Health Outcomes and Costs of Community Mitigation Strategies for an Influenza Pandemic in the United States

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Background. The optimal community-level approach to control pandemic influenza is unknown.

Methods. We estimated the health outcomes and costs of combinations of 4 social distancing strategies and 2 antiviral medication strategies to mitigate an influenza pandemic for a demographically typical US community. We used a social network, agent-based model to estimate strategy effectiveness and an economic model to estimate health resource use and costs. We used data from the literature to estimate clinical outcomes and health care utilization.

Results. At 1% influenza mortality, moderate infectivity (R_o of 2.1 or greater), and 60% population compliance, the preferred strategy is adult and child social distancing, school closure, and antiviral treatment and prophylaxis. This strategy reduces the prevalence of cases in the population from 35% to 10%, averts 2480 cases per 10,000 population, costs \$2700 per case averted, and costs \$31,300 per quality-adjusted life-year gained, compared with the same strategy without school closure. The addition of school closure to adult and child social distancing and antiviral treatment and prophylaxis, if available, is not cost-effective for viral strains with low infectivity (R_o of 1.6 and below) and low case fatality rates (below 1%). High population compliance lowers costs to society substantially when the pandemic strain is severe (R_o of 2.1 or greater).

Conclusions. Multilayered mitigation strategies that include adult and child social distancing, use of antivirals, and school closure are cost-effective for a moderate to severe pandemic. Choice of strategy should be driven by the severity of the pandemic, as defined by the case fatality rate and infectivity.

On 11 June 2009, the World Health Organization (WHO) determined that the spread of novel influenza A/H1N1 virus had become a pandemic [1]. By the end of October, the influenza A/H1N1 virus had likely infected millions in the United States and caused >1000 deaths [2]. To save lives once a pandemic virus reaches a US community, the stated goals of intervention are to decrease attack rates and delay new cases while awaiting distribution of a strain-specific vaccine, which could extinguish the spread but takes 6 months or more to become widely available [3]. This analysis evaluates the cost-effectiveness of mitigation strategies for a US community during this critical time.

Published models have predicted outcomes, such as influenza transmission, infection attack rates, and the cost effectiveness of vaccination strategies, but not comprehensive costs and benefits of specific influenza mitigation strategies, such as social distancing [4, 5]. Prior models have demonstrated the potential of both pharmacologic and nonpharmacologic interventions to lower attack rates and mortality [6–9]. Pharmacologic and nonpharmacologic interventions differ in both their costs and their effectiveness. Antiviral drugs, for example, involve pharmacy and distribution costs but could decrease attack rates, reduce the severity of illness

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Table 1. Definition of Terms Used in the Article

Term	Definition
Agent-based social network model	A type of model that follows individuals or groups (agents) throughout a network of social contacts based on rules for behavior. For this analysis, an infectious diseases transmission model is superimposed on this network model, and individuals transition between transmission states of the virus (eg, susceptible, latent, or infected) as they move through their contact network.
Social distancing	Strategies that aim to reduce contact frequency or intensity between persons to achieve reductions in transmission of the pandemic virus.
Child social distancing	A strategy in which nonschool, nonhousehold contacts between children are reduced by compliance (30%, 60%, or 90%). Household contacts of children double to account for more time spent at home.
Adult social distancing	A strategy in which businesses stay open but work contacts between adults is reduced by 50%. Nonhousehold, nonwork contacts between adults are reduced by compliance (30%, 60%, or 90%). Household contacts double for adults whose work is reduced.
Household quarantine	A strategy in which all nonhousehold contacts of symptomatic cases are reduced by compliance (30%, 60%, or 90%). Accordingly, household contacts then double.
School closure	A strategy that closes schools and reduces school contacts by 90%, after which household contacts for children then double.
Antiviral treatment	A strategy in which patients with diagnosed cases (80% of symptomatic individuals) are given an antiviral within 48 h of symptom onset at a probability of 30%, 60%, or 90%, depending on the compliance scenario, for 5 days.
Antiviral prophylaxis	A strategy in which the household contacts of patients with diagnosed cases are given an antiviral for prophylaxis immediately after diagnosis for 10 days with a probability of 30%, 60%, or 90% depending on the compliance. This strategy is assumed conducted in parallel with the treatment of case patients.
Alternate care site	In times of surging hospital demand, an alternative site other than a traditional hospital where medical care is provided.
Generation time	The average length of time it takes for a virus to go from initial infection of one individual to the initial infection of the next individual.
Basic reproductive number (R_o)	The average number of secondary cases that a typical case patient will cause in a fully susceptible population. This is frequently referred to in the text as "infectivity"
Quality-adjusted life-years (QALYs)	A measure of health outcome that accounts for both mortality and morbidity of disease states and associated therapies. QALYs are estimated by assigning to each period of time a weight, ranging from 0 to 1, corresponding to the quality of life during that period, in which a weight of 1 corresponds to perfect health and 0 corresponds to death.
Incremental cost effectiveness ratio (ICER)	The ratio of incremental cost to incremental effectiveness (typically in QALYs) for a given strategy as measured against a comparator strategy.

