HITAP
Health Intervention and Technology Assessment Program

Research Report

Systematic review of economic evaluations on preparedness and interventions against influenza pandemics

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Systematic review of economic evaluations on preparedness and interventions against influenza pandemics

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List of abbreviations

AVP = Antiviral Prophylaxis

AVT = Antiviral Treatment

CEA = Cost Effectiveness Analysis

CBA = Cost Benefit Analysis

CJ = Clinical Judgment

CUA = Cost Utility analysis

DALY = Disability Adjusted Life Year

EURONHEED = European Network of Health Economics Evaluation Databases

GNI = Gross National Income

HEED = Health Economic Evaluation Database

HEN = Health Evidence Network

HR = High Risk

HTA = Health Technology Assessment

ICER = Incremental Cost Effectiveness Ratio

NCS = Not Clearly Stated

NHS EED = National Health Service Economic Evaluation Database

PCR = Polymerase Chain Reaction

PoC = Point of Care test

QALY = Quality Adjusted Life Year

RCT = Randomized Controlled Trial

RePEc = Research Papers in Economics

SARS = Severe Acute Respiratory Syndrome

SSCI = Social Science Citation Index

UNICEF = United Nations Children's Fund

VAC = Vaccine

WHO = World Health Organization

Executive summary

This systematic review aims to assess the state of the art of and the results from economic evaluations of interventions to control and prevent influenza pandemics in order to support policymakers with resource allocation choices, and identify gaps for future research. MEDLINE as well as health economics, health technology assessment and social sciences databases were used to identify relevant published papers. To retrieve grey literature and additional conference proceedings, the search was expanded by using Google and Scirus. Additional reports were also obtained through correspondence with authors of full texts included in the final analysis and conference proceedings abstracts.

Thirty studies met the inclusion criteria and were included in the analysis. The majority of studies adopted cost-effectiveness and cost-utility approaches and mainly focused on vaccination and antiviral drugs. Although almost studies complied with the standard methodological guidelines for conducting economic evaluation, quality of evidence used was relatively poor, especially for estimating adverse events and complications of interventions, baseline clinical data and resource use. In addition, inadequacy in effectiveness and cost-effectiveness studies on non-pharmaceutical interventions, variation in vaccination protocols and drug regimens introduced in the evaluations of pharmaceutical interventions, and a limited number of studies assessing value for money across potential interventions were observed.

The combination of pharmaceutical and non-pharmaceutical interventions is relatively cost-effective compared to providing vaccines and/or antiviral drugs. For pharmaceutical interventions, incremental cost-effectiveness ratios (ICERs) vary largely from cost-saving to very high values. According to the average Gross National Incomes per capita used as ceiling thresholds, social distancing, antiviral prophylaxis for general population plus school closure, vaccination for general population plus school closure, and antiviral prophylaxis for household contacts plus school closure are amongst cost-effective strategies for all low-, middle- and high-income countries. Quarantine for household contacts seems unlikely to be cost-effective even for low- and middle-income countries.

To strengthen the WHO guidelines for preparedness and intervention against pandemic influenza, there are four major recommendations. Firstly, a repeat review should be performed again in the next two years because a number of published studies on baseline clinical data, clinical effect sizes, adverse events and complications, and value for money of different interventions from the recent pandemic will be increasingly available in the near future. Secondly, the WHO in potential collaboration with other relevant international agencies should take a leading role in facilitating studies on effectiveness and cost-effectiveness of interventions against pandemic influenza in the developing world. Thirdly, the WHO should bring together all relevant experts and stakeholders to seek consensus on certain important parameters used for future economic evaluations and identify priority research areas. Lastly, the WHO should devise guidelines or recommendations for assessing impact of pandemic influenza and its relevant interventions in a systematic and reliable manner.

1. Introduction

When a new subtype of influenza A virus which is infectious to humans gains human-to-human transmissibility efficiently enough to cause community level outbreaks, this virus is said to have pandemic potential. If this new subtype spreads globally causing disease and deaths, it becomes pandemic. Since the 16th century, influenza pandemics have occurred at intervals ranging between 10-50 years, creating varying levels of impact on the societies.[1] In March 2009, a new subtype of influenza A H1N1 virus was identified in Mexico and the USA. It spread to all continents in less than 9 weeks becoming the first pandemic of the 21st century. Children, young adults, pregnant women, and those with chronic illnesses were disproportionately affected and made up most of the hospitalization cases. The estimated case-fatality rate was 0.15–0.25%, with most deaths in middle-aged adults with underlying diseases.[2] The World Health Organization (WHO) published pandemic preparedness and response guidance in 1999 with two revisions in 2005 and 2009.[1, 2] These documents summarize the recommended WHO and national actions against pandemic influenza according to pandemic phases. For some recommendations, evidence is limited to observations or epidemiological models. In some cases inferences are drawn from other respiratory infectious diseases, such as seasonal influenza or SARS. With a view to incorporate important experience and evidence acquired during the pandemic H1N1 2009, WHO will revise the pandemic preparedness guidelines. Including cost-effectiveness evidence in the revision process will strengthen the guidance by providing a framework to prioritize the allocation of limited resources in impending, strenuous times.

The aim of this paper is to systematically review published and unpublished economic evaluations of interventions to control and prevent influenza pandemics. The analysis will describe and assess the identified studies and determine patterns in cost-utility ratios. The findings will contribute to the revision of the WHO guidance on pandemic influenza, potentially support policy-makers to take informed decisions on allocating resources effectively and identify gaps for future research.

2. Methods

In September 2010, a systematic search was started with a conventional database used for systematic review, MEDLINE. In addition, the specialist health technology assessment databases, namely National Health Service Economic Evaluation Database (NHS EED), Health Economic Evaluation Database (HEED), Cost-Effectiveness Analysis Registry (CEA Registry), European Network of Health Economics Evaluation Databases (EURONHEED), Health Technology Assessment Database (HTA), Health Evidence Network (HEN), EconLit and Research Papers in Economics (RePEc) were further explored. Since the abovementioned searches identified a majority of pharmaceutical interventions, a search through the Social Science Citation Index (SSCI), which is more focused on non-pharmaceutical issues and also covers conference proceedings, was also introduced.

To retrieve grey literature and additional conference proceedings, the search was expanded by using the generic search engine Google, and the science-specific search engine Scirus. Furthermore, reference lists of relevant publications were screened and cited reference searching of the first topic-specific economic evaluation (Meltzer et al.)[3] was also performed using Web of Science. Additional reports were obtained through correspondence between one reviewer (RPV) and authors of full texts included in the final analysis and conference proceedings abstracts.

The search strategies used controlled vocabulary thesaurus terms in combination with relevant free-text terms, including ‘H1N1’, ‘pandemic influenza’, ‘influenza pandemic’, ‘cost benefit’, ‘costs’, ‘cost effective’ and ‘economics’. The summarized search strategy from MEDLINE is shown as an example in appendix 1.

All identified abstracts were reviewed by two independent reviewers from a review team (AM, KW, NP, RPV and SK). Discrepancies were resolved by a third reviewer. The papers were included in the analysis if they met criteria shown in table 1.

Table 1 Inclusion and exclusion criteria employed in the abstract selection process

Inclusion Criteria	Exclusion Criteria
• Original economic evaluation studies considering prevention or control of 2009 pandemic or potential pandemic influenza • Partial economic evaluations if both costs and outcomes of one intervention either pharmaceutical or non-pharmaceutical was considered • Full economic evaluations if costs and outcomes of more than one pharmaceutical or non-pharmaceutical interventions were considered	• Reviews or editorial reports of original studies • Studies not including both costs and outcomes of interventions • Economic impact of pandemic influenza per se • Economic evaluations of interventions related to pandemic influenza complications • No provision of English full text (except Spanish, German, Thai, Dutch for which the review team possessed language translation ability)

A standardized data extraction form was devised. The articles were grouped according to type of evaluation: i) cost-minimization analysis if they compared costs of different interventions with evidence of equal effectiveness, ii) cost-benefit analysis if they measured health outcomes in monetary units, iii) cost-effectiveness analysis if they expressed health outcome in natural units, e.g. cases averted, hospitalization averted, or death averted, and iv) cost-utility analysis if they presented health outcomes in common units, e.g. quality-adjusted life-years (QALYs) or disability- adjusted life-years (DALYs).

The studies were appraised in two different ways for quality assessment purposes following approaches employed by Teerawattananon et al.[4] First, according to specific methodological and reporting practices for economic evaluation studies, the expression of perspective used for the analysis, relationship between time horizon and discounting, reporting of incremental cost-effectiveness ratio (ICER), performing uncertainty analysis, and declaration of funding support were examined.

Since it is widely recognized that the credibility of economic evaluations not only depends on the appropriateness of the methods employed but also on the quality of evidence used, various individuals and groups of health economists have devised guidance for selection of input parameters for economic evaluation to minimize bias. As a result, the review considers the hierarchy of data sources (see table 2). The hierarchy of evidence showed a list of

potential sources of i) clinical effect sizes; ii) adverse events and complications; iii) baseline clinical data; iv) resource use; v) costs; and vi) utilities, which were applicable only to cost-utility analysis studies. Data sources of each component are ranked from one to six in descending order. Rank 1 was given if its parameters were derived the most appropriate data sources.

