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Economic Evaluation of Influenza Pandemic Mitigation Strategies in the United States Using a Stochastic Microsimulation Transmission Model

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ABSTRACT

Objectives: To project the potential economic impact of pandemic influenza mitigation strategies from a societal perspective in the United States.
Methods: We use a stochastic agent-based model to simulate pandemic influenza in the community. We compare 17 strategies: targeted antiviral prophylaxis (TAP) alone and in combination with school closure as well as prevaccination.
Results: In the absence of intervention, we predict a 50% attack rate with an economic impact of $187 per capita as loss to society. Full TAP (FTAP) is the most effective single strategy, reducing number of cases by 54% at the lowest cost to society ($127 per capita). Prevaccination reduces number of cases by 48% and is the second least costly alternative ($140 per capita). Adding school closure to FTAP or prevaccination further improves health outcomes but increases total cost to society by approximately $2700 per capita.
Conclusion: FTAP is an effective and cost-saving measure for mitigating pandemic influenza.
Keywords: computer simulation, cost–benefit analysis, economics, human disease outbreaks, influenza, pharmaceutical models, theoretical.

Introduction

Influenza pandemic preparedness is a public health priority in light of the global epidemic of highly pathogenic H5N1 influenza infection in avian populations. Recent epidemiological models have explored various mitigation strategies for pandemic influenza in the United States. This research has shown the likely effectiveness of targeted antiviral use, low-efficacy vaccines, and nonmedical interventions such as school closure, case isolation, and household quarantine in reducing peak or cumulative illness attack rates, even for highly transmissible viruses [1,2]. Further modeling work highlights the importance of targeted antiviral use and social distancing measures [3], and has helped inform the US pandemic influenza plan [4].

Nevertheless, an important missing component is a cost-effectiveness analysis of proposed mitigation strategies [5]. Many economic evaluations of interpandemic influenza programs do not take into account the dynamic, nonlinear effects of interventions in infectious diseases, likely underestimating the cost-effectiveness of interventions [6].

Our objective was to evaluate the cost utility of alternative pandemic influenza mitigation strategies in the United States from the societal perspective using a stochastic, individual-level, microsimulation model [7]. We examined the cost utility of targeted antiviral prophylaxis (TAP), school closure, and prevaccination with low-efficacy vaccines. The time horizon of the analysis was 6 months, which reflects the time until a fully matched vaccine would be available in sufficient quantities to effectively protect the population. To our knowledge, this is the first economic evaluation of influenza pandemic mitigation strategies based on a dynamic influenza transmission model. The research also expands on current epidemiological models by incorporating severity of influenza illness, complications, mortality, and quality of life.

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Methods

Strategies

This article focuses on strategies that were shown to be the most promising ones in previously published influenza pandemic models [1,3,7]. We compared the economic impact of no intervention with 16 single and combination strategies (Table 1). Single prophylactic strategies included prevaccination, antiviral post-exposure prophylaxis (in combination with treatment of the index case), and school closure. TAP included household-only prophylaxis [household targeted antiviral post-exposure prophylaxis (HTAP)], and prophylaxis in the full set of contact groups for an index case [full targeted antiviral post-exposure prophylaxis (FTAP)]. Oseltamivir stockpiles in varying quantities were assumed to be available from the start of a pandemic, ranging from covering 25% of the total population (a single course of oseltamivir, one pack, consists of 10 capsules, enough for 5 days of treatment or 10 days of postexposure prophylaxis) to an "unlimited" stockpile (i.e., as much as needed). TAP was carried out by treating identified index cases (the first symptomatic illness in a contact group) and offering post-exposure prophylaxis to contacts of these index cases in households, neighborhood clusters, large day-care centers, small playgroups, schools, and workgroups. We assumed that 60% of symptomatic index cases could be ascertained [8]. We also