and rates of hospitalization, return people to work earlier, and lower mortality [6, 7, 10]. Nonpharmacologic strategies are less costly upfront, but they have higher nonmedical costs, such as lost income. They could also reduce attack rates and lower peak mortality rates, as suggested by mathematical models and historical analysis of the 1918 pandemic [6, 9, 11–14].

We evaluated the health outcomes, costs, and cost-effectiveness of antiviral and social distancing strategies that would likely be effective and available to a typical US community during an influenza pandemic. Specifically, we compared combinations of adult social distancing, child social distancing, school closure, household quarantine, antiviral treatment, and antiviral household prophylaxis. To do this, we extend results of detailed community-based simulation studies that include the interactions of community members within social networks to determine the effectiveness and cost of community containment strategies.

METHODS

We developed a model of influenza severity, health care utilization, and costs to use in conjunction with results from an agent-based, social contact network model developed by Sandia National Laboratories and published previously by Davey and Glass [6, 9, 15]. Our analysis evaluates 6 interventions that can be combined into 48 distinct strategies. Important terminology used in this article, including strategy definitions, are described in Table 1.

A schematic representation of the analysis is shown in Figure

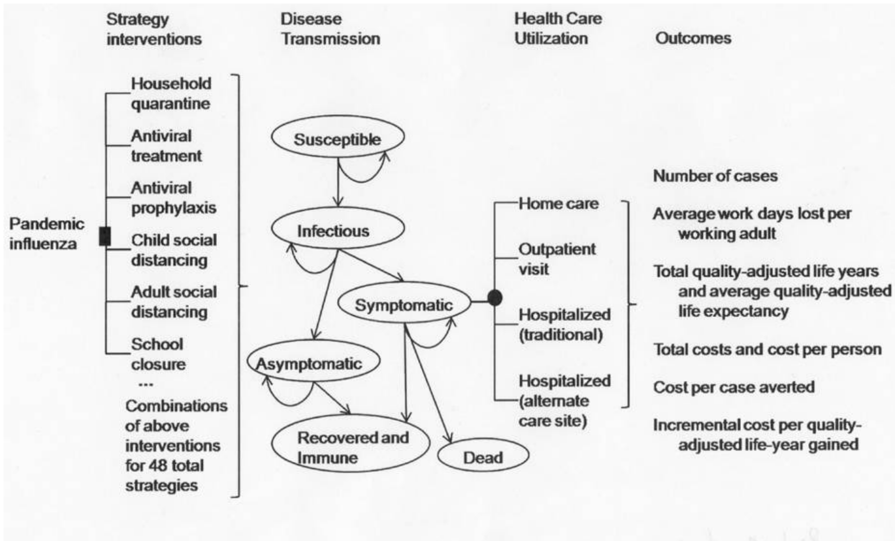

Figure 1. Schematic representation of decision analysis for community mitigation of pandemic influenza. The black box mode represents the choice of strategy for the community to mitigate pandemic influenza. The third column (disease transmission) shows an overview of the viral transmission states of persons in the population, including susceptible and infected (which either progress to symptomatic cases or remain asymptomatic), followed by recovery with immunity or death. Symptomatic case patients transition at a certain probability based on disease severity to various levels of health resource utilization (fourth column), such as outpatient visits and hospitalization. The straight lines in the transmission model (second column) and black circle represent probabilities of moving between 2 health (or transmission) states.

