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Mitigation of pandemic influenza: review of cost–effectiveness studies

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We conducted a review of economic evaluations of pandemic influenza control measures. In the studies found, we detected various interventions being investigated: antiviral stockpiling and treatment, prophylaxis, vaccination, school closure and restricting international travel. Cost–effectiveness varied but often showed potentials for the favorable economic profiles of these measures. Both static and dynamic models were used. We conclude that the choice of an appropriate model – in particular, a dynamic model – is crucial to arrive at valid cost–effectiveness ratios. Yet, of the economic evaluations considered here, only a few were based on dynamic modeling. We recommend that further research is directed toward linking dynamic epidemiological models for pandemic spread with economic outcomes by considering the full impacts on national economies, including direct, indirect, medical and nonmedical costs.

Keywords: cost–benefit analysis • cost–effectiveness analysis • infectious disease control • pandemic influenza

The recent spread of the new influenza A virus, H1N1 (also known as 'swine flu'), provides evidence for the continuous threat of an influenza pandemic. This current outbreak will probably add yet another occurrence to the history of pandemics. A pandemic for humans is caused by a novel virus, with little or no previous immunity being present in the world population. Another possible threat is the cross-species transmission from flocks to humans of the avian influenza A virus, H5N1, now circulating among wild and domesticated birds. If this virus acquires human-to-human transmission abilities, another influenza pandemic could emerge.

The most devastating pandemic documented hit the world in three waves during 1918–1919, causing at least 50 million deaths worldwide [1]. Two subsequent pandemics – the Asian flu in 1957–1958 and the Hong-Kong flu in 1968–1969 – had substantially lower case–fatality rates [1].

Dynamic models play an important role in exploring possible strategies to contain a pandemic outbreak of influenza through controlling transmission [2–6]. Such mathematical models aim to translate the individual-level effects of vaccines and antiviral drugs into effectiveness of control strategies. Based on such analyses, potentially effective mitigation strategies are proposed. One important component, often missing in pandemic contingency planning, is cost–effectiveness analyses of proposed mitigation strategies. Only scarce economic evaluations of pandemic control are available; even less is achieved using appropriate dynamic models. This may not be highly surprising as, for many economic evaluations of seasonal influenza programs, the dynamic, nonlinear effects of interventions in infectious diseases are not taken into account [7]. Notably, the development of appropriate dynamic models involves the development of highly complex mathematical structures.

This article aims to review published studies of pandemic preparedness that include an analysis of economic impact and/or a cost–effectiveness analysis of proposed strategies against an influenza pandemic. We further stress the importance of the use of dynamic models as the sole basis for valid calculations to be derived.

Theoretical background

Dynamic models

Since influenza is a communicable infectious disease, dynamic models are most suited to estimate the spread of the disease and the effect on the spread of interventions against transmission and disease. Static models are also used for analyzing cost–effectiveness of infectious diseases' control. However, static models do not

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take the spread of bacteria or viruses explicitly into account, whereas dynamic models do. In a static model, the clinical attack rate (CAR) – that is, the percentage of the population having symptoms, in this case influenza – is used to estimate healthcare resource use, illness-related deaths and sickness leave. Dynamic models incorporate indirect effects beyond the index people targeted by the intervention (e.g., reduced spread in the general population through vaccinating a subpopulation). Typically, dynamic models may include herd protection effects and age shifts [8–10]. Examples of dynamic models used to describe the spread of infection are the compartmental susceptible, exposed, infectious, removed (SEIR) model and variants of it [11,12], and stochastic microsimulation models on the individual level [2,3]. SEIR models can be either deterministic or stochastic. Deterministic models suffice when one can validly assume a large number of infections during all stages of spread, whereas stochastic models are useful when spread is crucially dependent on chance. This is often the case in the beginning of an influenza epidemic or pandemic. In the early stages, the spread from the first few cases may either take off or, alternatively, the spread expires. In stochastic models, the parameter values are randomly drawn from a defined distribution, giving different results depending on the specific values in place. Therefore, a number of trials of the model are performed to arrive at an estimated mean with corresponding variation surrounding it. Typically, the results from a stochastic analysis approach those from a deterministic model in case of large numbers of infections [5]. A key epidemiological variable in dynamic modeling of transmittable diseases is the basic reproductive ratio (R_0), which describes how many secondary cases of infections are caused by one primary case in a totally susceptible population [11]. Generally, an R_0 above 1 indicates that there is a potential for epidemic spread. For influenza, R_0 is typically in the magnitude of 1.5–2.5.