Table 2 Hierarchies for data sources (adapted from Cooper et al.[5])

Rank	Data components
Clinical effect sizes/adverse events and complications	
1+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes
1	Single RCT with direct comparison between comparator therapies, measuring final outcomes
2+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring surrogate outcomes Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring the final outcomes for each individual therapy
2	Single RCT with direct comparison between comparator therapies, measuring the surrogate outcomes Single placebo-controlled RCTs with similar trial populations, measuring the final outcomes for each individual therapy
3+	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes
3	Single placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes for each individual therapy
4	Case control or cohort studies
5	Non-analytic studies (e.g. case reports, case series)
6	Expert opinion
9	Not clearly stated
Baseline clinical data (if applicable)	
1	Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest
2	Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest
3	Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction
4	Old case series or analysis of reliable administrative databases. Estimates from RCTs
5	Estimates from previously published economic analyses: unsourced
6	Expert opinion
9	Not clearly stated

Continued next page

Table 2 Contd

Rank	Data components
Resource use	
1	Prospective data collection or analysis of reliable administrative data for specific study
2	Recently published results of prospective data collection or recent analysis of reliable administrative data: same jurisdiction
3	Unsourced data from previous economic evaluations: same jurisdiction
4	Recently published results of prospective data collection or recent analysis of reliable administrative data: different jurisdiction
5	Data source not known: different jurisdiction
6	Expert opinion
9	Not clearly stated
Costs	
1	Cost calculations based on reliable databases or data sources conducted for specific study: same jurisdiction
2	Recently published cost calculations based on reliable databases or data course: same jurisdiction
3	Data source not known: same jurisdiction
4	Using charge (price) rather than cost when societal perspective was adopted
5	Recently published cost calculations based on reliable databases or data sources: different jurisdiction
6	Data source not known: different jurisdiction
9	Not clearly stated
Utilities (if applicable)	
1	Direct utility assessment for the specific study from a sample either: (a) of the general population, or (b) with knowledge of the disease(s) of interest, or (c) of patients with the disease(s) of interest Indirect utility assessment from specific study from patient sample with disease(s) of interest, using a tool validated for the patient population
2	Indirect utility assessment from a patient sample with disease(s) of interest, using a tool not validated for the patient population
3	Direct utility assessment from a previous study from a sample either: (a) of the general population, or (b) with knowledge of the disease(s) of interest, or (c) of patients with the disease(s) of interest Indirect utility assessment from previous study from patient sample with disease(s) of interest, using a tool validated for the patient population
4	Data source not known: method of elicitation unknown
5	Patient preference values obtained from a visual analogue scale
6	Delphi panels, expert opinion
9	Not clearly stated

This review compared the value for money of different interventions for prevention and control of pandemic influenza; however, the evaluations were conducted in different settings and timeframe. This study adjusted cost-effectiveness ratio into a common currency and utility unit. International dollars (I$), at 2010 values, were presented using national gross

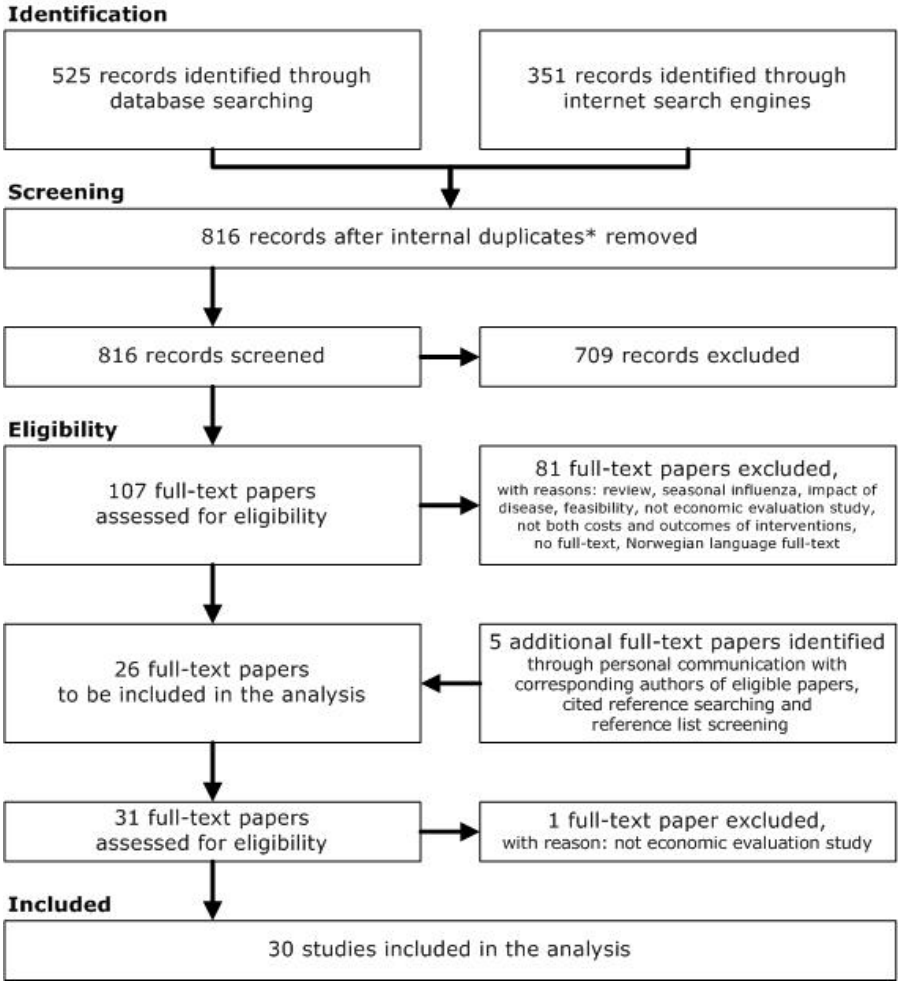
domestic product deflator values and implied purchasing power parity conversion rates from the International Monetary Fund.[6] In addition, exchange rates obtained from OANDA (http://www.oanda.com/currency/historical-rates) were applied when cost outcomes were reported in foreign currencies rather than local. In order to judge which interventions are cost-effective the ceiling thresholds, the amount of budget that decision-makers are willing to pay to gain a QALY, needs to be clearly specified. Because of a lack of explicit and implicit thresholds for most countries in the world, the World Bank thresholds for classifying countries into low-income, lower middle-income, upper middle-income and high-income countries were used as a maximum ceiling threshold, due to the fact that the World Bank thresholds refer to the 2009 Gross National Income (GNI) per capita.[6]

3. Results

3.1 Review profile

The search in the electronic databases identified a total of 525 records. In addition, 351 records were identified through internet search engines. There were 107 records that met the inclusion criteria and were assessed for eligibility, but 81 full texts were not included in the final analysis. These studies were excluded because they were reviews, epidemiological models, focused on seasonal influenza, impact of influenza or feasibility of influenza interventions, full text was unavailable or not in the eligible languages, or did not report both costs and outcomes of interventions. In addition, five full text grey papers were identified from correspondence with authors of eligible papers, cited reference searching, and reference list screening, of which one was excluded as it was an epidemiological model. Finally, 30 studies were considered in our analysis (figure 1).

Figure 1 Flow chart of search strategy



* Records duplicated inside an individual database or internet search results list.

3.2 Descriptive review results

Table 3 provides the characteristics of the studies included in the analysis. The majority of studies adopted CEA and CUA approaches (12 CEA, 12 CUA, 2 CEA and CBA, and 1 CEA and CUA) (see figure 2). Three studies reported CBA results. Figure 3 illustrates the relationship among study settings, year of study, and year of publication. Most studies (10 studies) were conducted in the year 2009, when the pandemic event occurred. Seven studies

assessed value for money of interventions in the US setting, followed by the UK and Canada (4 studies in each setting), the Netherlands and Singapore (3 studies in each setting), France (2 studies), and other six countries with one study each (see figure 4). There was one study conducted for multinational developed country settings.[7]