Table 1 Description of interventions

Intervention	Description
No intervention	No prevaccination, prophylaxis or treatment with antivirals
HTAP25	Household targeted antiviral prophylaxis, stockpile for 25% of population
HTAP50	Household targeted antiviral prophylaxis, stockpile for 50% of population
HTAP	Household targeted antiviral prophylaxis, stockpile unlimited
FTAP25	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile for 25% of population
FTAP50	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile for 50% of population
FTAP	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile unlimited
Prevaccination	Prevaccinating 70% of population with low-efficacy vaccine
School closure	Closing all schools for 26 weeks
HTAP25 + school closure	Household targeted antiviral prophylaxis, stockpile for 25% of population, plus closing all schools for 26 weeks
HTAP50 + school closure	Household targeted antiviral prophylaxis, stockpile for 50% of population, plus closing all schools for 26 weeks
HTAP + school closure	Household targeted antiviral prophylaxis, stockpile unlimited, plus closing all schools for 26 weeks
FTAP25 + school closure	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile for 25% of population, plus closing all schools for 26 weeks
FTAP50 + school closure	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile for 50% of population, plus closing all schools for 26 weeks
FTAP + school closure	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile unlimited, plus closing all schools for 26 weeks
Prevaccination + school closure	Prevaccinating 70% of population with low-efficacy vaccine, plus closing all schools for 26 weeks
Treatment only	Treating all cases with antivirals

evaluated a treatment-only strategy, i.e., only individuals with symptomatic illness are treated with antivirals.

Prevaccination assumes that 70% of the population are successfully vaccinated with a low-efficacy vaccine, before the outbreak of a pandemic. We also considered school closure as a measure of social distancing alone, or in combination with pharmaceutical interventions. We modeled the impact of closing schools for the duration of the pandemic (26 weeks).

Mathematical Model

We used a discrete-time, stochastic simulation model of influenza spread within a structured population to compare the effectiveness of various intervention strategies [7]. A recent publication demonstrates the comparability of our model predictions (influenza attack rate) to other published models [3]. The model simulates stochastic spread of influenza in a population of people interacting in known contact groups [7–9]. Each person is assumed to have daily contacts with household members and people in the three closest households (neighborhood cluster), as well as with people in the larger neighborhood and community. Preschool children attend either small playgroups or larger day-care centers, school-age children attend elementary, middle, or high school, as appropriate, and 63% of adults are in workgroups [10].

Once infected, people follow the clinical pathway as shown in Figure 1. An infected person may receive treatment, which modifies health outcome (probability of otitis media, bronchitis, pneumonia, hospitalization due to influenza, mortality) and resource use (probability of health-care contact). Stratification of the population by age and risk status is accounted for in the model. The age groups are children 0–4 years old, children 5–18 years, younger adults (19–64 years old), and older adults (≥65 years). Younger adults are further stratified into high and low risk. High-risk adults have underlying chronic conditions (e.g., cardiovascular, respiratory, or metabolic disease), which increase their risk for bronchitis, pneumonia, hospitalizations, and mortality.

Data

Transmission

Many of the transmission parameters were adopted from previous work [7–9]. The probability that an infected individual will be symptomatic is 0.67 [11]. An asymptomatic infection is assumed to be 50% as infectious as a symptomatic infection [7,12].

One hundred runs were performed for each intervention, and the results were averaged. The average R_0 was 2.0, with a range of 1.5 to 2.6. R_0 is defined as the average number of secondary infections produced by a typical infected person in a fully susceptible population [13].

Probabilities of Events

Probabilities of events used in the model are shown in supplementary Table A2. The probabilities of bronchitis, pneumonia, and otitis media for an untreated population were based on a large general practice database from the UK [19]. The mortality rate is based on data from previous pandemics [20] and captures all influenza-related deaths, including those due to complications.

Effectiveness of Interventions

We used current estimates of antiviral efficacy of oseltamivir (Table 2) [11,14–17]. The antiviral efficacy for symptomatic disease given exposure is 0.72, and weassumed that the antiviral efficacy for infectiousness is 0.62 [17]. Oseltamivir treatment effectively reduces incidence of otitis media, bronchitis, pneumonia, influenza-related hospitalizations, and mortality, and improves quality of life [18,21–23].

For a low-efficacy vaccine, we assumed the vaccine efficacy for susceptibility to infection to be 0.30, and vaccine efficacy for infectiousness to be 0.50 [12]. We assumed that two doses of vaccine would be needed [24].

Utilities

We calculated quality-adjusted life-years (QALYs) based on quality weights between 0 (death) and 1 (perfect health). The QALY penalties for influenza were derived from clinical trial data as used and described in a recently published health technology assessment on the prevention and control of influenza [21] and for bronchitis and otitis media from the literature [25,26] There were no quality weights published for bronchitis; we therefore assumed the same QALY penalty for bronchitis as for influenza. Future life-years were discounted at 3% per annum in line with US guidelines for economic evaluations [27].

