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Value for Money in H1N1 Influenza: A Systematic Review of the Cost-Effectiveness of Pandemic Interventions

Hélène Pasquini-Descomps, MSc[1,2,*], *Nathalie Brender, PhD*[1], *David Maradan, PhD*[1,2]

[1]*Haute École de Gestion Genève (Geneva School of Business Administration), HES-SO University of Applied Sciences Western Switzerland, Carouge, Switzerland;* [2]*University of Geneva, Switzerland*

ABSTRACT

Background: The 2009 A/H1N1 influenza pandemic generated additional data and triggered new studies that opened debate over the optimal strategy for handling a pandemic. The lessons-learned documents from the World Health Organization show the need for a cost estimation of the pandemic response during the risk-assessment phase. Several years after the crisis, what conclusions can we draw from this field of research? **Objective:** The main objective of this article was to provide an analysis of the studies that present cost-effectiveness or cost-benefit analyses for A/H1N1 pandemic interventions since 2009 and to identify which measures seem most cost-effective. **Methods:** We reviewed 18 academic articles that provide cost-effectiveness or cost-benefit analyses for A/H1N1 pandemic interventions since 2009. Our review converts the studies' results into a cost-utility measure (cost per disability-adjusted life-year or quality-adjusted life-year) and presents the contexts of severity and fatality. **Results:** The existing studies suggest that hospital quarantine, vaccination, and usage of the antiviral stockpile are highly cost-effective, even for mild pandemics. However, school closures, antiviral treatments, and social distancing may not qualify as efficient measures, for a virus like 2009's H1N1 and a willingness-to-pay threshold of $45,000 per disability-adjusted life-year. Such interventions may become cost-effective for severe crises. **Conclusions:** This study helps to shed light on the cost-utility of various interventions, and may support decision making, among other criteria, for future pandemics. Nonetheless, one should consider these results carefully, considering these may not apply to a specific crisis or country, and a dedicated cost-effectiveness assessment should be conducted at the time.

Keywords: cost-benefit, cost-effectiveness, H1N1 influenza, pandemic, value for money.

Introduction

The last influenza pandemic, known as the 2009 H1N1 crisis, was a very interesting challenge to global risk governance. Being the first pandemic to occur under the World Health Organization's new International Health Regulation [1], it triggered within American, European, and Asian countries a set of various interventions such as airport screenings, antiviral stockpiling, vaccination campaigns, bans on public events, and school closures.

Decisions on which interventions to undertake were made according to the recommendations of expert committees following each countries' national and regional plans. However, as the H1N1 virus proved to be relatively mild, the deployment of strategies sometimes tailored for more lethal viruses left an impression of "overreaction," especially in Europe. This controversy was magnified by the financial crisis [2].

Indeed, it has become increasingly difficult for governmental policymakers to defend their decisions to their publics without including economic evaluations of those interventions, even in an emergency context. However, such information might not have been available at the time of the H1N1 crisis. For example, the cost-effectiveness of some interventions, such as school closures, was unknown. In addition, studies on cost-effectiveness published before 2009 usually accounted for a case-fatality rate of at least 10 times higher than the recently estimated H1N1 case-fatality ratio (CFR) of 0.02% [3].

As a consequence, the lessons-learned documents from the H1N1 pandemic often mention the necessity to reassess "the cost-effectiveness of the strategy during the risk evaluation and response process: "a methodology for measuring the economic costs of interventions and the overall pandemic should be taken into account during pandemic preparedness" [4]. Post-2009, researchers acknowledged this demand and published additional cost-effectiveness studies on the pandemic interventions, including school closures.

The objective of this study was to systematically review significant articles, post-2009, that evaluate the cost-effectiveness of the interventions administered during the A/H1N1 pandemic. This type of systematic review of studies ranging from 2004 to 2011 has been performed previously [5]. Our

* *Address correspondence to:* Hélène Pasquini-Descomps, Haute École de Gestion de Genève, HES-SO University of Applied Sciences Western Switzerland, Route de Drize 7, Carouge GE 1227, Switzerland.
E-mail: helene.pasquini-descomps@hesge.ch.

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Table 1 – Influenza pandemic interventions and related cost studies included in our review.