Figure 2 Types of economic evaluation

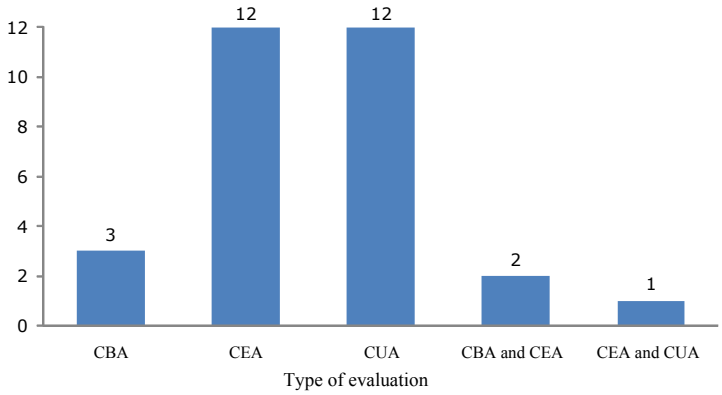
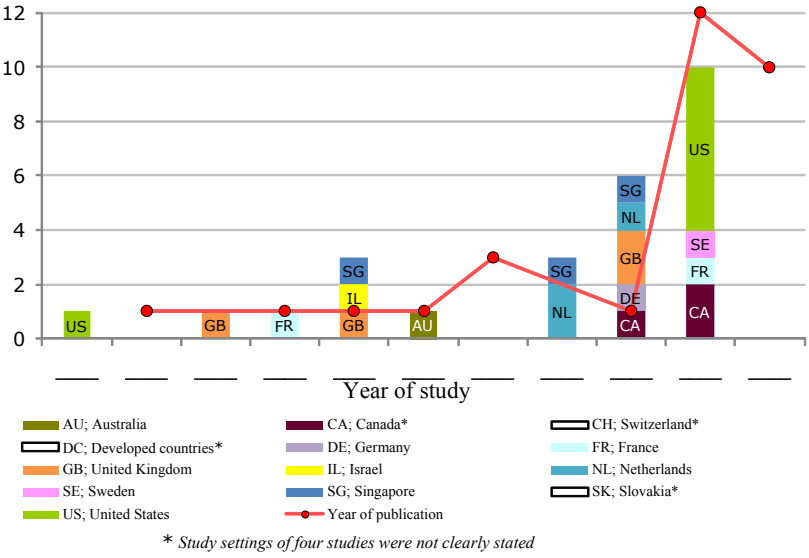


Figure 3 Study settings by year of study and year of publication



* *Study settings of four studies were not clearly stated*

Table 3 Characteristics of reviewed studies

Authors (year of publication)	Study setting	Study year	EE type	Approach	Perspective used	Outcome measured	Time Horizon	Discounting	Type of uncertainty analysis	Source of funding
Andradóttir et al. (2010)[8]	Canada	2008	CEA	Dynamic: Stochastic individual-level simulation	Societal	Cases averted	Lifetime	Performed unclear	Not performed	NCS
Baguelin et al. (2010)[9]	United Kingdom	2008	CUA	Dynamic: Deterministic SEIR/ SEEIIR model	Healthcare provider	QALYs gained	Lifetime	4%	Performed unclear	NCS
Balicer et al. (2005)[10]	Israel	2004	CBA	Static: Spreadsheet model	Societal	Benefit in monetary term	10 years	3%	Multivariate	NCS
Beigi et al. (2009)[11]	United States	2009	CUA	Static: stochastic decision analytic computer simulation	Societal	QALYs gained	NCS	3%	PSA	Domestic public funds
Brouwers et al. (2009)[12]	Sweden	2009	CEA	Dynamic: Stochastic, networked individual-level simulation ("MicroSim")	Societal	Cases averted	Less than 1 year	Not Applicable	Performed unclear	NCS
Brunovský et al. (2009)[13]	Slovakia	NCS	CBA	Static: Monte Carlo simulation	NCS	Benefit in monetary term	NCS	Performed unclear	PSA	Domestic public funds, EU, for-profit private

Continued next page

Table 3 Contd

Authors (year of publication)	Study setting	Study year	EE type	Approach	Perspective used	Outcome measured	Time Horizon	Discounting	Type of uncertainty analysis	Source of funding
Dan et al. (2009)[14]	Singapore	2008	CEA	Static: Markov model	Healthcare provider	Deaths averted	Less than 1 year	Performed unclear	Multivariate	NCS
Deuffic-Burban et al. (2009)[15]	France	2009	CEA	Static: Decision tree	Healthcare provider	LYs saved	NCS	3% benefit only	Univariate Multivariate	Domestic public funds
Doyle et al. (2006)[16]	France	2003	CEA	Static: Monte Carlo simulation	NCS	Deaths averted	NCS	Performed unclear	PSA	No funding support
Durbin et al. (Forthcoming)[17]	Canada	NCS	CEA	Dynamic: Non-homogeneous individual-based simulation (deterministic SIR model)	Societal	Deaths averted	Lifetime	5%	Multivariate	NCS
Khazeni et al. (2009)[18]	United States	2009	CUA	Dynamic: Compartmental epidemic model + Markov model (deterministic SIRD model)	Societal	QALYs gained	Lifetime	3%	Univariate PSA	Domestic public funds
Khazeni et al. (2009)[19]	United States	2009	CUA	Dynamic: Compartmental epidemic model + Markov model (deterministic SIRD model)	Societal	QALYs gained	Lifetime	3%	Univariate MultivariateP SA	Domestic public funds
Lee BY et al. (2009)[20]	NCS	NCS	CUA	Static: Computer-simulation decision tree	Societal	QALYs gained	NCS	3% costs only	PSA	Domestic public funds

Continued next page

Table 3 Contd

Authors (year of publication)	Study setting	Study year	EE type	Approach	Perspective used	Outcome measured	Time Horizon	Discounting	Type of uncertainty analysis	Source of funding
Lee BY et al. (2010)[21]	NCS	NCS	CUA	Static: Monte Carlo decision analytic computer simulation	Societal	QALYs gained	NCS	3%	Univariate MultivariateP SA	Domestic public funds
Lee VJ et al. (2006)[22]	Singapore	2004	CBA and CEA	Static: Decision tree	Societal	Benefit in monetary terms	4 years	Performed unclear	Univariate PSA	No funding support
Lee VJ et al. (2009)[23]	Singapore	2007	CBA and CEA	Static: Decision tree	Societal	Benefit in monetary term	50 years	3%	Univariate, MultivariateP SA	No funding support
Lugnér et al. (2009)[24]	Netherlands	2007	CEA	Dynamic: Deterministic SEIGR model	Societal	LYs saved	30 years	4% cost, 1.5% benefit	Univariate	No funding support
Lugnér et al. (2010)[25]	Netherlands	2007	CEA	Static and Dynamic: Decision tree/deterministic SEIR model	Societal	LYs saved	NCS	1.5% benefit only	Univariate	NCS
Lugnér et al. (2010)[7]	Germany, Netherlands, United Kingdom	2008	CUA	Dynamic: Deterministic SEIR model	Societal	QALYs gained	NCS	Not performed	Not performed	WHO
Medema et al. (2004)[26]	Developed countries	NCS	CEA	NCS: Computer based simulation	Healthcare system	Cases averted	NCS	5%	Univariate	NCS
Meltzer et al. (1999)[3]	United States	1997	CBA	Static: Monte Carlo simulation	Societal	Benefit in monetary term	Lifetime	3%	PSA	NCS

Continued next page

Table 3 Contd

Authors (year of publication)	Study setting	Study year	EE type	Approach	Perspective used	Outcome measured	Time Horizon	Discounting	Type of uncertainty analysis	Source of funding
Newall et al. (2010)[27]	Australia	2005	CEA	Dynamic: Hybrid transmission model and decision tree (deterministic SEIR model)	Societal	LYs saved	Lifetime	5%	Univariate, PSA	For-profit private
Perlroth et al. (2010)[28]	United States	2009	CUA	Dynamic: Networked individual-level computational model ("Loki-Infect")	Societal	QALYs gained	NCS	3%	Univariate Multivariate	Domestic public funds
Piercy et al. (2003)[29]	Switzerland	NCS	CEA	Static: Hybrid decision tree	Societal	LYs saved	1 year	5% benefit only	Performed unclear	NCS
Sander et al. (2006)[30]	United Kingdom	2002	CEA and CUA	Static: Decision tree	Healthcare provider	QALYs gained	1 year	1.5% benefit only	PSA	For-profit private
Sander et al. (2009)[31]	Canada	2009	CUA	Dynamic: Simulation model (stochastic SEIAR/SVEITAR model)	Healthcare system	QALYs gained	NCS	Performed unclear	Performed unclear	Domestic public funds
Sander et al. (2009)[32]	United States	2009	CUA	Dynamic: Discrete-time, stochastic, individual-level microsimulation	Societal	QALYs gained	Less than 1 year	3%	Performed unclear	Domestic public funds