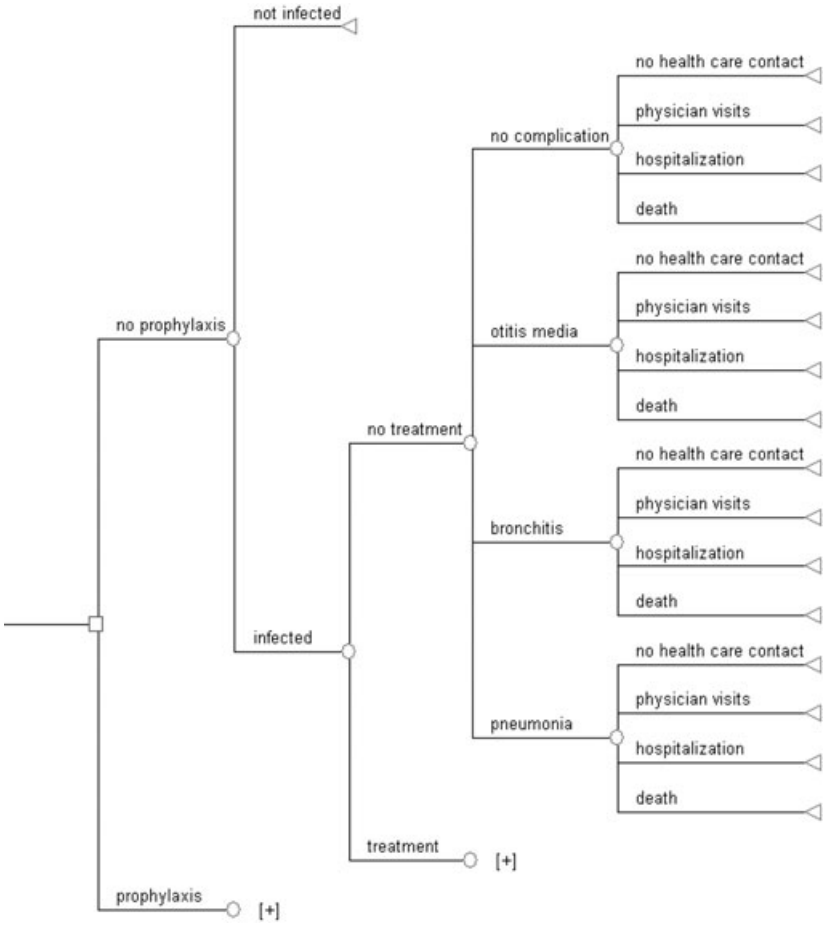

Figure 1 Simplified schematic representation of decision model. The "prophylaxis" arm extends in identical format to the "nonprophylaxis" arm. The "treatment" arm extends in identical format to the "no treatment" arm.

Costs

Resource use. We estimated resource use related to treatment of illness separately for children and adults, as well as resource use related to prophylaxis including school closure. We included physician visits, hospitalizations, use of antibiotics, and use of over-the-counter medicines. For prevaccination and TAP, we included both drug and delivery costs. For HTAP, we estimated travel and time cost to obtain prophylaxis, and assigned this cost once per household, assuming that the index case obtains prophylaxis for household members. For FTAP, we assumed three times this cost to account for prophylaxis of household members, contacts in the school or workplace, and contacts in the community.

We assume 2.5 days of work loss per week per household for children <12 years if 1) the child is sick; or 2) schools are closed. This estimate is based on best available data from the literature [10,21,28,29]. Babysitting pools or other similar arrangements should be avoided during a pandemic when school closure is in effect to minimize transmission.

For school closure, we assumed 2.5 person days per week time loss for affected households, and 5 days per week for teachers and other professionals, using a national ratio of teachers and other professionals per student [30]. If one parent stays home already because of a sick child, no additional work loss is added. For teachers and other school staff who are parents, the work loss is 5 days.

