14 children. School-aged children are assigned to an elementary school, middle school, or high school on the basis of their age. Two neighborhoods share one elementary school, and all four neighborhoods share a middle school and a high school. Elementary schools have, on average, 79 children per school, middle schools have an average of 128 students, and high schools have an average of 155 students.

For the purposes of our simulator, the ages of children were assumed to be uniform over the intervals 0–4 years and 5–18 years of age. Young adults (19–64 years) and older adults (≥65 years) were also uniformly distributed within their respective age groups. On average, in each generated population, 6.92 percent were aged less than 5 years, 22.08 percent were 5–18 years, 58.48 percent were adults aged 19–64 years, and 12.52 percent were adults aged 65 or more years. The probability that a household has one person is 0.33; two persons, 0.34; three persons, 0.13; four persons, 0.10; five persons, 0.07; six persons, 0.02, and seven persons, 0.01. The probability that an adult, in a family with children, is 65 or more years is 0.02. The probability that an adult in a household without children is 65 or more years is 0.28. The probability that a two-person home has one child and one adult is 0.01. In the simulations in this paper, each population is generated with 12 initial infective persons chosen at random. When vaccination is considered, the initial infective persons are unvaccinated.

Influenza parameters

Many of the parameters used in the influenza simulation model were adopted from Elveback et al. (20) but further refined by Halloran et al. (19). Figure 1 shows the distribution of the latent and infectious periods. The probability that a person will be symptomatic given that person has been infected is 0.67. An asymptomatic infection is assumed to be 50 percent as infectious as a symptomatic infection. Additionally, this model allows for persons to withdraw from all of their mixing groups except the family unit if they become infected. Figure 1 also shows the probability of withdrawal as well as the distribution of the number of days before withdrawal given a person does withdraw from the mixing groups.

The household transmission probabilities in appendix table 1 are from previously published estimates (40, 41). The other transmission probabilities were chosen to calibrate the model

APPENDIX TABLE 1. Transmission probabilities among children and adults, by mixing group

Contact group	Children					Adults
	Preschool		School			
	Small playgroup	Large day-care center	Elementary	Middle	High	
Small playgroups	0.04					
Large day-care centers		0.015				
Elementary school			0.0145			
Middle school				0.0125		
High school					0.0105	
Family						
Child	0.08	0.08	0.08	0.08	0.08	0.03
Adult	0.03	0.03	0.03	0.03	0.03	0.04
Neighborhood	0.00004	0.00004	0.00012	0.00012	0.00012	0.00016
Community	0.00001	0.00001	0.00003	0.00003	0.00003	0.00004

to pandemic influenza in each age group (table 1) (23). The case fatality rates per 1,000 cases of influenza used were 0.0263 in young children, 0.0210 in older children, 0.2942 in young adults, and 19.9797 in older adults. These rates were derived using the mortality rates published by Thompson et al. (1) in combination with illness attack rate data.

The probability of infection for each susceptible person each day is based on the transmission probabilities for each potentially infectious contact. As an example, consider the simplest case that no one is vaccinated. An elementary school-child is exposed to the number of child and adult infective persons in his household, I_{hc} and I_{ha}; his school, I_s; his neighborhood, I_n; and the population, I_c, with corresponding transmission probabilities for each contact of p_{hcc} (child to child), p_{hac} (adult to child), p_s, p_n, and p_c, respectively. The probability P for that child to become infected on that day is

$$P = 1 - (1 - p_{hcc})^{I_{hc}}(1 - p_{hac})^{I_{ha}}(1 - p_s)^{I_s}(1 - p_n)^{I_n}(1 - p_c)^{I_c}.$$

A uniform [0, 1] random number is selected. If the number is less than P, the child becomes infected and enters the incubation (latent) phase.

If exposed persons have been given antiviral agents, the transmission probabilities are multiplied by θ, the relative susceptibility, where protective efficacy $AVE_S = 1 - \theta$. If an infected person is using an antiviral agent, then the transmission probability from that infected person to a susceptible person not using an antiviral is multiplied by ϕ, the relative infectiousness of infective persons. The antiviral efficacy for infectiousness is $AVE_I = 1 - \phi$. If a person using an antiviral agent is infected, then the probability that he will become ill is multiplied by ψ, the relative probability of illness given infection. Thus, the antiviral efficacy for illness given infection is $AVE_D = 1 - \psi$. In addition, if a person taking antiviral agents does become ill, then his duration of illness is 1 day less than if he had not taken an antiviral agent. If a person takes an antiviral agent after he is infected, then the AVE_I and AVE_D apply as above, from the time such use begins. We assume that $AVE_s = 0.30$, $AVE_I = 0.80$, and $AVE_D = 0.60$. For vaccination, we use arguments similar to those above to define vaccine efficacy for susceptibility, VE_S, and vaccine efficacy for infectiousness, VE_I. We assume that $VE_S = 0.70$ and that $VE_I = 0.80$ (16–19).

We have set many of the parameters of the model according to the extensive literature on influenza, estimates from field studies, and randomized influenza vaccine and antiviral agent trials.

Rather than use fixed values for many of these parameters, we could put prior distributions on them and then use Monte Carlo techniques such as Latin hypercube sampling (42) to add the uncertainty about parameters to the simulation output. However, such an approach is prohibitive given the current speed of our simulations (i.e., on the order of a minute per stochastic realization). We are working on methods for speeding up the simulations so that Monte Carlo methods can be implemented. Similarly, we are restricted to a maximum of 200 stochastic realizations per scenario because of the run time. We have found that we get roughly the same results for ranges of 50–1,000 realizations per scenario. Thus, 200 seems be adequate. The source code for the population generation and simulation is written in computer programming language C and will be made available to interested researchers upon request.

Basic reproductive number

The basic reproductive number, R_0, is defined as the average number of secondary infections produced by a randomly selected infected person in a fully susceptible population (25). For a heterogeneous population, it is the average of all the secondary cases that this randomly selected initial infective person would infect over all the mixing groups of which he/she is a part. If these mixing groups do not overlap, that is, form a partition, and if the model is deterministic, then R_0 is the dominant eigenvalue of the next generation matrix (25, 26). In a stochastic model, the calculation is more involved, and an approximation is analytically tractable only when the mixing groups form a partition (43). Our model has overlapping mixing groups and is stochastic; thus, the R_0 must be empirically calculated. We do this directly from the definition of R_0. To calculate R_0, we assumed a scenario in which one randomly chosen, unvaccinated infected person is seeded into a population where everyone else's ability to transmit is 0. We then count the number of secondary infections. This is repeated 1,000 times. In this way, we generate the whole distribution of secondary cases due to a randomly selected infected person (figure 3). The mean of this distribution is R_0.