1. The analysis begins with the choice of strategy implemented by the community for mitigation of an influenza pandemic. For the base case assumptions, we assume all interventions are initiated at the same time in the evolution of the pandemic, once 10 persons (0.001% of the population) have become symptomatic. After a strategy is selected and the pandemic is underway, the model transitions individuals between viral transmission states (eg, susceptible, infected, and immune). Symptomatic persons transition to mild, moderate, or severe disease states (determining their need for hospitalization). If the disease state is severe, hospital capacity is then determined, and the individual transitions to either an available hospital bed or an alternative care site with associated costs and outcomes. Every symptomatic individual (case patient) eventually recovers from the disease or dies.

The agent-based, social network model assesses the spread of pandemic influenza by simulating contacts between persons within a large number of specific groups (eg, household, school classes, play groups, and adult work groups), each with realistic contact networks. Strategies are implemented on the basis of modifications to behavioral rules between individuals in the community and transmission rules (with the use of antivirals) for the disease. Strategies are rescinded after 2 generation times pass without newly diagnosed cases, according to supportive analysis by Davey et al [16]. Infectivity assumptions were based on previous work by Ferguson et al [7, 17] that matches data on viral shedding. The model emphasizes transmission among and from the young (making it more likely that children will become infected and infect others) and yields age-specific attack rates that are reflective of past epidemics [9].

This model analyzes the spread of influenza within a community of 10,000 people centered on a school system. These results are applicable to larger populations as long as the entire assumed community has similar demographic characteristics, contact networks, and contact rates; is similarly seeded with infected individuals; and implements the same strategies. Additional model details can be found in the Appendix, which appears only in the online version of the journal, and in Davey et al [6] and Glass et al [9].

The disease progression and economic model uses the average output over 100 simulations for the number of individuals infected, symptomatic, or receiving antivirals for treatment or prophylaxis and the number of work days lost resulting from the agent-based social network model. It then estimates the effects of case fatality rates, health resource utilization, and health state utility preferences to report overall effectiveness and costs. We adopted the recommendations of the Panel on Cost-Effectiveness in Health and Medicine for conducting and reporting a reference-case analysis from the societal perspective [18]. We gathered data about influenza disease progression, medical resource utilization, costs of treatment, and health state preferences by reviewing clinical studies from the peer-reviewed literature identified by searching the Medline database for the period from January 1966 through April 2009.

Base-case estimates and ranges tested in sensitivity analysis are shown for key clinical probabilities, disease parameters, and costs listed in Table 2. We estimated the cost of school closure on the basis of the assumption that lost school days would be made up during the typical 3-month summer break. We modeled hospital resource utilization, including the possibility of surge capacity for periods in which a high volume of case patients present to the health care system (described in Table 2). Our methods for calculating the cost of school closure and hospital resource utilization are further described in detail in the Appendix, which appears only in the online version of the journal.

We assumed that the sole antiviral agent used in the base case is oseltamavir, but we include the cost of zanamivir within the range tested for our sensitivity analyses. We assumed that antivirals reduce infectivity by 60% if given to a case patient [7, 19], reduce an individual's susceptibility to disease (if given prophylactically) by 30% [7, 19], and decrease the likelihood that an infected individual will experience progression to symptomatic disease by 65% [20–22]. We tested antiviral efficacy in sensitivity analysis by scaling these estimates down to 25% of their base case values. Given the possibility that antivirals will

Table 2. Estimates for Clinical Probabilities, Disease and Model Parameters, and Costs in the Decision Model