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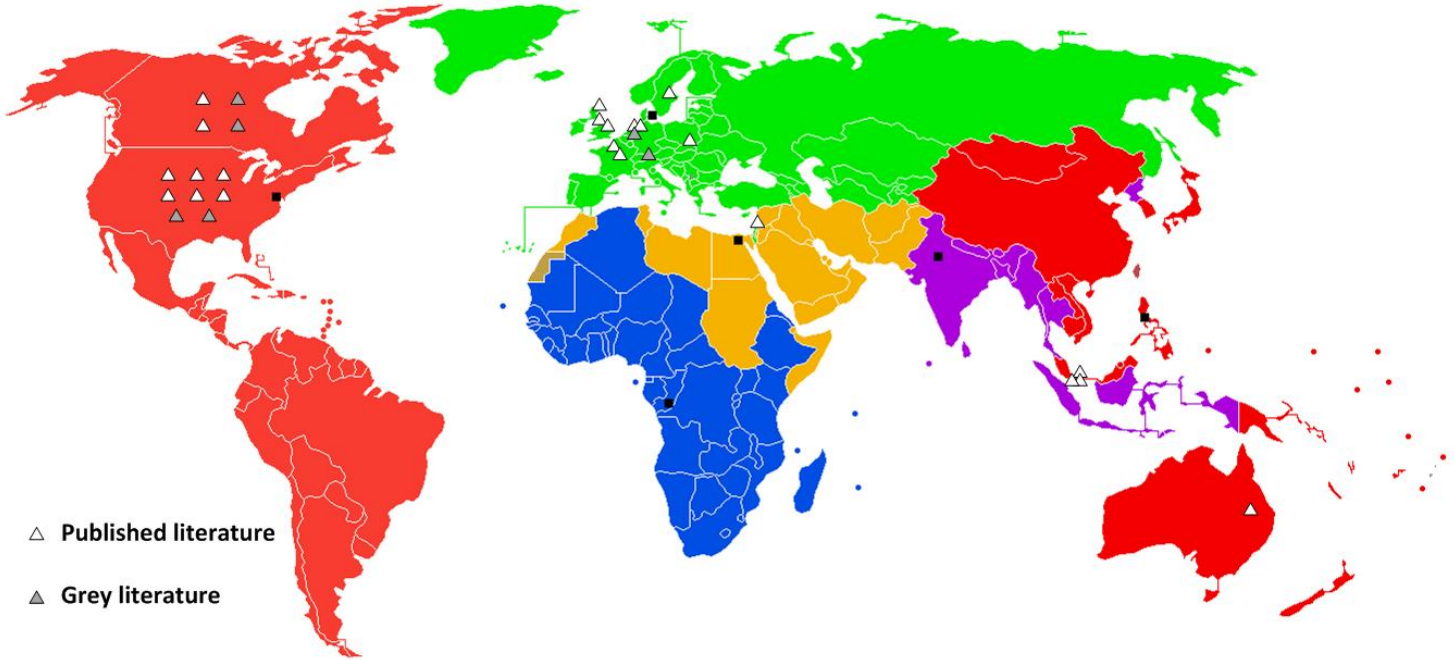
Table 3 Contd

Authors (year of publication)	Study setting	Study year	EE type	Approach	Perspective used	Outcome measured	Time Horizon	Discounting	Type of uncertainty analysis	Source of funding
Sander et al. (2010)[33]	Canada	2009	CUA	Dynamic: Simulation model (stochastic SEIAR/SVEITAR model)	Healthcare system	QALYs gained	Lifetime	5%	Univariate Multivariate PSA	Domestic public funds
Siddiqui et al. (2008)[34]	United Kingdom	2004	CUA	Static: Decision tree	Healthcare system	QALYs gained	30 years	4%	Univariate PSA	Domestic public funds, EU
Yarmand et al. (2010)[35]	United States	2009	CEA	Dynamic: Continuous-time simulation model (SEIR model)	NCS	Cases averted	Less than 1 year	Not Applicable	Univariate Multivariate	Domestic public funds

CBA = cost benefit analysis; **CEA** = cost effectiveness analysis; **CUA** = cost utility analysis; **EU** = European Union; **LYs** = life years; **PSA** = probabilistic sensitivity analysis; **QALYs** = Quality adjusted life years; **NCS** = not clearly stated; **SEIAR/SVEITAR**: Susceptible, Exposed, Infected, Asymptomatically Infected and Recovered/ Susceptible, Vaccinated, Exposed, Infected, Treated, Asymptomatically Infected and Recovered; **SEIGR**: Susceptible, Latent, Infectious, Recovering, Removed; **SEIR**: Susceptible, Exposed, Infected, Recovered; **SEEIIR:** Susceptible, Exposed, Latent, Infected, Recovered**, SIR**: Susceptible, Infected, Recovered; **SIRD**: Susceptible, Infected, Recovered, Dead

Figure 4 World map illustrating study settings of all 30 full-text papers included in the analysis



Modified from the WHO and the World Bank's classification for containment and mitigation of pandemic influenza,[36, 37] table Error! Reference source not found. depicts that vaccination (18 studies) and antiviral drugs (17 studies) were commonly evaluated for both targeted (specific groups, such as high-risk or priority population) and general population. Notably, there was no economic evaluation assessing economic value of travel restriction and public hygiene and disinfection measures.

Table 4 Classification of studies (using referencing number) by types of interventions modified from the WHO and the World Bank's taxonomy

		National		
Interventions*	**Community**	**Targeted**	**Broad-based**	**International**
Quarantine	28			
Travel restriction				
Public Communications & Advisories	14,35			
Social distancing	14		8	
Public Hygiene and disinfection				
Personal protective equipment	14			
Vaccination		7, 11, 16, 23, 29, 35	3, 7, 8, 12, 13, 16, 18, 23, 26, 31, 33	
Antiviral Drug		9, 10, 14-16, 22, 29, 34	8, 10, 16, 21, 22, 24, 25, 30, 34	

* *Categories highlighted in grey are not relevant categories for each intervention*

Table 4 demonstrates the discrepancy of drugs and vaccine regimens considered in the economic evaluation studies. Although the majority (19 studies) assessed oseltamivir, they used different dosages and durations for prophylaxis. For example, Yarmand[35] used oseltamivir 75 mg once daily for ten days for young adult prophylaxis in the US, whilst Balicer et al.[10] used the same dosage of oseltamivir for 50-day prophylaxis among the Israeli general population. Doses of vaccine ranged from one to three, without clearly specifying the duration of protection.

Table 5 Antiviral drugs and vaccine regimens

Authors	AV Prophylaxis				AV Treatment			Stockpiling	Vaccination	
	Duration	Dose			Duration	Dose		Shelf-life	Duration of protection	Dose
		Oseltamivir	Zanamivir	Amantadine or rimantadine		Oseltamivir	Zanamivir			
Andradóttir et al. (2010)[8]	10 days	NCS	NCS	NCS	5 days	NCS	NCS		NCS	1
Baguelin et al. (2010)[9]	NCS	Dose unspecified			NCS	NCS	NCS	NCS	Lifetime	1 (child < 2yr: 2 half-doses)
Balicer et al. (2005)[10]	50 days	75 mg once daily			5 days	150 mg once daily		10 years		
Beigi et al. (2009)[11]									NCS	2
Brouwers et al. (2009)[12]									NCS	2
Brunovský et al. (2009)[13]									NCS	2 to 3
Dan et al. (2009)[14]										
Deuffic-Burban et al. (2009)[15]					5 days	75 mg twice daily (adult & children > 13 years)				
Doyle et al. (2006)[16]	Post-exposure: 4 doses (5–6 y.o.), 6 doses (7–12 y.o.), 7 doses (1 dose/day for 7 days) (over 12 y.o.)	75 mg once daily							NCS	2
Durbin et al. (Forthcoming)[17]	NCS	NCS	NCS	NCS	NCS	NCS	NCS		NCS	1

Continued next page

Table 5 Contd

Authors	AV Prophylaxis				AV Treatment			Stockpiling	Vaccination	
	Duration	Dose			Duration	Dose		Shelf-life	Duration of protection	Dose
		Oseltamivir	Zanamivir	Amantadine or rimantadine		Oseltamivir	Zanamivir			
Khazeni et al. (2009)[18]									5 months	15 g adjuvant-antigen concentration
Khazeni et al. (2009)[19]	40 days	NCS	NCS	NCS	5 days	NCS	NCS	NCS	NCS	1 and 2 of 90 µg non-adjuvanted, 15 µg adjuvanted vaccine
Lee BY et al. (2009)[20]	10 days	75 mg once daily	10 mg once daily							
Lee BY et al. (2010)[21]					5 days	75 mg twice daily (adult & children > 13 years)	10 mg twice daily (adult & children > 5 years)			
Lee VJ et al. (2006)[22]	12 week	75 mg once daily						4 years		
Lee VJ et al. (2009)[23]								3.5 years	Short term	1
Lugnér et al. (2009)[24]	NCS	NCS	NCS	NCS				30 years		
Lugnér et al. (2010)[25]					NCS	NCS	NCS			
Lugnér et al. (unpublished)[7]									NCS	2
Medema et al. (2004)[26]									NCS	2 doses of 7.5 µg
Meltzer et al. (1999)[3]									NCS	NCS

Continued next page

Table 5 Contd

Authors	AV Prophylaxis				AV Treatment			Stockpiling	Vaccination	
	Duration	Dose			Duration	Dose		Shelf-life	Duration of protection	Dose
		Oseltamivir	Zanamivir	Amantadine or rimantadine		Oseltamivir	Zanamivir			
Newall et al. (2010)[27]	NCS	NCS	NCS	NCS	NCS	NCS	NCS	Vaccine: 3 years AV drugs: 5 years	NCS	1 and 2
Perlroth et al. (2010)[28]	10 days	Dose unspecified			5 days	Dose unspecified				
Piercy et al. (2003)[29]	6 or 12 weeks			100 mg twice daily (Elderly: 100 mg/day)	5 days	75 mg twice daily	10 mg twice daily		NCS	NCS
Sander at al. (2006)[30]	7-10 days	75 mg once daily								
Sander et al. (2009)[31]									NCS	NCS
Sander et al. (2009)[32]	10 capsules/10 days	75 mg once daily			10 capsules / 5 days	150 mg per commercial capsule		NCS	NCS	2
Sander et al. (2010)[33]									NCS	1 or 2
Siddiqui et al. (2008)[34]	NCS	Dose unspecified						AV drug: 5 years Test: 2 years		
Yarmand et al. (2010)[35]	10 days	75 mg once daily	Dose unspecified						Lifetime	2

NCS: not clearly stated

Table 6 shows the extent to which the 30 reviewed papers complied with standards for conducting and reporting economic evaluations. All studies complied with the recommendations on using discounting for costs and/or outcomes for studies with time horizon longer than one year. A relatively high proportion of studies described the study perspective(s), selection of comparators, performing uncertainty analysis, and reported ICERs. 67% of these studies disclosed funding sources.

