Cost-Benefit of Stockpiling Drugs for Influenza Pandemic

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We analyzed strategies for the use of stockpiled antiviral drugs in the context of a future influenza pandemic and estimated cost-benefit ratios. Current stockpiling of oseltamivir appears to be cost-saving to the economy under several treatment strategies, including therapeutic treatment of patients and postexposure prophylactic treatment of patients' close contacts.

The widespread epidemic of highly pathogenic avian influenza that emerged in east Asia continues today. As the epidemic grows, so does the probability that this virulent virus will acquire genetic traits for increased person-to-person transmissibility, potentially setting the stage for the next global influenza pandemic (1).

The next pandemic will be associated with major adverse health and economic outcomes, with estimated costs reaching US$166 billion in the United States alone (2). The World Health Organization recently encouraged health authorities to consider stockpiling antiviral drugs in anticipation of a pandemic (3). However, the cost-benefit of stockpiling has yet to be assessed, and the optimal strategy for antiviral use is still under debate. The Israeli Ministry of Health appointed a working group to address national preparation for an influenza pandemic. We set out to identify strategies for the use of the antiviral drug oseltamivir in the containment of a pandemic and to construct a mathematical model to appraise the cost and benefit of each strategy in terms of health-related and economic outcomes.

The Study

We estimated the health-related impact of pandemic influenza on the Israeli population, by using rates (illness, physician visits, hospitalizations, and deaths) derived from previous pandemics, according to Meltzer et al. (2). Costs related to these outcomes were calculated from data provided by a major Israeli healthcare organization (4) and by the Israeli Central Bureau of Statistics (5). We calculated direct costs to the healthcare system and overall costs to

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the economy, the latter including the value of lost workdays but not the potential value of lost lives. Point estimates of variables used in the base-case model are detailed in Table 1 and online Appendix 1 (available from http://www.cdc.gov/ncidod/EID/vol11no08/04-1156_app1.htm).

According to base-case assumptions, a pandemic would result in an estimated 1,618,200 patients (≈25% of the Israeli population), 781,921 physician visits, 10,334 hospitalizations, 2,855 deaths, and 6,536,240 lost workdays. These outcomes would result in an excess of $55.4 million in health-related costs and in overall costs to the economy of $523.5 million (≈0.5% of the Israeli gross domestic product).

We defined 3 strategies for the use of antiviral drugs during a pandemic: therapeutic use, long-term preexposure prophylaxis, and short-term postexposure prophylaxis for close contacts of influenza patients (with index patients under treatment). The first 2 strategies could target either the entire population or only those at high risk for complications. The efficacy of therapeutic treatment was based on currently available evidence regarding epidemic influenza (online Appendix 1). Systematic review and meta-analysis were used to estimate the efficacy of preexposure prophylaxis, while the expected efficacy of postexposure prophylaxis and the number of persons treated under this strategy were estimated by using the results of a recently published stochastic simulation model (6).

The impact of each strategy on health-related outcomes was analyzed in a spreadsheet model by using the formulas summarized in online Appendix 2 (available from http://www.cdc.gov/ncidod/EID/vol11no08/04-1156_app2.htm). Briefly, the economic benefit of each strategy was calculated by multiplying each of the reductions in adverse outcomes by its estimated economic value. The cost of each strategy was calculated by multiplying the estimated number of treated persons by the discounted cost of a single antiviral course. Oseltamivir was selected as the drug of choice, at a daily dosage of 75 mg for prophylaxis and 150 mg for treatment (7). Oseltamivir stockpiling costs were calculated with prices quoted in March 2004 by the manufacturer's representative in Israel for uncapsulated, water-soluble, bulk active powder with a 10-year shelf life.

We compared the economic outcomes of each of the 5 strategies with nonintervention, estimated stockpiling costs, and calculated cost-benefit ratios. Based on the historic incidence of 3 influenza pandemics over the last century, we adjusted all cost-benefit outcomes for a conservatively estimated probability of 3 pandemics every 100 years and applied a wide range of estimates for sensitivity analyses (online Appendix 1). Table 2 details the cost-benefit ratios of the competing strategies. Therapeutic treatment and postexposure prophylaxis were shown to be cost-saving, with a cost-benefit ratio of 2.44–3.68.

Table 1. Point estimate and range of values for selected model variables*

Variable	Point estimate	Range
Overall attack rate, %†	25	15–35
Probability of pandemic (per year)	3	1–10
Adult workdays lost, by age, y		
<1–≤18	3.7	2–5
19–64	4.9	3–7
≥65	0.5	0.25–2
Average hospital stay (days) by age, y		
<1–≤18	4.0	2–5
19–64	5.8	2–7
≥65	7.0	4-9
Patients seeking medical care within 48 h, %	80	70–90
Efficacy of antiviral prophylaxis, %		
Preexposure prophylaxis (50 days)	71	57–85
Postexposure prophylaxis (7 days)	36	25–47
Efficacy of antiviral therapy, %		
Reduction in hospitalizations	59	30–70
Reduction in antimicrobial drug use	63	40–80
Reduction in lost workdays under treatment	1	0.5–1.5

*Complete list and references available in online Appendix 1.
†Population attack rate was calculated by stratifying the population by age and risk and applying age- and risk-specific attack rates and ranges (online Appendix 1).

Since many characteristics of the next pandemic viral strain remain unknown, our modeling methods and parameter estimates were designed to consistently underestimate intervention-related benefits, thus yielding minimum estimates of the true cost-benefit ratios. In a series of multivariate sensitivity analyses that used the variable ranges detailed in Table 1, the model proved to be robust. Even under the most unfavorable estimates, prepandemic stockpiling remained cost-saving as long as the estimated probability of a pandemic remained >1 every 80 years. No consistent advantage to either therapeutic or short-term prophylactic use of antiviral drugs could be determined.