Variable	Value (range)	Reference(s)
Clinical probabilities		
Mortality from influenza-related illness or complications	0.01 (0.0025–0.05)	[26–28]
Excess mortality if need hospitalization but get alternative care site	0.01 (0–0.02)	Assumed
Scaling factor for antiviral effectiveness in reducing infectivity, reducing susceptibility and reducing probability of symptomatic disease (as compared to base case assumptions)	1.00 (0.25–1.00)	Assumed
Complications from antiviral treatment (nausea and vomiting)	0.10 (0.03–0.15)	[29]
Complications from antiviral prophylaxis	0.07 (0.02–0.10)	[29]
Risk reduction in mortality rate if treated with oseltamivir	0.00 (0–0.50)	Assumed
Days of usual health gained per case treated with oseltamivir	2.18 (1.26–2.64)	[30]
Days of work gained per case treated with oseltamivir (unless other social distancing strategies are imposed)	2.00 (0.25–2.2)	[30]
Medical care utilization		
Probability of hospitalization per symptomatic person	0.04 (0.01–0.10)	[28]
Probability of hospitalization prior to death	0.80 (0.5–1.00)	[31]
Hospital beds per capita	2.8 (2.0–4.0)	[32]
Hospital bed occupancy at the start of pandemic	0.80 (0.65–0.90)	Assumed
Proportion of initial hospitalized persons (not influenza cases) able to be discharged early at start of pandemic	0.25 (0–0.50)	[33]
Proportion increase in total beds in first 24 h of identified pandemic (surge capacity)	0.25 (0–0.50)	[34]
Risk reduction for hospitalization per symptomatic person with oseltamivir treatment	0.60 (0.3–0.9)	[10]
Likelihood of outpatient provider visit per symptomatic person	0.40 (0.12–0.60)	[28]
Disease and model parameters		
Population compliance, %	60 (30–90)	Assumed
R_0	2.1 (1.5–2.6)	[9, 17]
Population symptomatic before mitigation strategies implemented, %	0.1 (0.1–1)	[14, 15]
Costs, 2009 US$		
Outpatient visit to any medical site	260 (0–360)	[28]
Hospitalization (with survival)	23,670 (17,760–29,600)	[28]
Hospitalization (with influenza-related death)	79,900 (1,000–99,000)	[28]
Alternative care site cost as percentage of hospitalization cost	0.20 (0.05–1.00)	Assumed
Oseltamivir treatment per day	9.40 (5.70–16.20)	[35]
Oseltamivir prophylaxis per day	5.20 (3.60–8.60)	[35]
Antiviral dispensing cost (per course)	10 (7.5–12.5)	[36]
Median daily wage rate	208 (150–250)	[37]
Cost per student for each day of school missed (up to 64 maximum days)	19.00 (12.00–35.00)	Calculated
Health state utility values		
Age-adjusted average utility value for susceptible and recovered persons (per day)	0.93 (0.8–1.0)	[38]
Influenza, mild symptoms (for average of 7 days)	0.52 (0.28–0.93)	[39]
Influenza, severe symptoms (for average of 7 days)	0.05 (−1.0 to 0.93)	[40]

be ineffective during a pandemic, we also reported results for a subset of strategies consisting of social distancing interventions only. We assumed equal efficacy for oseltamivir and zanamavir, as supported by systematic reviews [20, 21].

Our results are expressed in clinical cases averted, deaths averted, total costs, total quality-adjusted life-years (QALYs), cost per case averted, cost by type of expenditure, and incremental cost-effectiveness ratios (ICERs) to society. We assumed population compliance of 60% for base case results and compared incremental costs and QALYs with a strategy of "do nothing" or the next best alternative. The base year for the analysis was 2009. We inflated all medical costs to 2009 using the gross domestic product deflator and discounted all costs and health effects at an annual rate of 3% [23].

RESULTS

Health outcomes. The number of cases, health outcomes, use of antivirals, and costs vary substantially between strategies (Table 3 and Figure 2). In general, strategies that use only 1 intervention are not as effective as strategies that combine interventions. The most cost-effective single intervention is the use of antivirals for treatment and prophylaxis (Figure 2). The single interventions of antiviral treatment and of adult and child social distancing each improve health outcomes and reduce total expenditures. School closure alone is somewhat effective but is associated with substantially higher costs than is the comparator strategy of "do nothing." The most effective strategy is adult and child social distancing, antiviral treatment and prophylaxis, and school closure, which resulted in the percentage of case patients in the population decreasing from 35% to 10% and the prevention of 2480 cases in a community of 10,000 persons. The effectiveness of this strategy is not significantly improved by adding household quarantine (which is, however, associated with additional costs). If antiviral drugs are either unavailable or ineffective, the most effective strategy is adult and child social distancing with school closure, which reduces the percentage of case patients to 22% of the population and averts 1340 cases in a population of 10,000.