Table 6 Extent to which the published economic evaluation studies included in this analysis met recommendations for good reporting of economic evaluation studies.[4]

Recommendations	Number of studies fulfilling recommendation*	Percentage (%)
Perspective specified	27/30	90
Description of comparator(s)	29/30	97
Used discounting for costs or/and outcomes if study period was > 1 year	13/13	100
Calculated and reported ICER	24/28	86
Performed uncertainty analysis	28/30	93
Disclosed funding sources	20/30	67

*Number of studies the recommendation is applicable
ICER: Incremental cost-effectiveness ratio

Nineteen studies adopted a societal viewpoint in the analysis. Four studies employed a healthcare provider's perspective and the same number of studies, a healthcare system's perspective. Regarding financial support for studies, eleven were supported by domestic public funders, followed by the for-profit private sector (3 studies). Surprisingly, 10 studies did not properly declare source of funding.

None of the studies were carried out alongside clinical trials, but all were model-based. Equal number of studies adopted dynamic and static models, whereas one study adopted both approaches.[25] Only one single study did not clearly state the approach used, which the reviewers were also unable to identify.[26] Time horizons (time window during which patients are followed and their resource use and health/cost outcomes measured) varied largely across studies, ranging from one month to a lifetime. Twelve studies (40%) did not clearly state time horizon employed, which is one of the major methodological flaws found in our review.

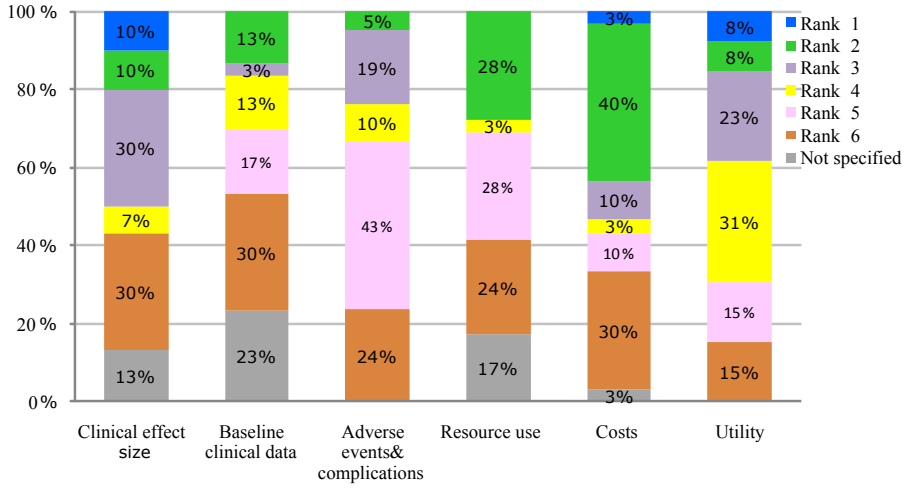
Quality of evidence used in the economic evaluation of pandemic influenza interventions was analysed in depth and the results are presented in table 7 and figure 5. They illustrate the poor

quality of data used for estimating adverse events and complications of interventions following with baseline clinical data and resource used. More than half of the reviewed studies used information from non-analytic studies (e.g. case report or case series), expert opinions, and unsourced information to estimate adverse events and complications, and baseline clinical data. Although information used for estimating clinical effect sizes and cost have relatively better overall quality, only a few of them derived from systematic review of randomized controlled trials measuring final outcomes for clinical effect sizes and cost calculation based on reliable data sources conducted for study settings.

Table 7 Quality of evidence used in 30 economic evaluations of interventions for prevention and control of pandemic influenza

Level of information (hierarchies of data sources)	Clinical effect sizes [n (%)]	Baseline clinical data [n (%)]	Adverse events & complications [n (%)]	Resource use [n (%)]	Costs [n (%)]	Utility [n (%)]
Rank 1	3 (10)	0 (0)	0 (0)	0 (0)	1 (3)	1 (8)
Rank 2	3 (10)	4 (13)	1 (5)	8 (28)	12 (40)	1 (8)
Rank 3	9 (30)	1 (3)	4 (19)	0 (0)	3 (10)	3 (23)
Rank 4	2 (7)	4 (13)	2 (10)	1 (3)	1 (3)	4 (31)
Rank 5	0 (0)	5 (17)	9 (43)	8 (28)	3 (10)	2 (15)
Rank 6	9 (30)	9 (30)	5 (24)	7 (24)	9 (30)	2 (15)
Rank 9 (not specified)	4 (13)	7 (23)	0 (0)	5 (17)	1 (3)	0 (0)

Figure 5 Rank of evidence used in the economic evaluation studies



3.3. Incremental Cost-Effectiveness Ratios (ICERs)

Figure 6 compares the cost per QALY of each intervention. No evidence suggests that target population, e.g. general or high-risk population, has significant influence on ICERs. The X axis of the figure is arranged according to population risk (as defined by researchers of each study), with relative low risk on the left-hand side and relative high risk on the right-hand side, and no downward trend is observed among similar interventions.

The combination of pharmaceutical and non-pharmaceutical interventions (represented by grey bars) was relatively cost-effective compared to providing vaccines and/or antiviral drugs. For pharmaceutical interventions, ICERs can vary largely from cost-saving to very high values (>I$ 1,000,000 per QALY). One obvious observation is that antiviral prophylaxis and treatment are cost-saving for the general population but relatively high ICERs for high-risk populations (i.e. influenza-like illness patients and pregnant women).

According to the predefined ceiling thresholds, 'social distancing' (strategy in which non-school, non-work and non-household personal contacts are reduced, as defined by Perlroth et. al.[28]), antiviral prophylaxis for general population plus school closure, vaccination for general population plus school closure, and antiviral prophylaxis for household contacts plus school closure are amongst cost effective strategies for all low, middle and high income countries.

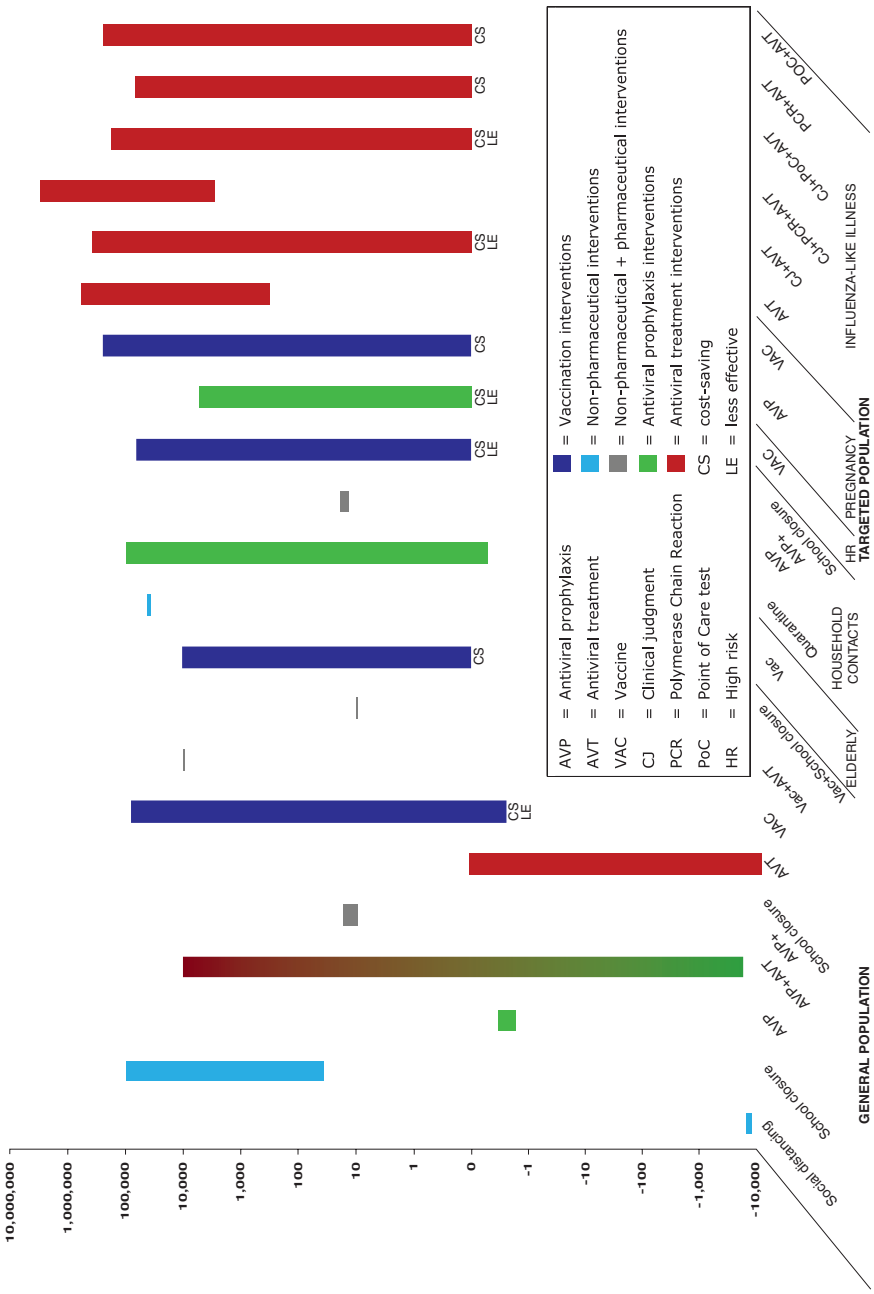


Figure 6 Summary of Incremental Cost Effectiveness Ratio (ICER) for pandemic influenza intervention by type of interventions (I$ per QALY gained)