Relationship between epidemiological & economic models & cost–effectiveness estimations

The outcomes from an epidemiological dynamic model, expressed as numbers of individuals in different stages of disease at specified times, are used as inputs in an economic decision tree or Markov model [13]. Through this linking, estimates of resource use and costs are multiplied with numbers of infections and are used to calculate the costs during the time period and/or cost–effectiveness of certain interventions. For analyses in the area of influenza, this mostly entails that cumulative numbers of individuals that have been infected during the pandemic are estimated with the dynamic model, with and without an intervention. Healthcare resource use, medical costs and work loss, as well as deaths, are subsequently estimated in a decision tree or spreadsheet model for the different scenarios using straightforward proportional calculus.

Interventions

Interventions to mitigate a pandemic include vaccination, prophylactic or therapeutic antiviral drug therapy, and nonpharmaceutical interventions. Vaccination not only protects the vaccinated individual against infection but, owing to herd protection, unvaccinated individuals are also protected if the vaccination coverage is substantial.

However, since there might not be any effective vaccine available at the start of a new pandemic, antiviral drug therapy has long been considered as the option of first choice for treatment and mitigation of an outbreak. Antiviral drug therapy can be given therapeutically when an individual presents symptoms to reduce illness and complications, as prevention to reduce transmission in people to be exposed and are likely to be infected (e.g., healthcare professionals) or as postexposure prophylaxis to individuals who have been in contact with an infected individual but are not (yet) infected themselves. To be able to provide the population with these drugs sufficiently and on time, many countries have invested in stockpiling these drugs.

Nonpharmaceutical interventions generally refer to various measures of social distancing aiming to reduce contacts between infected and susceptible individuals. These measures typically include the closing of schools and enforcing restrictions on travel.

Method

Published literature was searched via PubMed using the keywords ‘pandemic’, ‘influenza’, ‘cost effectiveness’, ‘cost’, ‘model’ and ‘modeling’, in various combinations. To be included in the review, the article would have to be original work (no reviews) written in English, include an estimation of only cost or of costs and effects of a human pandemic (not including seasonal influenza epidemics) and estimate only costs or costs and effects of interventions against a pandemic. Article abstracts were read and evaluated on their appropriateness for the review, and 16 articles were read in total. Of these, 12 articles were judged to adhere to the aforementioned inclusion criteria [14–25] and four were discarded from this review [26–29]. With one exception ([22]), all reviewed articles were published in 2004 or later. To facilitate the comparisons, we recalculated the costs to 2008 prices using country-specific consumer price indices and converted these into Euros (€) using the average exchange rate in 2008.

Results

Many of the evaluations are directly or indirectly based on the methodology of the study by Meltzer *et al.*, published in 1999 [22]. We note the great impact of that one article on other papers included it in this review, either directly [14,17] or indirectly [15,18–20]. The articles were evaluated and compared on various issues, including type of modeling and specific values for health–economic input variables. In particular, we considered what modeling approach was used (dynamic, static and/or decision tree) (Table 1). In addition, health economic aspects were specified (Tables 2 & 3). Results on the economic impact (without interventions) of a pandemic were compared for those countries where this has been estimated. Furthermore, the costs per health-outcome reported in the different studies were reviewed. Finally, the cost–effectiveness results, often expressed as cost per life-year gained or quality-adjusted life-year (QALY) gained reported in the studies were highlighted and are discussed.

Table 1. Study approach and basic characteristics.

Study (year)	Country	Topic	Model type	R_0	CAR (%)	Range of case fatality rates	Ref.
Dynamic models							
Lugnér *et al* (2009)	The Netherlands	Therapeutic treatment AVD – comparison of modeling approaches	Deterministic SEIR	1.73		0.0000147–0.0169	[19]
Lugnér and Postma (2009)	The Netherlands	Stockpiling AVD	Deterministic SEIR	1.73		0.0000147–0.0169	[20]
Sander *et al* (2009)	USA	Different strategies to mitigate pandemic	Stochastic, individual level microsimulation	2.0		0.025	[24]
Epstein *et al* (2007)	USA	Restricting international air travel	Stochastic SEIR	1.7		NA	[16]
Static models							
Lugnér *et al* (2009)	The Netherlands	Therapeutic treatment AVD – comparison of modeling approaches	Decision tree		38	0.0000147–0.0169	[19]
Hak *et al* (2006)	The Netherlands	Direct and medical costs due to pandemic	Decision tree		30	0.038–10.8 per 1000	[17]
Lee *et al* (2006)	Singapore	Stockpiling AVD	Decision tree		30	5–1700 per 100,000	[18]
Siddiqui and Edmunds (2008)	UK	Stockpiling AVD and near-patient test	Decision analytic		25	0.003–0.023	[25]
Medema *et al* (2004)	Developed countries	Impact of vaccination with different coverage	Simulation model		35	1.87%	[21]
Meltzer *et al* (1999)	USA	Vaccination of US population	Monte Carlo simulation		25	0.024–0.42 per 1000	[22]
Doyle *et al* (2006)	France	Intervention strategies (preparedness plan France)	Monte Carlo simulation		25	0.5–2.0%	[15]
Balicer *et al* (2005)	Israel	Stockpiling AVD	Spreadsheet model		25	0.024–4.195 per 1000	[14]
Sadique *et al* (2008)	UK	Cost of school closure	Straightforward calculus		NA	NA	[23]