Conclusions

In light of recent episodes of human infection with avian influenza, the World Health Organization reiterated its 1997 call for all countries to prepare for the next "inevitable, and possibly imminent" pandemic (3). Strain-specific vaccine, the most effective tool for influenza control, will most likely not be available in the early stages of a pandemic because of its prolonged development time (3), and early control measures will have to employ alternative options, mainly the judicious use of antiviral drugs. These drugs are likely to be in short supply if not preemptively stockpiled (3). Compared with neuraminidase inhibitors, the M2-inhibitor drugs have several major disadvantages, mainly high rates of viral resistance (as shown in recent H5N1 and H9N2 isolates) and adverse effects (8).

Our model suggests that prepandemic stockpiling of oseltamivir is cost-saving to the economy over a wide range of treatment strategies. Stockpiling is also directly cost-saving to the healthcare system, if oseltamivir use is limited to treating patients at high risk. Investment in stockpiling remains cost-saving to the economy as long as the estimated annual pandemic risk remains >1 pandemic every 80 years. In the last 400 years, at least 31 pandemics have been recorded (8), so that regardless of recent events in Southeast Asia, present investments in antiviral agents can be expected to yield a substantial economic return of >$3.68 per $1 invested, while saving many lives.

This favorable cost-benefit ratio can be achieved if stockpiled antiviral drugs are administered either solely as a therapeutic measure or as short-term prophylaxis for exposed contacts, a strategy termed "ring prophylaxis" (9) or "targeted prophylaxis" (6). Only 1 study published to date (6) used dynamic mathematical modeling to examine the expected effectiveness of this latter control measure on the population level; that study suggested that this strategy may significantly reduce illness and death. This epidemiologically directed short-term prophylaxis of close contacts may require antiviral stockpiles considerably larger than necessary for therapeutically treating patients, but our model suggests that this investment may still prove cost-saving, providing that the outbreak dissemination patterns and population attributes correlate with those assumed by Longini et al. (online Appendix 1).

When one considers a ring prophylaxis strategy, the risk of "strategy failure" due to early antiviral stockpile depletion must be considered. If postexposure prophylaxis does not confer sufficient immunity upon exposed contacts who underwent prophylaxis, and if vaccines or additional

Table 2. Cost-benefit ratios of antiviral utilization strategies*

Strategy		Cost-benefit ratio, relative to nonintervention	
		All costs to economy	Direct healthcare costs
NI	No intervention (base case)	Ref.	Ref.
1a	Therapeutic use (all patients)	2.44	0.30
1b	Therapeutic use (limited to patients at high risk)	3.68	1.51
2a	Preexposure long-term prophylaxis of entire population	0.38	0.04
2b	Preexposure long-term prophylaxis, limited to high-risk population	0.37	0.10
3a	Postexposure short-term prophylaxis for all close contacts ("ring prophylaxis"), including treatment of index patients	2.49	0.27

*Ref., reference value of zero divided by zero.

antiviral agents do not become available, rapid consumption of available stocks may leave the population vulnerable to additional outbreak waves, potentially caused by influx of new cases. The probabilities of similar "failure" scenarios are difficult to assess and were not included in our analysis. Application of this strategy for the entire population without surplus antiviral reserves should therefore be considered cautiously and monitored closely.

This study aimed to elicit minimum cost-benefit estimates for investment in a national antiviral stockpile. Among our conservative assumptions, we chose to exclude indirect costs of preventable deaths, which, if added, would have increased cost-benefit ratios up to 6-fold (online Appendix 1). Furthermore, in view of recent events in east Asia, the probability of a pandemic has probably risen to >3 per 100 years, and new strains may prove more pathogenic than previous pandemic strains. In modeling the benefits of therapeutic strategies, we omitted the beneficial effects of decreased viral shedding afforded by neuraminidase inhibitors (7), such as a lower secondary attack rates among untreated contacts. We also ignored the possibility that a fully implemented prophylactic strategy might achieve full containment of the outbreak (probability estimated at ≈6% for 7-day postexposure ring prophylaxis (6), dependent on several factors such as compliance, delay in treatment initiation, and basic reproductive number (6,10). Finally, as witnessed during the epidemic of severe acute respiratory syndrome (SARS), the economic consequences of a rapidly disseminating disease extend well beyond direct costs to the healthcare system and lost workdays. Canada had losses >$1 billion during the SARS epidemic, although the disease directly affected <500 patients (11). From an economic viewpoint, mitigating a pandemic could prevent extensive indirect economic losses.

The conclusions of this study must be considered carefully during the planning of antiviral stockpiling. Drug prices can be expected to change substantially as a result of contractual negotiations with manufacturers (although our results indicate stockpiling may remain cost-saving even if drug costs are more than tripled, as would be the case if preprepared capsules are purchased). Powder-form antiviral drugs have considerable advantages in terms of cost and shelf life, but the logistical aspects of their preparation and distribution should be further assessed to confirm feasibility. Finally, we assumed that strain-specific vaccine would not be available in sufficient quantities during the first stages of the pandemic. Efforts are currently being directed towards shortening this delay. Once available, strain-specific vaccines would likely be the favored intervention, with antiviral agents serving as adjunct treatment.

In summary, prepandemic stockpiling of antiviral drugs can be expected to prove cost-saving. Cost-beneficial strategies for their use may involve treatment of patients, and, if backed by adequate antiviral stockpiles, short-term postexposure prophylaxis of close contacts. These strategies should be considered when planning stockpiling efforts.

Several countries have already begun active stockpiling efforts (12), sufficient in some cases to allow antiviral treatment of up to 25% of the population (13). We believe that antiviral stockpiling should be considered a prudent investment that may help mitigate this impending global threat.

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