Table 8 presents the four types of parameters found to be important in uncertainty analysis. These are epidemiological parameters and those related to natural disease progression (infectivity, e.g., attack rate or reproduction number; probability of pandemic; pandemic duration; disease severity, e.g., case fatality or probability of developing complications), those related to the intervention (efficacy, coverage, stockpiling capacity, timing of the intervention), resource use and cost parameters (healthcare costs, resources consumed, value of life, cost of intervention) and others (utility and discounting rate). There was no study that systematically analysed the relative importance of parameters. Since all studies purposively selected parameters for uncertainty analysis, we cannot make a firm conclusion on which parameters are important to determine value for money of pandemic influenza preparedness and interventions. However, we recommended that future studies should apply a more transparent and systematic approach to analyse uncertainty surrounding these parameters. This can be achieved by using the value of information approach.[38]

<INSERT TABLE 8>

Due to the importance of contact patterns in the outcomes of dynamic models, we also reviewed the mode in which populations interact. Consideration of contact patterns is especially important in modelling non-pharmaceutical interventions (e.g, social distancing), because the effectiveness of these interventions is highly dependent on how the population interact or behave in the initial phase of the pandemic.[35] It is noteworthy that a number of papers under review did not provide detailed information about contact patterns and relevant assumptions, but they refer to other epidemiological studies. In this regard, we reviewed the relevant sources and found that the quality of evidence used ranges from assumption35 to data from a large study of conducted in the European Union.[7, 9, 27]

In general, all epidemic models have an underlying network of mixing patterns, even though this network may not be explicit. Some compartmental models included in this review do not allow for variability (i.e., assume that communities are homogenous, not taking account of variability derived from age, sex, behaviour, social and spatial structure)[18, 19, 35], although some include modifications that allow for some level of heterogeneity, such as age-specific mixing patterns.[7, 9, 24, 25, 27] On the other hand, almost half of the studies included are agent based models, which appear to reflect the heterogeneity in contact patterns as occurs in the real world, especially those with a social network design[8, 12, 17, 28, 31-33] (Appendix 2).

Table 8 Types of parameters affecting the ICERs*

Intervention	Epidemiological and natural disease progression				Intervention efficacy and coverage				Resource use and costs	Utility and discount rate
	Pandemic probability	Infectivity	Pandemic duration	Disease severity	Intervention efficacy	Intervention coverage	Size of eligible population	Timing of intervention		
Vaccination		20, 11, 21, 22, 2, 12, 16		4, 20, 11, 21, 2, 12,16	4, 20, 16, 26, 28, 12	22, 20, 12	4	28, 22	10, 11, 21, 2, 5, 6, 26, 28, 16	28, 2, 10
Non-pharmaceutical intervention		7		7			7			
Non-pharmaceutical+pharmaceutical intervention		14, 29, 27, 30	29, 30	29, 30	29	29		30		29
Antiviral prophylaxis		22, 12, 25		12	12, 25	22, 12	13	22		
Antiviral treatment		8, 16, 18, 22		16	8, 16			22	8, 16	29
Antiviral stockpiling (treatment and prophylaxis)	3	3, 15, 17, 29	29	3, 15, 29	29	17, 29				

* References 9, 19, 1 and 24 do not state the sensitivity parameters

4. Discussion

The review identified a fair number of economic evaluation studies on preparedness and interventions against pandemic influenza though the majority (25/30, 83%) focused on only pharmaceuticals i.e. vaccine and antiviral drugs. This may be explained by several reasons which make effectiveness and cost-effectiveness studies of non-pharmaceutical interventions difficult and unattractive for researchers. First, ethical dimension plays an important part in hindering assessment of particular interventions. For instance, it may be unethical to restrict travel in or to introduce public communication and advisory measures to some population groups.

Second, there is a lack of standard protocols for non-pharmaceutical interventions resulting in a large variability of practice across settings. For example, no consensus exists on the way to carry out quarantine, travel restriction and social distancing. Third, most of non-pharmaceutical interventions are complex involving multidimensional aspects and difficult to control confounding factors. Assessing this group of interventions is likely to be costly and require strong support from decision makers in health and non-health sectors and public acceptance. Lastly, in absence of pandemic event it is difficult to introduce radical public measures e.g. travel restrictions, school closure and quarantine, which do not provide opportunity to generate the robust and reliable evidence on the effectiveness.

Despite a large number of economic evaluations of pharmaceutical interventions, existing evidence on their value for money is inconclusive. Since different vaccination protocols and drug regimens were examined across studies, the findings on costs and outcomes of these interventions are incomparable. Even the studies considered the same vaccination protocols and drug regimens, most modeled parameters, i.e., clinical effect size, baseline clinical data, and adverse events and complications are drawn from different sources with various levels of quality, ranging from expert opinion, computer simulation, small observational studies, to meta-analyses of randomized controlled trials.

Regarding methods for economic evaluation, the overall quality is relatively high. This may be because these studies were conducted in settings where health economics were well established. National methodological guidelines for conducting economic evaluation exist in

most of these settings. This would affect the choice of method employed by the researchers. If future evaluations are conducted in developing countries where no national guidelines are available, it is likely that a large variability in research quality can be observed. To ensure the quality of future evaluations, it is important to introduce internationally accepted methodological guidelines. Although a *WHO guide for standardization of economic evaluations of immunization programmes*[39] is publicly available, it is applicable only to vaccination, but not to antiviral drugs and non-pharmaceutical interventions. Despite the fact that the WHO guidelines on generalized cost-effectiveness analysis were introduced, they have been widely criticized and are not in line with other guidelines in many countries.[40-42] We strongly encourage the development of new guidelines for evaluations in developing countries with no national guidelines. In addition, these guidelines should be acceptable and feasible to follow by those conducting studies in developed countries in order to facilitate international comparison.

In figure 6, we present a novel approach to summarize cost-effectiveness evidence across interventions and target populations. This is useful not only for decision-makers in each country, but also for international organizations which guide and support countries to allocate resources, such as the WHO, the UNICEF and the World Bank. Even though figure 6 was contributed by 13 out of 30 reviewed studies, table 9 illustrates that the information in the figure was dominated by only three. These included Lee BY et al.[21], Perloth et al.[28] and Sander et al.[33], which assessed a wide range of pharmaceutical and non-pharmaceutical interventions that met the eligibility criterion to be included in the figure, i.e. presenting results in terms of cost-utility ratios.

Table 9 Number of interventions by type of interventions

Author	General									Targeted													
	Non-pharma		Pharma					Pharma + non-pharma		Pharma								Non-pharma	Pharma				Pharma +non-pharma
										Elderly		ILI						House-hold contacts	HR	House-hold contacts	Pregnancy		House-hold contacts
	School closure	Social distancing	AVP	AVP +AVT	AVT	VAC	VAC +AVT	AVP+ School closure	VAC + School closure	Immuned VAC	Non-immuned VAC	AVT	CJ + AVT	CJ +PCR +AVT	CJ +PoC +AVT	PCR +AVT	PoC +AVT	Qua-rantine	VAC	AVP	AVP	VAC	AVP + School closure
Andradóttir et al. (2010)[8]																							
Baguelin et al. (2010)[9]																			✓				
Balicer et al. (2005)[10]																							
Beigi et al. (2009)[11]																						✓	
Brouwers et al. (2009)[12]																							
Brunovský et al. (2009)[13]																							
Dan et al. (2009)[14]																							
Deuffic-Burban et al. (2009)[15]																							
Doyle et al. (2006)[16]																							
Durbin et al. (unpublished)[17]																							
Khazeni et al. (2009)[18]						✓																	
Khazeni et al. (2009)[19]				✓			✓																