Category	Pandemic interventions/public measures	Studies included in our review
Surveillance	Disease surveillance networks	Wang et al., 2012 [16]
Planning	Emergency preparedness planning/drills	–
	Prevention behavior programs	–
Stockpiling	Stockpiling antiviral medicine	Carrasco et al., 2011 [20]
	Stockpiling low-efficacy vaccine	–
Trade and travel restriction	Travel restriction	–
	Border scanning	–
	Close borders to people	–
	Close borders to goods	–
	Ground airplane travel	–
	Tracking exposed people	Wang et al., 2012 [16]
Quarantine	Quarantine existing cases (household quarantine)	Perlroth et al., 2010 [22]
	Quarantine hospital	Dan et al., 2009 [23]
Antiviral	Antiviral treatment	Lee et al., 2010 [26]
		Lee et al., 2011 [25]
		Nagase et al., 2009 [27]
		Lavelle et al., 2012 [28]
		Perlroth et al., 2010 [22]
	Antiviral prophylaxis	Perlroth et al., 2010 [22]
Vaccination	Low-efficacy/seasonal/PCV vaccine distribution	Rubin et al., 2010 [38]
	High-efficacy vaccine (targeted to specific agent) production and distribution	Brouwers et al., 2009 [32]
		Beigi et al., 2009 [35]
		Durbin et al., 2011 [33]
		Sanders et al., 2010 [36]
		Khazeni et al., 2009 [34]
		Prosser et al., 2011 [31]
		Wang et al., 2012 [16]
Hospitalization	Observation	–
	Respiratory assistance	–
Social distancing	School closure	Brown et al., 2011 [40]
		Halder et al., 2011 [41]
		Perlroth et al., 2010 [22]
	Stay at home (self-isolation)	Perlroth et al., 2010 [22]
	Business closure	–
	Ban on public gathering	–
	Public transportation ban	–
Hygiene recommendation	Facemask	Tracht et al., 2012 [49]
	Prevention behavior recommendation	–
Animal-to- human transmission	Animal culling	–
	Food restriction	–

A dash mark ("–") indicates that no studies were found matching our selection criteria for this intervention.
PCV, pneumococcal vaccine.

study, however, includes articles from 2009 to 2014, and it brings two new elements: First, we systematically convert the results to a cost-utility measure to allow for comparisons among studies. Second, we graphically present the results of the studies in their contexts of severity and infectivity. This framework enables policymakers to easily understand which cost-utility measures are relevant for a specific pandemic scenario [6]. In addition, our review helps to identify which pandemic interventions are still missing an economic evaluation, which we hope will raise the interest of researchers for further studies in the domain.

Methods

Data

We searched for recent economic studies on H1N1 pandemic interventions using the following protocol: In December 2014, we performed a systematic search in the MEDLINE database via PubMed (January 1, 2009–December 31, 2014) and in EBSCO Business Source Premiere (January 1, 2009–December 31, 2014). The search terms were "cost(s)," "effectiveness," "benefit," and "H1N1" in various combinations and also in conjunction with terms from the interventions' categories, such as "surveillance" (see Table 1). In addition, reference lists of relevant publications on this topic were screened, including the references of the previous systematic review [5]. A total of 87 studies were identified.

Study Selection

The resulting articles were manually sorted by the research team on the basis of their titles and abstracts to include only the following:

1. Peer-reviewed academic studies published in English.
2. The year of publication should be post-2009 and/or include an

H1N1 pandemic scenario.

3. Studies that compute results from a societal point of view (i.e., studies taking the patient's point of view were excluded).
4. Studies had to be a cost-effectiveness analysis (CEA), with results in dollars per case-averted and/or dollars per death-averted; a cost-utility analysis (CUA), with results in dollars per quality-adjusted life-years (QALYs) lost or disability-adjusted life-years (DALYs) lost; or a cost-benefit analysis (CBA), with results expressed as an intervention's total saving or loss in dollar amounts [7].
5. Studies had to compare the results of an intervention to a base-case scenario of no intervention or a basic-care scenario.

As a result, 18 studies were finally selected (see Table 1).

Data Extraction and Analysis

A data extraction process was established (for category details, see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.05.005), and the following data were extracted:

1. Descriptive characteristics: categories of interventions, author(s) and publication years, geographic locations, population sizes, conclusions on the cost-effectiveness of interventions, and recommendations.
2. Parameters of the studies: types of evaluation (CUA, CEA, or CBA), epidemiological models, infectivity and severity, and willingness-to-pay thresholds.
3. Cost-utility results: incremental cost-effectiveness ratios against a base case (namely, for CUA studies) and converted ratios (for CEA and CBA studies), as explained hereafter.

To maximize the number of studies contributing cost-utility data, we decided to convert, whenever possible, the quantitative results of the CEAs into a cost-utility measure in dollar per DALY using the following original method.