Costs and cost-effectiveness. In the base case scenario, a strategy of adult and child social distancing, school closure, and antiviral treatment and prophylaxis costs $1250 per community member. This results in an average quality-adjusted life expectancy of 20.207 years per community member, for a cost of $2700 per case averted and a cost per QALY gained of $31,300 over the same strategy, not including school closure (Table 3 and Figure 2). This second strategy, adult and child social distancing with antiviral treatment and prophylaxis, costs $420 per community member and results in an average quality-adjusted life expectancy of 20.180 years, for a cost per case averted of $1600. If antivirals are not available or are not effective, a strategy of adult and child social distancing and school closure is most effective, resulting in an average quality-adjusted life expectancy of 20.182 years, at a cost per community member of $1400, a cost per case averted of $4200, and a cost per QALY gained of $40,800, relative to a strategy of adult and child social distancing.

The total costs and relative importance of the components of cost vary by strategy. In general, antiviral costs are a small proportion of total costs. The largest components of the most effective strategies (multilayered) are attributable to work days lost, primarily by parents of students whose schools are closed, and the direct costs of school closure. For example, total costs for the strategy of adult and child social distancing, antiviral treatment and prophylaxis, and school closure are $12.4 million (for a community of 10,000 persons), with 74% of the cost originating from work days lost, 15% from the direct costs of closing schools, 1% from the use of antivirals, and 10% from medical expenditures (Appendix Figure A2, which appears only in the online version of the journal).

Sensitivity analyses. The variables that most influenced the results were the infectivity (R_o), case fatality rate, level of population compliance, and antiviral effectiveness. In Figure 3, we report the ICERs for the strategy of adult and child social distancing, antiviral treatment and prophylaxis, and school closure, compared with a similar strategy that does not include school closure, for combinations of case fatality rates, infectivity (R_o), and population compliance. For a severe virus (R_o of 2.1) with an associated case fatality rate of 0.05% or higher, the addition of school closure was cost-effective at a threshold of <$100,000 per QALY gained. For a low-infectivity virus (R_o of 1.6) and case fatality rate of 0.5% or less, school closure costs >$85,000 per QALY at any level of compliance. Low (30%) compliance is associated with greater costs for fewer life-years gained, leading to high incremental cost per QALY gained under all ranges of infectivity and case fatality. In general, higher compliance lowers the incremental cost per life-year gained for closing schools. The exception was for mild pandemics (R_o of 1.6), in which the incremental cost per life-year gained began to increase again for the highest compliance of 90%, suggesting that the marginal cost of closing schools during a very mild pandemic outweighs the gain in QALY.

Regarding the sensitivity to antiviral effectiveness, we found the relative effectiveness and preference for specific strategies did not change as antivirals became less effective. When antivirals were ineffective, the most effective single strategy became adult and child social distancing and school closure, although again with much higher costs for school closure than for the other single interventions. Total costs for all strategies did increase as antivirals were less able to mitigate the virus (higher medical costs), and greater dependence on social distancing strategies conferred higher numbers of lost work days. At 25% of the assumed antiviral efficacy in the base case, the preferred

Table 3. Clinical and Cost-Effectiveness Outcomes in the Event of a Pandemic for Key Strategies at 60% Compliance