Continued next page

Table 9 Contd

Author	General									Targeted													
	Non-pharma		Pharma					Pharma + non-pharma		Pharma								Non-pharma	Pharma				Pharma +non-pharma
										Elderly		ILI						House-hold contacts	HR	House-hold contacts	Pregnancy		House-hold contacts
	School closure	Social distancing	AVP	AVP +AVT	AVT	VAC	VAC +AVT	AVP+ School closure	VAC + School closure	Immuned VAC	Non-immuned VAC	AVT	CJ + AVT	CJ +PCR +AVT	CJ +PoC +AVT	PCR +AVT	PoC +AVT	Qua-rantine	VAC	AVP	AVP	VAC	AVP + School closure
Lee BY et al. (2009)[20]												✓	✓	✓	✓	✓	✓						
Lee BY et al. (2010)[21]																					✓		
Lee VJ et al. (2006)[22]																							
Lee VJ et al. (2009)[23]																							
Lugnér et al. (2009)[24]										✓	✓												
Lugnér et al. (2010)[25]																							
Lugnér et al. (2010)[7]																							
Medema et al. (2004)[26]																							
Meltzer et al. (1999)[3]																							
Newall et al. (2010)[27]																							
Perlroth et al. (2010)[28]	✓	✓		✓	✓													✓					
Piercy et al. (2003)[29]																							

Continued next page

Table 9 Contd

Author	General									Targeted														
	Non-pharma		Pharma					Pharma + non-pharma		Elderly		Pharma						Non-pharma	Pharma				Pharma +non-pharma
										Immuned	Non-immuned	ILI						Household contacts	HR	Household contacts	Pregnancy		Household contacts
	School closure	Social distancing	AVP	AVP +AVT	AVT	VAC	VAC +AVT	AVP+ School closure	VAC + School closure	VAC	VAC	AVT	CJ + AVT	CJ +PCR +AVT	CJ +PoC +AVT	PCR +AVT	PoC +AVT	Quarantine	VAC	AVP	AVP	VAC	AVP + School closure
Sander at al. (2006)[30]																				✓			
Sander et al. (2009)[31]						✓																	
Sander et al. (2009)[32]						✓																	
Sander et al. (2010)[33]	✓		✓		✓	✓		✓	✓											✓			✓
Siddiqui et al. (2008)[34]												✓					✓						
Yarmand et al. (2010)[35]																							

In comparison to the work by Lugnér and Postma[44], who reviewed economic evaluation studies of pandemic influenza interventions from MEDLINE as sole source, our review is more comprehensive since it includes 30 economic evaluations obtained from a variety of resources. Table 10 shows that conducting evidence synthesis from economic evaluations available in MEDLINE is likely to leave out a large number of economic evaluations, especially for non-biomedical interventions and those reported in grey literature. Based on our experience, personal communication with corresponding authors is an effective way to identify unpublished literature. By contacting 14 experts and indicating our work was commissioned by the WHO, we obtained four papers, three of which were included in the final analysis. In addition, we found that the SSCI is a valuable source to retrieve conference proceedings, but they were not useful for this review. Getting in contact with the corresponding authors of recent conference abstracts, we found that full reports of those studies were not available yet. For older conference abstracts, there are some duplicates which were already published and identified by other means.

Another point is that Lugnér and Postma[44] only provided descriptive results of the review and methodological recommendations for future economic evaluations. Whilst our review aims to offer policy recommendations, it does not fully succeed due to the aforementioned limitations, i.e. the lack of effectiveness and cost-effectiveness studies on non-pharmaceutical interventions, the variation in the vaccination protocols and drug regimens introduced in the evaluations of pharmaceutical interventions, and the limited number of studies assessing value for money across interventions.

Table 10 Searches performed on electronic sources of information

	Sources of information (searched in Sept/Oct 2010)	Search records	Relevant records that met inclusion criteria (†)
1.	MEDLINE (via PubMed, 1950-23.09.2010) *(see appendix 1 for detailed search strategy)*	227	**22**
2.	NHS EED (via CRD, 1992-20.09.2010) *(MeSH Influenza A Virus, H1N1 Subtype) OR (pandemic NEAR influenza) OR H1N1*	22	13 (1)
3.	HEED (via Wiley Online Library, 1992-09.2010) *pandemic AND (influenza OR flu OR H1N1)*	24	16 (2)
4.	CEA Registry (1976-2008) *influenza*	35	5 (2)
5.	EURONHEED (via INSERM, 1980-2009) *grip$ OR flu OR influenza*	34	0 (0)
6.	HTA (via CRD, 1988-20.09.2010) *(MeSH Influenza A Virus, H1N1 Subtype) OR (pandemic NEAR influenza) OR H1N1*	13	1 (1)
7.	HEN (via WHO/Europe, on 30.09.2010) *Topic: influenza, Source: all*	24	0 (0)
8.	EconLit (via Ovid, 1969-09.2010) *pandemic AND (influenza OR H1N1)*	33	1 (0)
9.	RePEc (via Ideas, on 29.09.2010) *(pandemic | pandemia) + (flu | influenza | grippe | gripe) + (cost | economic | coste | kosten | cost-effective | coste-efectivo | kosten-effektiv)*	17	2 (1)
10.	SSCI (via ISI Web of Knowledge, 1970-01.10.2010) *pandemic AND (influenza OR H1N1) AND (cost* OR economic* OR cost-effective**	70	16 (8)
11.	Google (www.google.co.uk, on 06.10.2010) *pandemic "cost effective" influenza OR H1N1 OR flu (domains .ac, .edu, .gov, .mil, .int, .org, .pdf -past year)*	123‡	20 (1)
12.	Scirus (www.scirus.com, 01.01.2009-07.10.2010) *pandemic AND (influenza OR H1N1 OR flu)) ("cost-effective" OR economic OR costs)* *(Sections: conferences, thesis and dissertations)*	194	6 (3)
13.	Web of Science (via ISI Web of Knowledge, 1970-11.10.2010) cited reference search for: *Meltzer et al, Emerg Infect Dis. 1999; 5(5):659-71.*	212	7 (1)

† *New papers compared to MEDLINE, but may be duplicated compared to other data sources*
‡ *20 best-matches of each search were screened*

5. Moving forward

To strengthen the WHO guidelines for preparedness and intervention against pandemic influenza, there are four major recommendations. Firstly, the pandemic just occurred in 2009 we suppose a number of published studies on baseline clinical data, clinical effect sizes, adverse events and complications, and value for money of different interventions will be increasing available in the next few years. We recommend a repeat review to be performed in the next two years.

Secondly, we encourage the WHO to have a leading role in facilitating studies on the effectiveness and cost-effectiveness of interventions against pandemic influenza in the developing world. In addition, the WHO should coordinate the development of new acceptable guidelines for economic evaluation of interventions to complement the existing guidelines.

Thirdly, the WHO should bring together all relevant experts and stakeholders to seek consensus on certain important parameters used for future economic evaluations and identify future priority research areas. It is noticed that not all parameters need to be uniform across settings. By nature, resource used, cost data, compliance to interventions differ amongst countries but infectivity, clinical effect sizes, or adverse reactions and complications do not significantly diverse amongst ethnicities.

Finally, because the pandemic is a rare event, occurring presumably once every 30 years, the global community should be ready for the next pandemic by measuring consequences of pandemic influenza and its related interventions. We request the WHO devise guidelines or recommendations not only for preparedness of pandemic influenza but also for assessing its impacts in a systematic and reliable manner.

Acknowledgements

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Appendix 1 Search strategies employed for MEDLINE (via PubMed)

Economic evaluation of interventions - pandemic human influenza (1950-23/09/2010)		**Abstracts**
#11	Search #4 AND #10	228
#10	Search #5 OR #6 OR #7 OR #8 OR #9	291,197
#9	Search economic$[tiab]	87,997
#8	Search cost effective [tiab]	36,428
#7	Search costs[tiab]	94,574
#6	Search cost benefit [tiab]	5,885
#5	Search "Costs and Cost Analysis" [Mesh]	150,457
#4	Search #1 OR #2 OR #3	7,158
#3	Search "influenza pandemic" [tiab]	1,436
#2	Search "pandemic influenza" [tiab]	1,766
#1	Search H1N1$ [tiab]	5,180

Appendix 2 Description of contact patterns across dynamic models included in the review