Considering that a CEA study will provide the dollars per case-averted or death-averted ratios, we can express DALYs in the following way:

$$\begin{aligned}\text{DALYs} &= \text{Years of disability averted} + \text{Years of life lost}\\ &= \text{Cases averted} \times \text{Average days of sickness}\\ &\times \text{Factor of disability}/365 + \text{Deaths averted}\\ &\times \text{Average loss of years}\end{aligned}$$

It is therefore possible to transform the results from a cost-effectiveness study (i.e., dollars per case-averted and dollars per deaths-averted) into a "converted cost-utility measure" (CCUM) by expressing the cases averted or deaths averted in DALYs using the following formula:

$$\begin{aligned}\text{CCUM (in dollars per DALY)} &= \$/\text{Cases averted}\\ &\times 1/(\text{Average days of sickness} \times \text{Factor of disability}/365)\\ &+ \$/\text{Deaths averted} \times 1/\text{Average loss of years}\end{aligned}$$

If no dollars per death-averted ratio is provided, then,

$$\begin{aligned}\text{CCUM (in dollars per DALY)} &= \$/\text{Cases averted}\\ &\times 1/(\text{Average days of sickness} \times \text{Factor of disability}/365)\\ &+ \$/\text{Cases averted} \times 1/\text{CFR} \times 1/\text{Average loss of years}\end{aligned}$$

where CFR is the *case-fatality ratio* of the pandemic.

To perform this conversion, we incorporated data provided by the authors to calculate the DALY equivalents whenever the data were available. In the absence of such data, we adopted the default parameters of 5 days of sickness on average and a factor of disability of 1 corresponding to a maximal disability during sickness. By default, the average population would stand to lose on average 22 DALYs per premature death (according to the age distribution of DALYs for an average life expectancy of 80 years, and [without indication from the studies' authors] an average age of death of 37 years from H1N1 influenza). For studies providing only a number of cases averted for the base scenario, we assumed the number of deaths averted to be the CFR times the number of cases averted. The same logic was applied for QALY.

For CBA studies, we estimated the cost per DALYs in a similar manner: We extracted from the studies the costs reported and the number of cases and deaths avoided against the base cases, since this information was provided, ending up with a cost-effectiveness ratio that we then converted using the above method.

Results

Nonmedical Interventions' Lack of Economic Evaluation

As an immediate observation, academic studies on cost-effectiveness have often favored some types of interventions while rarely assessing others. We identified 28 pandemic interventions [8] that governments commonly put in place before and during a pandemic. However, our selected studies cover only 12 of them (see Table 1). Moreover, two-third of the studies included in our review cover the topic of antiviral drugs or vaccinations. Little attention is given to preparedness measures, for which we found only two studies (on the topics of surveillance networks and stockpiling). Despite often being triggered during pandemics, social distancing and other nonpharmaceutical interventions (such as hygiene recommendations and travel restrictions) are lacking in economic studies, with the exception of school closures (three studies found) as a requirement from the lessons-learned reports of the 2009 H1N1 crisis, self-isolation (one study), and the use of facemasks (one study). One reason for this could be that the effects of nonmedical measures are more difficult to evaluate scientifically. In addition, the unquestionable medical effectiveness of a targeted vaccine, once available, draws the attention of researchers, leaving little room for such attention to be given to nonmedical measures that could potentially be cost-effective: "Japan's low incidence/death cases (during H1N1) may be due to individuals' prevention behavior" [9].

Cost-Utility of Interventions in the Infectivity and Fatality Context

Figure 1 presents in a graphical way the cost-utility results, or CCUM, of several pandemic interventions grouped by certain categories; infectivity is seen on the X-axis and severity (fatality) on the Y-axis. The size of the circle represents the CCUM value (i.e., the larger the circle, the more costly the intervention is in dollars per DALY/QALY).

Indeed, the sensitivity analysis of the studies' parameters shows that among those parameters, infectivity and severity play a large role [10–12]. In our graphical representation, the infectivity parameter of a study is represented in terms of the reproductive number (Ro) and fatality in terms of the CFR. The Ro and the CFR are the one mentioned in the studies, if such parameters were provided. For studies using an H1N1 scenario without providing Ro, if a secondary attack rate (SAR) was provided, we considered Ro to be equal to the SAR (because the SAR is a lower-bound estimate for Ro) [13]. In other cases, we estimated Ro for an H1N1 scenario to be 1.4 [14,15]. If the CFR was expressed for an age distribution, we averaged it by taking the mean over the proposed age classes.

Diagramming the (converted) cost in this setting helps to give an overview of the range of results and to draw conclusions depending on the context and type of the intervention, as we describe below.