Unit costs. Unit medical cost estimates were based on US fee and price schedules [27,31]. Oseltamivir is priced at the stockpile acquisition cost for adults and children. Oseltamivir costs were converted from euros to US dollars using the Interbank rate as of July 5, 2006 [32]. The low-efficacy vaccine is priced at one-third of the current price per dose [31]. Because mass vaccination is anticipated to be less costly than current vaccination practices, we assumed only 50% of the usual cost for vaccine delivery. We added 20% to both oseltamivir and vaccine cost to reflect the cost incurred by the government for storage and distribution. Hospitalization costs were derived from Diagnosis Related Group (DRG) codes [33] for children (0–17 years) and adults (≥17 years) with (used for high-risk adults and older adults) and without complications (used for low-risk adults). In the absence of a DRG code for influenza, we assumed hospitalization costs for influenza to be similar to bronchitis.

We valued productivity loss using the human capital approach by applying average compensation (salary plus fringe benefits) [34] to days of work lost for sick adults and caregivers of sick children, as well as caregivers for households affected by school closure. We used average earnings for teachers [35] to value work loss for teachers due to school closure. Productivity loss because of premature mortality was not included because this is reflected in the measure of health outcomes (QALYs) [33].

Because resource use and cost data on health-care services used during an influenza pandemic are not readily available,

Table 2 Effectiveness of interventions

Intervention	Incidence reduction/ QoL improvement (%)	Source
Oseltamivir		
Infection given exposure	30	Halloran et al. 2007 [11], Hayden et al. 1999 [16], Hayden et al. 2000 [14], Welliver et al. 2001 [15], Yang et al. 2006 [17]
Symptomatic disease given infection	60	Halloran et al. 2007 [11], Hayden et al. 1999 [16], Hayden et al. 2000 [14], Welliver et al. 2001 [15], Yang et al. 2006 [17]
Symptomatic disease given exposure	72	Calculated
Infectiousness	62	Yang et al. 2006 [17]
Low-efficacy vaccine		
Susceptibility to infection	30	Longini et al. 2005 [12]
Infectiousness	50	Longini et al. 2005 [12]
Bronchitis		
Children <5 years	52	Kaiser et al. 2003 [18]
Children 5–18 years	52	Kaiser et al. 2003 [18]
Low-risk younger adults	60	Kaiser et al. 2003 [18]
High-risk younger adults	33	Kaiser et al. 2003 [18]
Older adults	33	Kaiser et al. 2003 [18]
Pneumonia		
Children <5 years	63	Kaiser et al. 2003 [18]
Children 5–18 years	63	Kaiser et al. 2003 [18]
Low-risk younger adults	85	Kaiser et al. 2003 [18]
High-risk younger adults	24	Kaiser et al. 2003 [18]
Older adults	24	Kaiser et al. 2003 [18]
Otitis media		
Children <5 years	62	Data on file
Influenza deaths (all)	Same as reduction in hospitalizations	Assumption
Influenza hospitalizations		
Children	61	Kaiser et al. 2003 [18]
Low-risk younger adults	64	Kaiser et al. 2003 [18]
High-risk younger adults	39	Kaiser et al. 2003 [18]
Older adults	39	Kaiser et al. 2003 [21]
QoL improvement (influenza)		
Children and low-risk younger adults	11	Data on file
High-risk younger adults	4	Data on file
Older adults	5	Data on file

QoL, quality of life.

some of the estimates are assumptions based on the available literature on annual influenza and expert opinion.

Analyses

Base-Case

In the base-case analysis, we estimated the expected health outcomes (number of cases, number of deaths, QALYs) and costs from the societal perspective for one pandemic wave, assuming a death rate of 2.5% per influenza case. We chose the societal perspective to capture productivity loss due to potentially very high absenteeism rates and the potential impact due to school closure, which do not incur any costs to the health-care payer, but may cause substantial disruption. Because quality of life is important to patients and decision-makers, we ranked strategies by expected QALYs and performed a cost-utility analysis, calculating costs per QALY gained. This approach also enables comparison with other public health interventions. In the base-case, costs were not discounted because all costs occur within 1 year.

Sensitivity Analyses

As the sensitivity related to the effectiveness of oseltamivir has been tested and reported previously [1,7,12], we focused our analysis on a number of other key variables in the model (R_0, mortality, school closure, and probability of a pandemic). We explored the lower end of the possible range for the basic reproduction number by fixing R_0 at 1.6, and also investigated a situation with R_0 fixed at 2.0 to address the effects of uncertainty surrounding R_0.

To assess the sensitivity of results to variations in health-care resource use, we define a low-intensity and high-intensity resource use scenario, varying a number of resource use parameters at the same time.