Study	Contact patterns	References
Andradóttir et al. (2010)[8]	Age- and contact-group-specific per-contact transmission probabilities within contact groups (household, community, daycares/playgroups, schools and workgroups), adjusted to calibrate baseline (no intervention) results to age-group-specific illness attack rates and R_0 estimates. Once infected, people enter a 1–3 day latent period (state 1; average length 1.9 days). Then, they become infectious on the last day of the latent period, and are half as infectious as they will be after the latent period ends. After the latent period, 67% of infectives become symptomatic (state 2), and 33% are asymptomatic (state 3). These infectious states last between 3 and 6 days. Symptomatic infectives are twice as infectious as asymptomatics, and have a chance of withdrawing home during each day of illness ; upon withdrawal, they only make contacts within their household and neighborhood, with transmission probabilities doubled in the household contact group, until they recover. If a school child withdraws home due to illness, one adult in the household also stays home. Each day in states 2 and 3, an infectious person has a chance to exit the state and be removed from the simulation (i.e., to recover or die — state 4). Contact patterns were explicitly presented in the study.	Longini et al., 2004; 2005 Assumptions Statistics Canada, 2006
Baguelin et al. (2010)[9]	Rates at which individuals from different age groups come into contact with each other based on the reported frequency of close contacts by UK respondents in Mossong et al, 2008. The method of Hens et al. was used to take into account uncertainty in contact patterns. Two sets of contact patterns were used: one for term-time and one during summer holidays when schools are closed. School holidays were assumed to start 46–52 days after June 1. Each of these model realisations were compared to the 20 weeks of data by minimising the Poisson deviance between the number of cases each week reported by the HPA.	Mossong et al., 2008 Hens et al., 2009 Directgov., 2009
Brouwers et al. (2009)[12]	Individuals spend their day in different settings, depending on their disease level. Choice of place determined randomly. Persons with the same disease level spend the day in different settings: at home from work, at work, visits the emergency room. Disease level 0 represents all individuals who are not infected, as well as those infected without symptoms. By using different SCB (Statistics Sweden) register data individuals linked to workplaces and residences. Individuals are also linked in families. Each person object contains the family identifier, birth year, gender, coordinates for family residence, and workplace identifier. Workplace representations include the workplace identifier, county, and coordinates of the workplace. The workplace identification number is used to connect the person and the workplace. Place objects include a list of members; for residences, family members and for workplaces, employed individuals. It was decided that a maximum number of persons, x, to belong to any one unit, ie., an individual is in close contact with a maximum of x other individuals at his/her workplace, school, nursery centre, etc. At large places, possible to transmit infection between units. Individuals in the model lack memory, then possible for them to visit primary care one day, go to work the next day and visit primary care again on the third day. To avoid this issue, a place choice rule to limit emergency room visits to one was created.	Asumption Statistics Sweden Medlock and Galvani, 2009

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Study	Contact patterns	References
Durbin et al. (Forthcoming)[17]	Each individual is an object in the simulation with various characteristics including age, vaccination status, home location, work location and household membership. Household membership indicates which members of the population live in the same dwelling. In addition, once infected, each individual will be contagious for a randomly generated number of days which is calculated as a function of age. Transportation routes used for daily commutes are also assigned to individuals. In order to establish contact leading to disease transmission between individuals, contact networks are used. Each individual in the population has a certain level of contact with every other member of the population (the level of contact may be nothing). The time and type of contact between two individuals can vary. In a contact network, each person is represented as a node, and contact between individuals are arcs. The uniform reproduction number was replaced by the individualized probabilities for each person transitioning from a susceptible state to an infected state in a given time period.	Aleman et al., 2009 Rust et al., 2009 Skowronski et al., 2006 Hibbert et al., 2006
Khazeni et al. (2009)[18]	Homogenous mixing of case-patients and contacts assumed. According to influenza A virus infections, it was assumed that 67% of infected individuals developed symptoms. 50% of these individuals entered a state of isolation, either voluntarily or because of physical limitation secondary to illness or admission to a hospital. It was assumed that those who were not in isolation continued to infect contacts. On the basis of information to date on pandemic (H1N1) 2009 and other influenza A viruses, it was assumed that infected individuals had a mean incubation time of 3 days, had symptoms (if they were symptomatic) for 10 days, and could transmit the virus for 4 days. Incorporating the results of a complex network model of pandemic spread through communities , it was assumed that these non-pharmaceutical interventions are reducing contacts by 15%. A recent randomized trial of facemasks and hand washing found that under optimal circumstances, these measures reduced transmission among households by 66%. Population: 8, 300,000 ; age range: 0–100 years; Female: % 53; preexisting population immunity: % 10 (0–20); reduction in contacts from non-pharmaceutical interventions: % 15 (0–70) (assumed); infected individuals at start of pandemic: 10, 000 (1,000–50,000); susceptibility to reinfection after recovery: % 5 (2–25); timing of waning immunity, months 5 (2–8) As previous research had shown, individuals may intentionally reduce contact rates in response to high influenza mortality. That analysis used a simple modification to an SEIR model to calculate reactive distancing. For example, if the threshold K is 10 per 10,000 and the mortality rate over the last $T=30$ days is also 10 per 10,000, then the population would reduce its contacts by 50%. It was assumed that 90% of the symptomatic patients requiring inpatient treatment received it at an Influenza Care Center.	Thorson et al., 2006 Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2006 CDC, 2009 etc
Khazeni et al. (2009)[19]	Similar to above	

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Study	Contact patterns	References
Lugnér et al. (2009)[24]	Key epidemiological parameters were included, such as contact rates among and within age groups, length of the infectious period and probability of transmission of the virus during a contact. Infected individuals: 10,369,87; with intervention: 8,594,056. Based on previous study by the author.	Lugner et al., 2009
Lugnér et al. (2010)[25]	Key epidemiological parameters were included, such as contact rates among and within age groups, length of the infectious period and probability of transmission of the virus during a contact The use of AV-drugs affects the recovery rate and the length of the infectious period. Transmission is dependent on contacts between susceptible and infected individuals. Contact patterns between and within age groups were derived from self-reported social contact data. Durations of latent and infectious periods were based on observational data from a Japanese household study and calibrated according to generation interval matches. The population was divided into six age groups and two risk groups. The frequency of contacts between individuals was dependent on their age groups.	Wallinga et al., 2006 Hirotsu et al., 2004 Wallinga and Lipsitch, 2007
Lugnér et al. (2010)[7]	Multitype,age-structured, with country-specific demographic characteristics and social contact patterns. Country-specific details in demography and age-specific contact patterns were calculated from data on self-reported conversational contact rates for Germany, the Netherlands, and the UK. In all three countries, people primarily tend to mix within their own age group. It was assumed that 60% of the infected persons developed influenza-like illness (ILI) and that the rest were asymptomatic. A proportion of the symptomatic individuals seek medical help.	Mossong et al., 2008
Newall et al. (2010)[27]	The Australian population was divided into 3 age groups: 0–19 years (26% [5,513,878], 20–64 years (61%12,744,215], and >65 years (13% [2,759,129]) (15). Rates of mixing were age dependent and based on a recent large study of contact patterns in the European Union. The matrix 0 was calculated using data from this study. In order to construct our matrix, (unweighted) average of the matrices for close contacts over all countries was calculated. It was then reduced this to a 3x3 matrix describing contacts between 0-19, 20-64 and 65+ age groups by taking the average over the relevant sub-matrices.	Mossong et al., 2008

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Study	Contact patterns	References
	Contacts between persons within a large number of specific groups were simulated (e.g., household, school classes, play groups, and adult work groups), each with realistic contact networks. Strategies were 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 were rescinded after 2 generation times pass without newly diagnosed cases. 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. 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. Population compliance, % 60 (30–90) Assumed.	Davey et al., 2008 Glass et al., 2006
Sander et al. (2009)[31]	Same as Sander et al, 2010	
Sander et al. (2009)[32]	Population interacting in known contact groups and assumed to have daily contacts with household members and people in the three closest households (neighborhood cluster), and 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. Population: 1.632 million, communities of around 2,000 people, each of which is further subdivided into 4 smaller neighbourhoods. The model tracks the number of close contacts that a typical person makes in the course of a day within specified contact groups. Each person is assumed to have daily contacts with household members and with people in the three closest households (neighbourhood cluster), as well as with people in the larger neighbourhood and community. The age and approximate household size distributions are matched to those of the US Census 2000 (3). Preschool children attend either small play groups or larger daycare centres, and school-age children attend elementary, middle, or high school, as appropriate. Small play groups have four children each, and there are between 4 and 6 small play groups per neighbourhood. Large daycare centres have, on average, 14 children. School-age children are assigned to either an elementary school, middle school, or high school based on their age. Two neighbourhoods share one elementary school, and all 4 neighborhoods share a middle and high school. Elementary schools have, on average, 79 children per school, middle schools have an average of 141 students, and high schools have an average of 110 students. 10% of high school students attend a high school in a neighbouring community. 63% adults are in workgroups of average size Workgroups are made up of adults from different communities, allowing for transmission of infection from one community to another. Contact probabilities vary by contact group and, in some cases, by the ages of the infectious and susceptible persons (data explicitly shown).Probabilities do not vary over time.	Longini et al., 2004 Halloran et al., 2002 Elveback et al., 1976 Weycker t al., 2005

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Study	Contact patterns	References
Sander et al. (2010)[33]	Individuals were assigned an age class, a community, a household and, depending on age, a daycare, school or workplace, if employed. Every simulated individual was scheduled to spend a certain amount of time each day in each of these locations as determined by their infection status, and contact rates and transmission probabilities per contact for each location were specified. Age-assortative contact mixing was assumed within community, workplaces and classrooms, and homogeneous, age-independent mixing was assumed within households. The contact rates in each location and the transmission probability per contact were calibrated so that the number of hospitalizations, intensive care unit (ICU) admissions, and deaths predicted by the model matched the reported number of these events	Public Health Agency of Canada, 2010
Yarmand et al. (2010)[35]	$R0$ was considered to be limited since it does not link policy to outcome. Therefore, contact rate (β) as the input parameter determining the infection rate was used instead and assumed to be equal to 1.6 contacts per day per person. Although the population was almost homogeneous population (undergraduate students in the same age group and with similar social behaviour), the model could have been more general by incorporating non-homogeneity into the model (e.g. considering different age groups or classifying people according to their contact rate).	Assumption