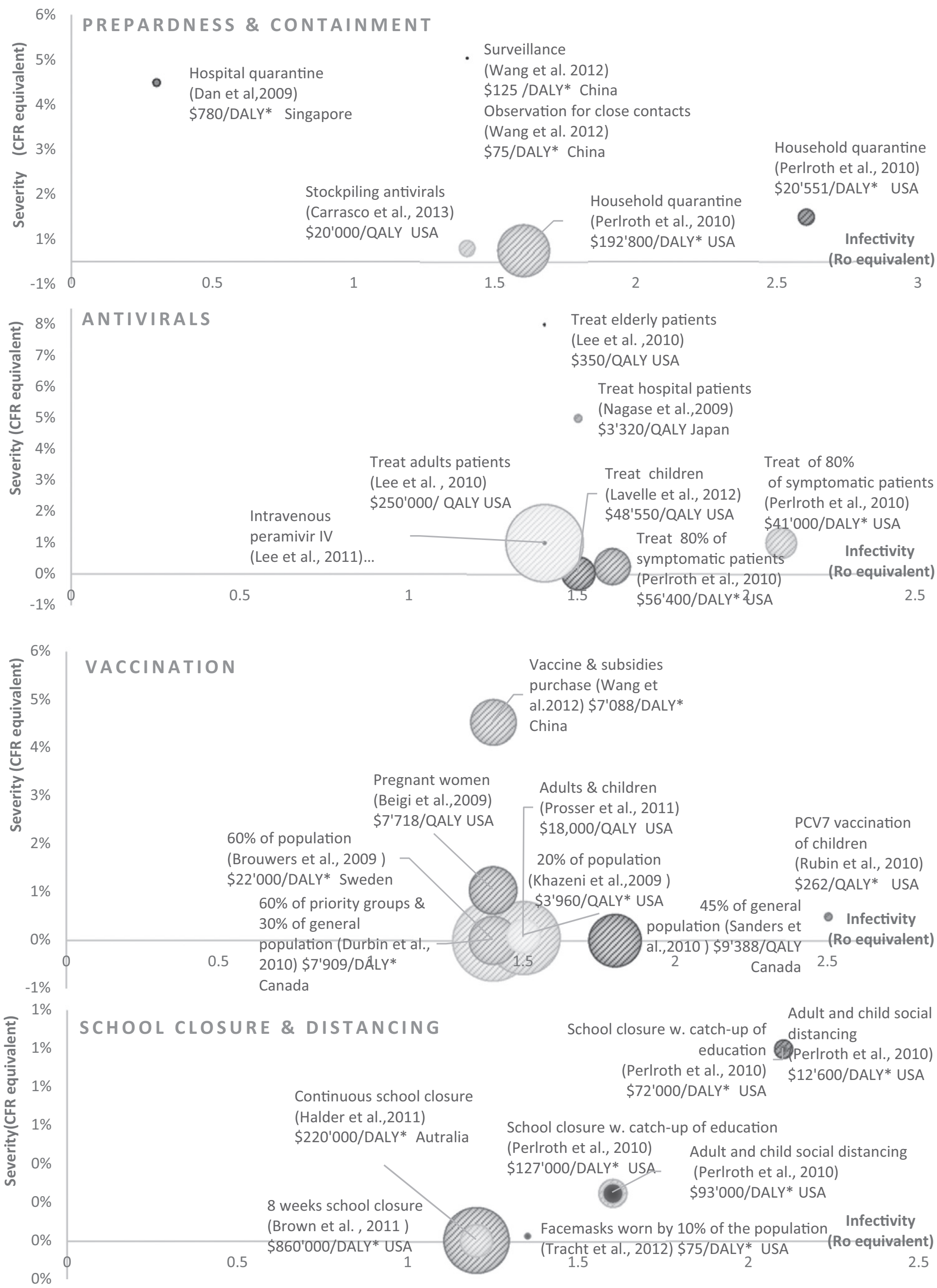

Fig. 1 – Cost-utility of pandemic interventions given severity and infectivity.The following graphics represent the incremental cost-effectiveness ratios (ICERs) found in CBA studies and the converted cost-utility measures (CCUM) computed from CEA or CBA studies as described in the Methods section (noted by an asterisk mark *). Each circle represents an intervention. The circle's size represents the cost-utility of the intervention in dollar per DALY or dollar per QALY (the bigger the circle, the more costly the intervention). The circles are positioned along the infectivity and severity axes, corresponding to the parameter of the study. Infectivity is represented in terms of reproduction number (Ro) equivalent, and severity (fatality) in terms of case-fatality ratio (CFR). CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; DALY, disability-adjusted life-year; QALY, quality-adjusted life-year.