Death rates are age and risk-group specific. The lowest and highest values are cited.
AVD: Antiviral drug; CAR: Clinical attack rate; NA: Not applicable; R_0: Basic reproductive ratio; SEIR: Susceptible, exposed, infectious, removed (compartmental dynamic model).

Modeling approach

Only four out of the 12 economic analyses were based on a dynamic transmission model [16,19,20,24]. Sander *et al.* used a stochastic, individual-level microsimulation model to estimate 15 different interventions to mitigate a pandemic in the USA, comparing them with each other and with a nonintervention scenario [24]. The assumed basic reproductive ratio was 2.0 on average and resulted in a CAR of 50%. The output was placed into a decision tree to estimate healthcare resource use, costs and life-years gained in different age groups. Next to various pharmaceutical interventions, the effects of school closure during a pandemic (modeled as lasting 26 weeks) were modeled. The model was based on a previously published model [2] and applied to the US healthcare and societal setting.

Lugnér *et al.* used a deterministic SEIR model to estimate the cost–effectiveness of therapeutic antiviral drug therapy in The Netherlands [19] and to investigate the cost–effectiveness of stockpiling antiviral drugs [20]. The age-group-specific contacts (six age groups) were calibrated so that the efficient contact rates resulted in an R_0 of 1.7. The CAR was estimated at 38% of the Dutch population. The results were also used as input into a decision tree to calculate the cost–effectiveness of therapeutic treatment with antiviral drugs. Furthermore, the results were compared with a static model, using the CAR of 38%. In the base case, the cost–effectiveness ratios were equal but the static model appeared to be quite insensitive to the CAR. The dynamic model adequately predicted different cost–effectiveness for different CARs and R_0s. These analyses were also based on a previously published model and specifically targeted at the intervention with antiviral drugs [30].

Epstein *et al.* investigated the effect of restricting international air traveling on the numbers of infected individuals, both worldwide and for the largest US cities [16]. The model consisted of a

Table 2. Health economic aspects of reviewed studies.

Study (year)	Country	Intervention strategies	Outcome	Costs included	Main findings	Ref.
Meltzer *et al.* (1999)	USA	Vaccination	Net returns to vaccination	Healthcare costs (GP and hospitalization), vaccination costs, production losses	Vaccinating 20–64-year olds not at high risk would give higher net returns than vaccinating risk groups older than 64 years	[22]
Balicer *et al.* (2005)	Israel	Therapeutic treatment AVD Pre-exposure prophylaxis AVD: • Long and short term	Cost–benefit ratio	Healthcare costs (GP, AVD and hospitalization), production losses	At CAR of 50%, many interventions are cost saving. Attack rates are reduced to 6 and 4% with prepandemic vaccination or targeted prophylactic treatment combined with school closure, but with high costs	[14]
Sander *et al.* (2009)	USA	Postexposure prophylactic treatment AVD: • Household targeted • Full targeted Therapeutic treatment AVD prevaccination School closure	Cost per QALY	Healthcare costs (GP, medication, AVD, vaccination and hospitalization), costs for travel and time lost, production losses	At a CAR of 50%, many interventions are cost saving. In combination with school closure, attack rate are reduced to 6% and 4%, respectively, but with high costs	[24]
Siddiqui and Edmunds (2008)	UK	Therapeutic treatment AVD, Test and treat positive cases with AVD	Cost per QALY	Healthcare costs (GP, hospitalization, AVD and tests), stockpiling costs	Treat-only program is cost effective Program with prior testing is not cost effective	[25]
Lugnér *et al.* (2009)	The Netherlands	Therapeutic treatment AVD	Cost per life-year gained	Healthcare (GP, medication, hospitalization and AVD), production losses	Cost effective to therapeutically treat with AVD	[19]
Lugnér *et al.* (2009)	The Netherlands	Stockpiling AVD for therapeutic treatment	Cost per life-year gained	Healthcare (GP, medication, hospitalization and AVD), production losses	Cost effective to stockpile for treating therapeutically	[20]
Doyle *et al.* (2006)	France	Vaccination (strain specific) Therapeutic treatment AVD Prophylactic treatment postexposure Priority population	Cost per avoided event	Medication costs	Vaccinating total population costs the least per avoided case	[15]
Medema *et al.* (2004)	Developed countries	Egg- or cell culture-based vaccine production method	Cost per avoided event	Healthcare costs (GP and hospitalization), vaccination costs	Cell culture-based vaccine manufacture prevents more influenza cases than an egg-based vaccine	[21]
Lee *et al.* (2006)	Singapore	Prophylactic treatment AVD Therapeutic treatment AVD	Costs and lives saved	Healthcare (outpatient treatment care, AVD, hospitalization), production losses	Cost effective to treat therapeutically with AVD. Maximizing economic benefit: 40% stockpile. Maximum treatment benefit: 60% stockpile	[18]