Severity of a pandemic is difficult to predict; we therefore tested a 5% mortality rate. To minimize social disruption because of school closure, staff—i.e., teachers and other professionals—may be assigned to different tasks, such as teaching by distance or supporting health-care workers and other essential services. We assumed 50% productivity loss for teachers and other staff during school closure, instead of 100% in the base case.

There is an additional sensitivity analysis (reported in the supplementary materials), assuming a pandemic occurs within 33 years, and that stockpiles need to be renewed.

Results

Base-Case

All base-case results are shown in Table 3. In the absence of any intervention, we projected an illness attack rate of 50%, resulting in 13 deaths per 1000 population. All interventions reduced the illness attack rate and hence morbidity and mortality. Many interventions are also cost saving compared with no intervention, meaning that additional costs of intervention (antivirals, vaccine) are offset by the lower number of cases requiring treatment and incurring productivity loss. FTAP is the most effective single strategy, reducing the attack rate by 54%. If a low-efficacy vaccine is available and administered before the onset of the pandemic, then, prevaccinating 70% of the population is expected to reduce

Table 3 Base-case results (ranked by expected QALYs)

Intervention	Illness attack rate (%)	Deaths per 1000	QALYs* per 1000	Incremental QALYs† per 1000	Courses per 1000	Total cost in million $ per 1000
No intervention	50	13	21,141	—	—	0.19
FTAP25	48	12	21,157	16	246	0.18
FTAP50	45	11	21,175	34	481	0.18
HTAP25	48	11	21,181	40	250	0.19
School closure	39	10	21,210	69	—	2.72
HTAP50	42	8	21,239	98	498	0.17
Treatment only	49	8	21,241	100	243	0.19
HTAP	41	7	21,264	123	651	0.17
Prevaccination	26	6	21,271	130	—	0.14
HTAP25 and school closure	31	7	21,273	132	204	2.70
FTAP25 and school closure	23	6	21,300	159	150	2.66
FTAP50 and school closure	22	5	21,310	169	279	2.66
HTAP50 and school closure	27	5	21,316	175	374	2.68
HTAP and school closure	24	4	21,330	189	395	2.67
FTAP	23	5	21,351	210	2,447	0.12
FTAP and school closure	6	1	21,403	262	640	2.61
Prevaccination and school closure	4	1	21,403	262	—	2.62

*Expected average quality-adjusted life expectancy.
†Compared with no intervention.
Note: QALY ranking differs slightly from illness attack rate ranking because QALYs take into account the differences in morbidity and mortality (life expectancy) across age groups, i.e., it is important in which age groups cases and deaths occur.
HTAP, household targeted antiviral prophylaxis; FTAP, full targeted antiviral prophylaxis; QALY, quality-adjusted life-year.

the number of cases by 48% and is the second least costly strategy. FTAP, however, dominates (i.e., has the lowest morbidity, mortality, and costs) all single strategies and most combination strategies, which are therefore eliminated from further analysis. The expected illness attack rate is smallest (6% and 4%, respectively) if either 60% of close contacts of ascertained index cases receive prophylaxis (FTAP), or 70% of the population is prevaccinated with a low-efficacy vaccine, and schools are closed for the duration of the outbreak. School closure, however, incurs high costs to society (about $2.7 million per 1000 population). Total costs are therefore much higher than for FTAP or prevaccination alone. Strategies involving school closure are approximately 14 to 21 times as costly as single intervention strategies with antivirals or prevaccination.

Table 4 shows the results for the incremental cost-utility analysis. Eliminating all dominated interventions leaves only three strategies for comparison: FTAP, FTAP in combination with school closure, and prevaccination in combination with school closure. Compared to FTAP not involving school closure, FTAP plus school closure or prevaccination plus school closure gains 51 QALYs, but increases total cost by approximately $2.5 million for a population of 1000. School closure incurs substantial costs to society, driven by extensive work loss for carers and teachers. The incremental cost-utility ratio (ICUR) for either strategy compared to FTAP is $48,500/QALY gained. Figure 2 shows the cost-effective frontier. The options connected by a line are the set of potentially optimal choices. All other options are dominated, i.e., not as effective and more costly.