Surveillance Networks and Stockpiling of Antivirals

Only a couple of cost studies focused on preparedness measures despite the fact that their CCUM looked quite effective, within the range of $125 to $20,000 per QALY. The Wang et al. [16] CBA does not study the costs of surveillance per se, but it does include the costs of the medical analysis laboratories' monitoring of influenza viruses during the pandemic. In this study, such costs represent 5.61% of the total costs incurred during the H1N1 pandemic. If costs are assumed to be proportional to the overall benefits of the global response, the resulting CCUM for the surveillance network would be $125 per QALY, a very efficient result. However, apart from the issue of assuming proportionality between costs and benefits, several issues prevent generalizing

this result. First, the study in question assumed a high CFR of 4.54%. Second, the direct costs found in the study are the operating costs of the laboratories during the crisis. However, the laboratories also have activities such as early detection and investigation—based on a comprehensive assessment of the first 100 or so cases—and relay and exchange of information with the World Health Organization [1]. In addition to the in-crisis and off-crisis activities, the setup costs of the laboratories should be amortized over several years [17], or at least a fraction of them should be attributed to influenza among other diseases. The costs for an event-based surveillance network (an analysis of news from all media, including the Internet) must also be evaluated, potentially including that of the surveillance network for severe acute respiratory infection [1,18]. The benefits of those networks will not be easy to assess. Indeed, knowing and identifying the viruses does not in itself reduce the related days of sickness or the toll of death. Nonetheless, it is a step that is necessary in order for a pandemic response to occur. Indirect benefits, such as increasing a country's knowledge on viruses and testing practices for seasonal influenza and other communicable diseases, should also be considered. In addition, a diminution of costs is observed when laboratories report the cases with an electronic system through a wizard, and also if data are used for local evaluation and management [19].

The cost-effectiveness for stockpiling antivirals, according to Carrasco et al. [20], is about $20,000 per QALY for developed countries—if stocking for an optimum 10% to 20% of the population and doing so only for treatment and not prophylaxis. The cost of stockpiling generally consists of buying a determined quantity of the antivirals and stocking it in appropriate conditions. Because the drugs have a limited shelf life (about 7 years for commonly distributed forms), these purchases occur periodically, and such costs must be annualized over the average period when the pandemic happens. The stockpile will be depleted by seasonal or pandemic influenza incidents, however. The Carrasco et al. approach is very consistent in both the considered costs and in the usage of random variables for pandemic occurrences over an observation period of 30 years. The benefits of stockpiling are considered only if there is a shortage of antiviral drugs through normal channels. This probability of a shortage should not be underestimated, as it proved to be the case for the 2009 pandemic, despite its mild nature. Regarding sharing the stockpile internationally—a topic often mentioned to reduce the costs and use it where the pandemic starts while the industry increases production—the very fast propagation of H1N1 in the last pandemic might be a counterargument. The true bone of contention, however, concerns the effectiveness of the antivirals [21], upon which the results depend heavily, as is discussed later in our Antiviral section. The purchase of a national stockpile could cost several millions, which could trigger criticism from the public if the drug's benefits are not clearly proven [22].

Tracking Exposed Persons, Households, and Hospital Quarantines

Strategies such as tracking an exposed person or quarantining home or hospital are often considered and used at the beginning of a pandemic. We found three studies regarding the cost-effectiveness of such interventions. Two of them found that tracking exposed people has good cost-effectiveness (below $1000 per DALY) [16] as does establishing quarantines at hospitals [23]; however, the studies also account for a higher mortality scenario than 2009's H1N1. The tracking of exposed people and isolating their close contacts may account for only 3.41% of the overall costs [16], making it very cost-effective if proportional to the overall benefits. Regarding quarantining hospitals [23], optimum cost-effectiveness occurs with the Disease Outbreak Response System Condition (DORSCON) Green Protocol (i.e., protection measures on the susceptible patient only, even for a high CFR). Isolating a large section or the whole hospital (red protocol) is suboptimal and could result in costs ranging in millions of dollars per death-averted [23].

The third study [22] suggests that a household quarantine could be inefficient for a scenario similar to H1N1. This multi-intervention cost-utility study found that quarantining is one of the most costly social-distancing measures, especially for low infectivity, and could cost several thousands of dollars per DALY for a low-mortality scenario such as H1N1. In practice, the self-isolation behavior is very difficult to maintain, even for a disciplined population [24].