Strategy	No. (%) of cases[a]	No. of cases averted[a]	AV courses, % of population	No. of work days lost per worker	Total cost, US$ per person	Cost, US$ per case averted	QALE	ICER, US$ per QALY
R_o of 2.1 and case fatality rate of 1%								
Adult and child SD, school closure, AV treatment and prophylaxis	1031 (10)	2480	16	9.8	1250	2700	20.207	31,300
Adult and child SD, school closure	2175 (22)	1340	…	9.7	1400	4200	20.182	Dominated
Child SD, school closure, AV treatment and prophylaxis	1471 (15)	2040	23	9.2	1250	6100	20.197	Dominated
Adult and child SD, AV treatment and prophylaxis	2276 (23)	1240	36	1.2	420	1600	20.180	Dominated
AV treatment and prophylaxis	2614 (26)	900	39	1.3	420	3700	20.173	Dominated[b]
Adult and child SD	3212 (32)	300	…	1.6	490	5600	20.159	Dominated[b]
Quarantine	3317 (34)	200	…	3.9	720	15,300	20.158	Dominated[b]
AV treatment	3250 (32)	260	16	1.7	460	18,200	20.159	Dominated[b]
School closure	3169 (33)	350	…	8.4	1330	32,100	20.161	Dominated
Do nothing	3515 (35)	…	…	1.8	540	…	20.153	Dominated[b]
R_o of 1.6 and case fatality rate of 0.25%								
Adult and child SD, school closure, AV treatment and prophylaxis	251 (3)	2210	4	9.9	1140	5140	20.227	156,200
Adult and child SD, school closure	560 (6)	1900	…	12.1	1370	7210	20.225	Dominated
Child SD, school closure, AV treatment and prophylaxis	410 (4)	2050	7	10.3	1180	5770	20.226	Dominated
Adult and child SD, AV treatment and prophylaxis	1280 (13)	1175	22	0.7	180	1540	20.221	Dominated
AV treatment and prophylaxis	1620 (16)	840	26	0.8	210	2490	20.219	Dominated[b]
Adult and child SD	2200 (22)	260	…	1.1	290	11,270	20.215	Dominated[b]
Quarantine	2240 (22)	220	…	2.8	510	23,350	20.215	Dominated[b]
AV treatment	2085 (21)	375	10	1.1	260	6830	20.216	Dominated[b]
School closure	1480 (15)	975	…	12.8	1510	15,460	20.220	Dominated
Do nothing	2460 (25)	…	…	1.2	380	…	20.214	Dominated[b]

NOTE. AV, antiviral; ICER, incremental cost-effectiveness ratio; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life-year; R_o, basic reproductive number; SD, social distancing.

[a] Based on population of 10,000 persons.

[b] By extended dominance.

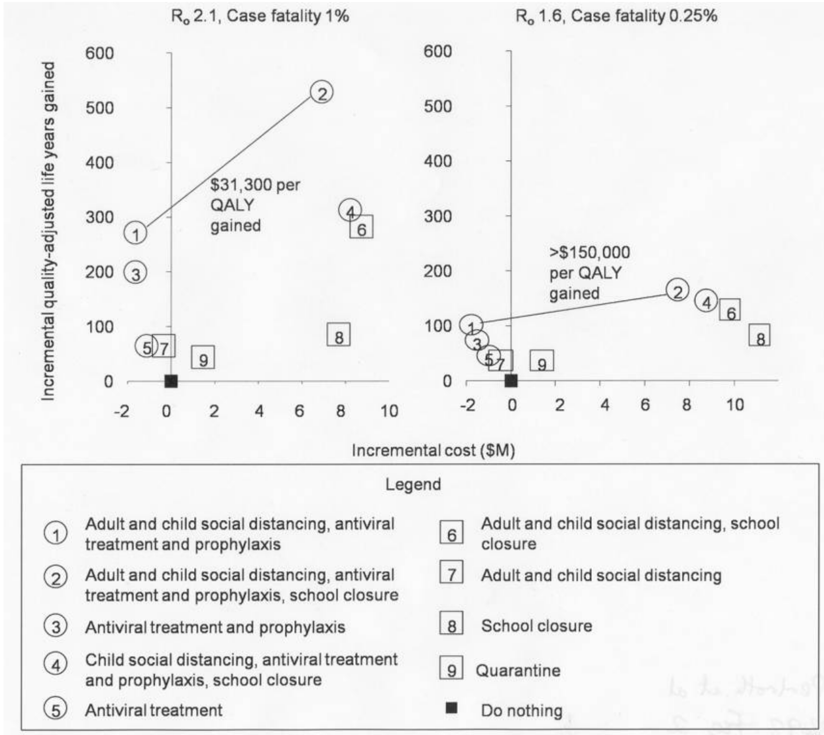

Figure 2. Incremental costs and quality-adjusted life-years (QALYs) of key strategies at 60% population compliance. *A,* results for a severe pandemic with R_o of 2.1 and case fatality rate of 1%. *B,* results for a milder pandemic with R_o of 1.6 and case fatality rate of 0.25%. The incremental cost-effectiveness ratios (US$ per QALY gained) are shown for the comparison of the preferred strategies connected by a solid black line.