Sensitivity Analyses

The basic reproductive number is a key driver in the model, because it determines the number of influenza cases, and therefore the subsequent impact on the economy. It also affects the relative effect of the different interventions. Fixing R_0 at 2.0 does not change the ranking of strategies compared to the base-case. FTAP remains the most effective (26 of the 100 cases) and least costly single strategy ($140/capita). This is despite the fact that it is estimated to consume almost three packs on average per capita. As in the base-case, the school closure strategies are very expensive from the society's perspective, but adding school closure to any FTAP strategy or to prevaccination effectively eliminates the pandemic (0.2 to 7 cases per 100). If school closure is added to FTAP, no more than about 50% antiviral stockpiling is needed to effectively control the pandemic. For a low R_0 of 1.6, a pandemic can be effectively controlled with FTAP25. The cost savings are also highest for this scenario, with a cost of $3/capita compared with $130/capita for baseline.

Variations in health-care resource use have some impact on the cost-utility ratios but not the ranking of strategies. In the best-case scenario (low resource use for treatment of influenza cases), the ICUR for FTAP plus school closure, and vaccination plus school closure compared to FTAP alone is just below $28,000 per QALY gained. For the worst-case scenario (high resource use for treatment of influenza cases), the ICUR for FTAP plus school closure, and vaccination plus school closure compared to FTAP alone is below $83,000/QALY.

Table 4 Incremental cost utility for noneliminated strategies (pandemic occurs within 1 year)

Intervention	Total cost in million $ per 1000	Incremental cost in million $ per 1000	QALYs per 1000	Incremental QALYs per 1000	Incremental cost-utility ratio ($)
FTAP	0.12	—	21,352	—	—
FTAP and school closure	2.73	2.48	21,403	51	48,472
Prevaccination and school closure	2.73	2.50	21,403	51	48,638

Note: FTAP plus school closure and prevaccination plus school closure are individually compared to the same baseline (FTAP).
FTAP, full targeted antiviral prophylaxis; QALY, quality-adjusted life-year.

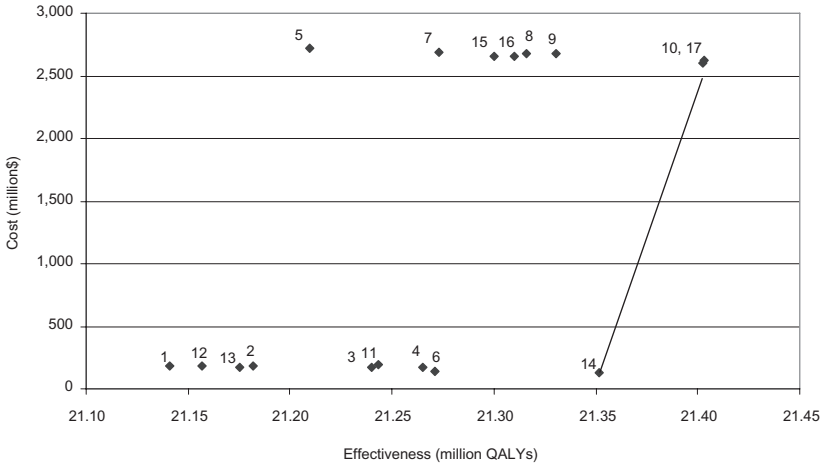

Figure 2 Cost-effectiveness frontier base-case. 1 = no intervention; 2 = HTAP25; 3 = HTAP50; 4 = HTAP; 5 = school closure; 6 = prevaccination; 7 = HTAP25 and school closure; 8 = HTAP50 and school closure; 9 = HTAP and school closure; 10 = prevaccination and school closure; 11 = treatment only; 12 = FTAP25; 13 = FTAP50; 14 = FTAP; 15 = FTAP25 and school closure: 16 = FTAP50 and school closure.
HTAP = household targeted antiviral prophylaxis; FTAP = full targeted antiviral prophylaxis; QALYs = quality-adjusted life-year.

The ranking of strategies is unaffected when changing assumptions about mortality and school closure. Assuming a higher case fatality rate of 5%, the ICUR for FTAP plus school closure, and vaccination plus school closure compared to FTAP reduces from $48,500/QALY to $18,500/QALY gained, making these strategies more attractive at higher mortality rates. When teachers and professionals incur only half the productivity loss, ICURs are only slightly lower than in the base case ($41,500/QALY for FTAP/vaccination plus school closure compared to FTAP). This is because most of the productivity loss (60%) during school closure can be attributed to parents (carers) being unable to work.