Antivirals

The distribution of antivirals is well studied in terms of cost-effectiveness, with costs ranging from a few hundred to several thousands of dollars per QALY. One can see in Figure 1 that, for very lethal epidemics, antivirals have a good cost-effectiveness ratio ranging from $350 to $3500 per QALY or DALY [25–27]. However, for less severe infections, antiviral costs are in the $40,000 to $250,000 per QALY range [22,26,28]. Those results are to be considered very carefully because they are highly dependent on antiviral effectiveness, which was recently raised as a subject of controversy in a meta-study from the Cochrane Collaboration [29]. In the studies, the expected effects of antivirals are to reduce complications [25] such as pneumonia and fatality for patients already sick with influenza (hence the good score for a high-fatality pandemic) and to reduce the length of influenza for otherwise healthy patients. In addition, antivirals if taken as a prophylactic could potentially diminish the transmission of the virus to a healthy individual; treating exposed persons during a pandemic could be more effective than using antivirals for treatment alone [22,29]. However, the effects on healthy people have been questioned, notably concerning the antiviral's capacity to reduce the mortality rate and the length of sickness [21]. The emergence of influenza viruses with resistance to antivirals is also a concern. The cost-effectiveness of oseltamivir treatment for severe pandemics may vanish if the resistance-emerging rate becomes larger than 27% [27]. When considering antiviral target groups, it seems optimal to treat older adults (>65 years) in case the pandemic influenza is 2 times more severe than seasonal influenza, as this category of population seems to be more exposed to complications [26,27]. Oseltamivir treatment of children seems cost-effective but is highly dependent on resistance among circulating influenza viruses [28]. In addition, it seems that antiviral treatment by itself is less cost-effective than if combined with social distancing [30].

Vaccination

Vaccination is by far the most studied intervention in terms of cost-effectiveness. The various studies seem to agree on $10,000 to $20,000 per QALY for a low-infectivity, low-mortality pandemic such as H1N1 [31,32], whereas more severe conditions would lead to results under $10,000 [16,33–36] or even lead to cost savings. This result is in accordance with a pre-2009 meta-study in which costs in the $23 to $256 range per DALY were found [37]. The pneumococcal vaccine also seems very cost-effective for a high transmission rate [38]. There is an overall agreement on the effectiveness of vaccination; however, vaccination for attack rates similar to those of seasonal influenza might not be efficient [31]. The vaccination measure can be implemented in many different ways to optimize costs, and a wrong implementation could even trigger the measure to become ineffective in terms of costs: First, the timing of the availability of the vaccine is important. The earlier the vaccination starts, the more of the

Table 2 – Assumption of cost-effective interventions by scenario for a willingness-to-pay threshold of $45,000 QALY.

Cost-effective interventions (<$45,000 QALY) for H1N1-like pandemic based on existing studies			
High CFR >4%	• Quarantine at hospital (DORSCON Green)	• Stockpiling of antivirals* • Quarantine at hospital (DORSCON Green) • Vaccination $7,088 • Disease surveillance network $125 • Tracking exposed people $75 • Antivirals treatment* $3,320	• Stockpiling of antivirals* • Quarantine at hospital • (DORSCON Green) • Disease surveillance network • Tracking exposed people • Household quarantine • Antivirals treatment* • Vaccination • PCV vaccination
Medium CFR between 1% and 4%	• Quarantine at hospital (DORSCON Green) $780	• Stockpiling of antivirals* • Quarantine at hospital • (DORSCON Green) • Vaccination	• Stockpiling of antivirals* • Household quarantine • Quarantine at hospital • (DORSCON Green) • Antivirals treatment* • PCV vaccination • Vaccination
Low CFR ≤1%		• Stockpiling of antivirals* $20,000 • Vaccination $22,000	• Stockpiling of antivirals* • Household quarantine $20,551 • Antivirals treatment* $41,000 • PCV vaccination $262 • Vaccination
Fatality/infectivity	Low Ro <1.2	Medium Ro 1.2–2	High Ro >2
Inefficient interventions (>$45,000 QALY) for H1N1-like pandemic			
High CFR >4%			
Medium CFR between 1% and 4%			
Low CFR ≤1%	Household quarantine Antivirals treatment School closure	Household quarantine $198,200 Antivirals treatment $48,500 School closure $127,000	School closure $72,000
Fatality/infectivity	Low Ro <1.2	Medium Ro 1.2–2	High Ro >2

The interventions that are deemed effective for a scenario are automatically assumed effective for a more severe crisis, in terms of both fatality and infectivity. Interventions that are not cost-effective are assumed not effective for a less severe crisis. A $ value listed next to the intervention represent the cost-utility of the intervention (in $ per DALY or QALY) if it was evaluated for a crisis corresponding to this scenario.
CFR, cost-fatality ratio; DALY, disability-adjusted life-year; DORSCON, Disease Outbreak Response System Condition; PCV, pneumococcal vaccine; QALY, quality-adjusted life-year; Ro, reproductive number.
* Studies were done before the recent questioning on the antivirals' effects.

cost can be saved. If the vaccination comes after the peak, it might not be cost-effective [31,34]. Second, in terms of target population, some recommend vaccinating at least 60% of the population [32], whereas others believe that vaccinating 60% of the priority groups and subsequently 30% of the general population is cost-effective from a societal perspective [33]. Vaccinating pregnant women seems cost-effective [35]. For a pandemic similar to 1957, vaccination must focus on children 5 to 19 years old and adults 30 to 39 years old [39].