strategy remained either adult and child social distancing with antiviral treatment and prophylaxis for a total cost of $4.9 million (compared with $4.2 million in the base case) or a similar strategy that included school closure at $13.75 million (compared with $12.50 million) for a population of 10,000 persons. This resulted in an incremental cost per QALY gained of $38,800 for adding school closure to a strategy of adult and child social distancing and antiviral treatment and prophylaxis. Results were robust in sensitivity analyses to other model variables (Appendix Table A1, which appears only in the online version of the journal).

DISCUSSION

We used results from a detailed community-based simulation model of influenza transmission along with a model of disease severity, utilization, and costs to assess the outcomes of influenza mitigation strategies. Four important findings emerge. First, mitigation strategies with multilayered interventions are the most effective and are generally cost-effective for case fatality rates >1% at all levels of infectivity (R_o) tested. Second, the preferred policy choice considering cost and outcomes should be based on the severity of the influenza pandemic, as defined by the infectivity and case fatality rate. Third, the most expensive strategy, school closure, is cost effective unless the pandemic is of low severity (case fatality rate <1% for R_o of 1.6 or less, or case fatality rate <0.025% for R_o of 2.1 or greater). Finally, increasing compliance with social distancing and antiviral strategies for moderate-to-severe pandemics (R_o of 2.1 or greater) can substantially reduce total costs to society.

If compliance is high, strategies with multilayered interventions are more effective and cost less for moderately severe pandemics, compared with strategies that use a single intervention. The severity of the pandemic has a critical influence on the effectiveness and cost effectiveness of mitigation strategies. For low-severity pandemics with case fatality rates <0.5% and R_o of 1.6 or below, such as the current influenza A/H1N1 pandemic, the preferred policy choice suggested by our analysis is a combination of adult and child social distancing with the use of antivirals for treatment and prophylaxis to the extent available to the community. For moderately severe pandemics, such as the 1918 influenza pandemic (R_o of 2.1 or greater), our results indicate that it would be cost-effective to close schools and that higher population compliance would lower costs and increase effectiveness substantially. Moreover, household quarantine, either alone or in addition to the preferred strategy, was not cost-effective if antivirals were effective.

The mortality rate and infectivity of the 2009 influenza A/H1N1 epidemic remain uncertain, but initial estimates from Mexico indicated a case fatality rate of 0.4% and R_o of 1.4–1.6 [24]. At this level of severity, school closure alone is modestly