Our analysis indicates that the higher the attack rate, the more worthwhile are interventions providing broad coverage, such as school closure, FTAP, and prevaccination. At low attack rates, targeted strategies provide similar effects, but at lower cost.

Discussion

The base-case analysis clearly demonstrates that both FTAP and prepandemic vaccination effectively reduce the burden of pandemic influenza. In comparison with no intervention, both are cost saving from a societal perspective, the costs of the intervention (i.e., stockpiling up to 2.5 courses of antivirals per capita or prevaccinating 70% of the population) being more than offset by the substantial savings made in terms of both health-care costs and productivity losses. Further reductions in infection rate, morbidity, and mortality can be achieved by the addition of school closure to these strategies, but at a much higher cost to society (approximately 14 to 21 times that of a single intervention). Nevertheless, because of the further benefits realized in terms of health outcomes, with the addition of school closure in this setting, this approach could still be cost-effective (~$48,500/QALY gained) from a societal perspective.

To our knowledge, this study represents the first economic analysis of pandemic mitigation strategies using a dynamic nonlinear model. Although the analysis has a number of limitations due to uncertainties about factors such as the characteristics (infectivity and associated morbidity/mortality) of the pandemic strain and the current feasibility of some of the mitigation strategies evaluated (e.g., timely availability/efficacy of a pandemic vaccine), this analysis provides an important economic evaluation of a number of relevant mitigation strategies that may be considered in the event of a pandemic.

Because the severity of a future pandemic is unknown, we used a distribution for R_0 (~1.5 to 2.6), the basic reproduction number, to account for this uncertainty. Our results, therefore, reflect what to expect on average. There is a strong R_0 threshold just under 2.0, below which interventions aimed at the population at large (prevaccination, school closure) are less valuable. In addition, R_0 also has an impact on the quantity of antivirals required to mitigate a pandemic outbreak, the number of doses used exhibiting a highly nonlinear dynamic threshold. Thus, given the uncertainty regarding R_0, our base-case analysis best captures the information required for pandemic planning.

The current analysis is based on the assumption that the required quantity of either pandemic vaccine or oseltamivir is available for timely use. This requires adequate stockpiling in advance of an epidemic. For prevaccination in the model, it is assumed that 70% of the population are vaccinated with a low-efficacy vaccine at least 14 days before exposure to the virus. Although vaccination would, in principle, be a very effective intervention in the event of a pandemic, significant limitations to this approach exist in terms of the degree of virus strain match, production capacity, and shelf life. These, together with the constantly changing antigenic nature of the virus, would adversely affect both the opportunity for advanced stockpiling and the required rapid availability of vaccines at the onset of a pandemic. In contrast, oseltamivir is not strain-dependent and has a much longer shelf life than pandemic vaccines. Although the emergence of antiviral-resistant pandemic strains has been identified as a potential issue, development of resistance to oseltamivir over more than 7 years of use in epidemic influenza setting has been very low. In addition, it has been suggested that based on the reduced fitness and thus low transmissibility of resistant strains [36], the benefits of oseltamivir are highly unlikely to be offset by drug resistance.

To provide a national aggregate perspective on our estimates, it is useful to compare them with estimates produced from aggregate economic models. The Congressional Budget Office estimated that the impact of severe pandemic would reduce Gross Domestic Product (GDP) by 4.25%, equivalent to a typical business cycle recession [37]. With a projected GDP in the order of $14 trillion, this would imply a loss of $595 billion. This "severe" scenario, however, assumed an attack rate of 30% and 2 million deaths. Our base case scenario generates an attack rate of 50% and a projected 3.9 million deaths. We estimate only the direct and indirect costs related to medical treatment in this scenario, and they amount to a projected $59 billion. School closure dramatically increases the costs to $840 billion, reflecting the broader economic impact of parents missing work to care for

their children at home. By comparison, stockpiling one course of antiviral treatment for every American would cost $7 billion for the first 5 years of coverage. FTAP alone would cost 2.5 times this for the stockpile, and FTAP plus school closure would cost 64% of this for the stockpile.

Conclusions

All interventions reduce the illness attack rate, morbidity, and mortality. Many interventions are also cost saving compared with no intervention. Stockpiling TAP in the event of a pandemic is cost saving to the society, and will avoid loss of life. Adding school closure provides the greatest benefit and is likely to be an attractive strategy if transmission and mortality rates are high.

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Supporting information for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

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