On must note that the largest part of the cost seems to come from vaccine distribution [39], while the biggest driver of cost-effectiveness is to prevent morbidity (in opposition to preventing mortality, which draws public attention) as well as absenteeism [33,36]. Finally, while comparing vaccinations to other measures, vaccination seems more cost-effective than self-isolation [30]. However, self-isolation would become more effective than vaccination if more than 20% of the population would agree to self-isolate [30].

School Closure and Social Distancing

School closure is one of the few measures that the studies found to possibly not be cost-effective, especially for a less severe pandemic in which costs would be above $200,000 per QALY [40,41]. Although the studies generally agree that the measure is effective in reducing the overall attack rate [42], which was higher among children for H1N1 [43,44], the lost working days of parents from taking care of their children and loss of education account for a substantial portion of the costs [22]. A school closure of 1 to 4 weeks produces only a modest effect on the epidemic, whereas extending the closure to 8 weeks significantly decreases the number of cases but at the expense of vastly increased costs [40]. Even for higher fatality pandemics, it seems that school closure may exhibit a net cost [22,40]. However, limited school closure in combination with antiviral treatments and other social-distancing policies has often been regarded as an optimum strategy in multiintervention studies [22,41,45]. Indeed, schools and workplaces are big vectors for transmitting disease [46,47], creating opportunities for cost-effective social-distancing policies (e.g., using remote teaching and working [48] or facemasks [49]). Studies have also suggested that adult and child social distancing (meaning voluntarily staying home) is more cost-effective than closing schools [22], with increased cost-effectiveness if a high percentage of the population complies [30]. However, analogous to the case of isolating exposed persons during a disease's

Table 3 – Vaccination's costs and benefits.

Costs and benefits usually accounted for vaccination	
Direct	
Costs or benefits that are directly associated with influenza disease, e.g., medicines, hospital, machines, and employees	
Costs	
Vaccine purchase	All
Vaccine administration	[16,31–33]
Vaccine promotion	[31,33]
Benefits	
Cases avoided or days of sickness avoided ("burden of disease")	All
Death avoided ("burden of death")	All
Reductions in physician visits	[32,34,37]
Reduction in antibiotics	[16,33,37]
Reduction in laboratory testing	[33]
Reduction in hospital costs	[16,32–34,36]
Reduction in emergency department visits and intensive care unit	[33,34,36]
Reduction in mechanical ventilation and extracorporeal membrane oxygenation	[36]
Indirect	
Costs or benefits for the overall society, in other areas than health, i.e., number of days out of work, GDP loss, missed education, missed opportunities	
Costs	
Patient time to receive vaccination	[31,34]
Time to be with a child during the vaccination	
Benefits	
Reduction in lost work days of an adult with influenza	[16,32,33,37]
Time taken off from work to take care of a child with influenza	[16,32,33]
Externalities	
Side effects from the intervention	
Costs	
Negative side effects related to vaccination—Guillain-Barre syndrome, anaphylactic reaction	[31,33,34]
Benefits	
Herd effect and protection for future pandemics	
Discount rate	
For costs or benefits covering more than 1 y, a discount rate is applied	
Economists may want to choose the country-specific rate of return of long-term government bonds as the social discount rate for costs. WHO CHOICE uses a discount rate of 3% for the base case—a discount rate of 6% is also explored using sensitivity analysis [22].	

CHOICE, CHOosing Interventions that are Cost-Effective; GDP, gross domestic product; WHO, World Health Organization.

contact-tracking phase, it seems unrealistic that all citizens would comply with self-isolation [50]. The less severe the infection, the less people will agree to stay home when sick [50] unless a change in behavior is induced by targeted campaigns [51] and corporate policies.

Discussion

By reviewing the recent evaluation of pandemic interventions in terms of (converted) cost-utility, policymakers will get a general idea of the comparative cost-utility ratio of various interventions, provided a given severity and fatality context [6]. For instance, by choosing a willingness-to-pay threshold of $45,000 per DALY [23,25,27,34–36], one could build a synthesis of which intervention would be cost-effective for a different level of infectivity and severity, as presented in Table 2.