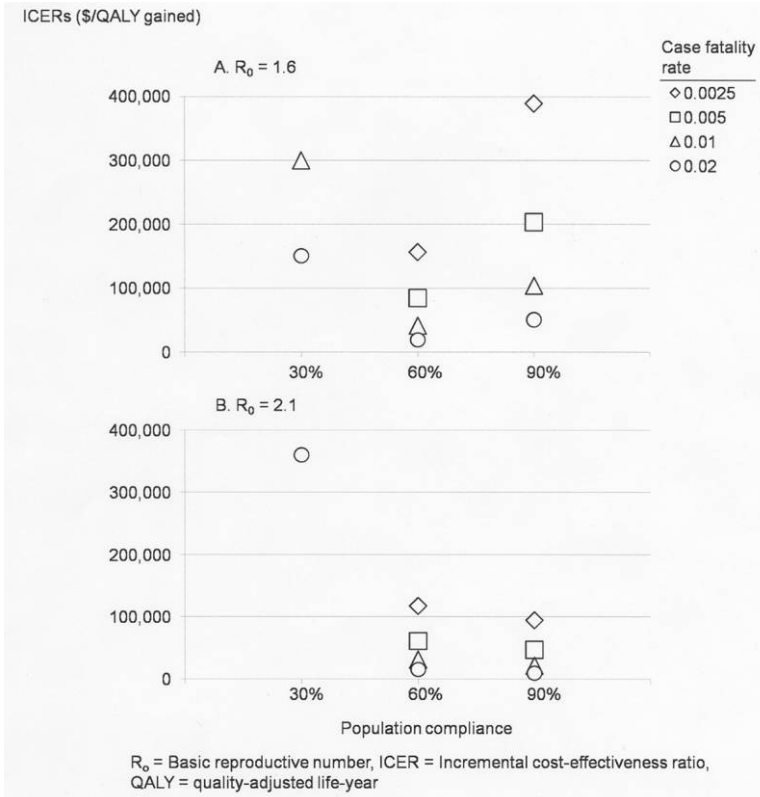

Figure 3. Incremental cost-effectiveness ratios (ICERs) for school closure in the event of pandemic influenza, based on infectivity (R_o), case fatality rate, and population compliance. The ICER (difference in costs divided by the difference in quality-adjusted life-years gained) between the strategy of adult and child social distancing and antiviral treatment and prophylaxis with and without school closure is shown. The R_o is 1.6 for *A* and 2.1 for *B*. The case fatality rate (0.25%, 0.5%, 1%, and 2%) is represented by unique symbols according to the legend in the upper right hand corner. The population compliance (30%, 60%, and 90%) increases along the horizontal axis. Only case fatality rates with ICERs <$400,000 are shown. This excludes case fatality rates of 0.5% and above for R_o of 2.1, and 1% and above for R_o of 1.6 (ICERs ranged up to $2.4 million).

effective but would cost almost $300,000 per QALY gained. A strategy of adult and child social distancing and antiviral treatment and prophylaxis, if available, is cost saving under this scenario, achieving 62 additional QALYs and saving $90 per person. There are at least 2 important caveats to these conclusions. First, we did not evaluate limiting closures to schools with identified cases for brief periods, as was done in the United States in the early stages of the 2009 A/H1N1 outbreak. Second, our analysis assumes that child social distancing is essentially without cost and that children outside of school simply do not gather and play (eg, in parks, libraries, or private homes), and it assumes that adult social distancing does not involve workplace closure but rather would achieve modest contact reductions at work. This might occur through the substitution of video or teleconferencing for direct meetings, working from home when possible, and reduced "face time" at the office. In practice, such measures may incur costs that we did not capture.

Lost work days account for a substantial portion of the costs for strategies, including school closure, that effectively mitigate a moderate-to-severe pandemic. The burden of lost income to the individual that results from these strategies could dramatically lower compliance, unless mitigated by income replacement provisions. The cost of these provisions, however, would likely be offset by substantially lower mortality rates and health care costs. Compliance with social distancing strategies, such as school closure, could be substantially increased by finding ways to limit the lost income resulting from individuals spending time at home.

Our analysis is subject to important qualifications. First, the model is most applicable to suburban communities centered on schools with an age and sex make-up matched to the overall US average. Our results may not apply to dense urban populations, in which mixing, patterns of contact, and demographic characteristics may be different. However, the underlying model and its contact assumptions have been validated by studies that show that it accurately fits the spread of influenza observed in previous pandemics [9]. Second, the implementation of nonpharmacologic strategies depends on the ability of communities to reach assumed levels of contact reduction, which may be difficult for some locales. Communities where the population relies heavily on employment in service industry jobs may find it difficult to decrease work contacts by 50%. Third, antivirals may not be distributed to the target populations in time to be most effective. Fourth, we did not consider long-term outcomes, such as the future health expenditures and economic productivity of survivors. Finally, as in other cost-effectiveness analysis, intangible costs, such as the avoidance of a much-feared outcome (illness from pandemic influenza) and multiplier effects to the local or regional economy from lost income, were not included.

Although federal agencies have advocated the use of social distancing to mitigate pandemic influenza, it is unknown when these strategies become cost-effective to society [3, 25]. We find that, for an influenza pandemic with moderate severity (R_o of 2.0 or greater and case fatality rate >1%), the most cost-effective strategy is multilayered. It involves a combination of adult and child social distancing, school closure, and antiviral treatment and prophylaxis, if available. For mild pandemics (such as the 2009 H1N1 pandemic as experienced to date within the United States), we find that a multilayered strategy of adult and child social distancing and antiviral treatment and prophylaxis is effective and cost-effective but that the addition of school closure is relatively expensive because of lost work days for adults who stay at home with children. The preferred mitigation response to a pandemic thus greatly depends on its severity.

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