However, one should bear in mind the limitations of our review. First, we report many differences in the valuation approaches of our selected studies [12]. Second, we made numerous assumptions for converting the CCUM. For instance, the same conclusions would not be valid for cases in which the mortality distribution of a new virus strain shows a greater variation among age classes than does H1N1 [3,43,44]. As an example, school closure may become highly cost-effective for a disease with a higher mortality among children. Therefore, a dedicated cost-effectiveness assessment of the interventions under consideration should be conducted at the beginning of a new crisis, in light of the available parameters at the time. The same remark can be made about the country's parameters, such as the characteristics of the population or the cost of treatments, which may cause divergence in the cost-utility results [52].

One must also notice that the cost-effectiveness found for an intervention is highly dependent on the modeling assumptions [10,11] and on the costs and benefits accounted for in the studies. To illustrate this last point, we may consider vaccination (see Table 3). The costs and benefits that are accounted for in the studies are the purchase of the vaccine (direct cost) and the sickness and death avoided (direct benefit). Other costs and benefits, such as vaccine distribution, adverse effects, absenteeism of the caretakers, and reduction in inpatient visits and hospitalization, are not systematically taken into account, as illustrated in Table 3. This issue may also create uncertainty in the expected cost-utility of the interventions.

On the positive side, severity and fatality parameters play a central role in the benefit estimations [10,45]. If they are taken into consideration, studies' results generally end up within the same range, allowing conclusions to be drawn. In addition, most studies in the review relate to developed economies. Therefore, one may expect less variance in the unit costs and

cost-utility results among similar countries [20], and the choice of an appropriate willingness-to-pay threshold [20] may help to adjust the conclusion to the economic differences between countries.

Conclusions

The question examined in this article concerned the cost-effectiveness of the interventions available to public health officials during an influenza pandemic. For this review, we selected CEA, CUA, and CBA studies available post-H1N1 (2009–2014) with different categories of pandemic interventions. We then presented their (converted) cost-utility results (in dollar per DALY or QALY) in the pandemic context of infectivity and severity (Fig. 1). We found that the research on cost-effectiveness has mostly focused on antivirals, vaccines, and school closures, whereas there is a lack of economic evaluation for preparedness, prevention, trade and travel restrictions, hygiene recommendations, and human-to-animal transmission interventions.

The few studies on preparedness interventions concern surveillance networks and antiviral stockpiling, and they suggest that preparedness might be highly cost-effective, with a CCUM ranging from $125 to $20,000 per QALY. However, the cost utility of antiviral stockpiling was assessed before the recent questioning of antiviral effectiveness [29]. Regarding mitigation strategies, quarantining individuals at a hospital (Green protocol) and tracking exposed persons are assumed to be cost-effective interventions, even for crises of medium to low severity. Vaccination, when available, also seems very cost-effective, even for lower infectivity and severity pandemics, by reducing the burden of disease. Vaccination has an estimated effectiveness level below $20,000 per QALY for a medium crisis. The assumption, however, is to be able to vaccinate a certain proportion of the population (30%–60%), which may not be realistic in a low-fatality scenario.

Treatment with antivirals does not qualify for a crisis with low mortality. Antivirals may be economically effective to reduce the burden of death in the case of a high-fatality pandemic, but this capacity has recently been questioned [21]. School closure and social distancing by themselves do not seem to be cost-effective, with costs above $100,000 per DALY for medium-severity to low-severity pandemics; they could be replaced in such cases by adults and children voluntarily staying home, wearing face-masks, and working and teaching remotely. Multi-intervention studies do suggest, however, that closing schools could be part of the optimum strategy if used moderately, especially for very infectious viruses.

One must, however, use those conclusions carefully, because the original studies and our CCUM use numerous assumptions that may not apply to a specific country or crisis. Therefore, a dedicated cost-efficiency assessment of the interventions under consideration should be conducted at the beginning of a new crisis, in light of the available parameters at the time.

Future research should focus on less-studied interventions and the improvement in the economic utility of pandemic measures. Such research could propose a larger range of scenarios for extreme events [53,54] and innovative models for preparedness. Our review also shows the need for a unified framework [10,12] to serve as a basis for cost-effectiveness assessment, as well as the need for tools enabling a quick value-for-money evaluation of the strategic response to a pandemic crisis, thus expanding the guidance provided by World Health Organization CHOICE (CHOosing Interventions that are Cost-Effective) [52] to these situations. This need for additional guidelines on the economic evaluation of influenza measures was also raised in the previous systematic review [5].

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.05.005 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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