Two articles [16,23] did not involve unit cost estimates for resource use.
AVD: Antiviral drug; CAR: Clinical attack rate; GNP: Gross national product; GP: General practitioner; QALY: Quality-adjusted life-year.
Costs inflated to 2008 using HCPI for European countries [101] and CPI calculator for the USA [102]. Average exchange rate 2008 is used for expressing other currencies in euros [103].

Table 2. Health economic aspects of reviewed studies (cont.).

Study (year)	Country	Intervention strategies	Outcome	Costs included	Main findings	Ref.
Hak *et al.* (2006)	The Netherlands	None	Healthcare costs	Healthcare costs (GP and hospitalization)	Preventive measure that would prevent 50% deaths is cost effective	[17]
Epstein *et al.* (2007)	USA	Restrict air travel	Cost as percentage of GNP	GNP losses	GNP loss due to (passenger) flight restrictions is estimated to be small (1% of GNP)	[16]
Sadique *et al.* (2008)	UK	Closing schools	Productivity losses	Production losses for parents caring for a child <16 years of age (16.1% of labor force)	Production losses would be €0.28–169 billion per week	[23]

Two articles [16,23] did not involve unit cost estimates for resource use.
AVD: Antiviral drug; CAR: Clinical attack rate; GNP: Gross national product; GP: General practitioner; QALY: Quality-adjusted life-year.
Costs inflated to 2008 using HCPI for European countries [101] and CPI calculator for the USA [102]. Average exchange rate 2008 is used for expressing other currencies in euros [103].

set of stochastic differential equations, specifying the relationships between five mutually exclusive classes. In the base case, simulations were carried out assuming an R_0 of 1.7.

In the remaining studies, the cost–effectiveness calculations were based on static models (e.g., decision trees or similar constructions) [14,15,17,18,21–23,25].

Economic impact of a pandemic

Three studies were found to have estimated the costs for a pandemic in the USA. The earliest study, by Meltzer *et al.* [22], estimated that a pandemic (CAR at 35%) would cost approximately €160,730 million. These costs are almost four-times as high as estimated by Sander *et al.* [24]. In this latter model, costs for an uncontrolled pandemic were estimated at €0.20 million per 1000 population, corresponding to a total of €42,330 million (with a US population of 306.1 million). One contributing factor is that production losses due to deaths are included in the earlier model [22], whereas these are not included in more recent calculations since these are reflected in the QALYs [24].

The third estimate expressed the costs as a percentage of the US gross national product [16]. According to this model, restricting national and international air travel would cost less than 1% of the US gross national product (estimates in 2006) [16]. However, benefits of such restrictions were estimated to minimal or even negative if not combined with a set of other control measures.

The Netherlands, with a population of approximately 16.4 million, is another country for which different estimates are made for the cost of an uncontrolled pandemic. Hak *et al.* estimated healthcare costs due to a pandemic at approximately €904 million (using Dutch guideline prices for healthcare services as published in 2004, here inflated to 2008) [17]. Lugnér *et al.* estimated direct healthcare costs using one static and one dynamic model for an uncontrolled pandemic to be approximately €214 million (static model) and €183 million (dynamic model) [19]. As in the case for the USA, a static model, indeed, estimated the costs to be higher than a dynamic model. The greater than fourfold higher costs derived in the first estimate by Hak *et al.* is mainly explained by much higher hospitalization rates and unit cost estimates.

One estimate has been published on the economic impact of a pandemic for the UK (population of approximately 59.8 million). Siddiqui and Edmunds estimated healthcare costs to be approximately €164 million in an uncontrolled pandemic [25]. The authors analyzed two options for the uncontrolled epidemic, one assuming a course as in 1918 and one simulating a 1957–1969-like epidemic. Costs were estimated similar in both options, major differences resulted in the projected numbers of deaths at 344,000 and 44,000, respectively.

An estimate for Singapore shows that the costs for an uncontrolled pandemic would be approximately €0.76 billion and there would be approximately 1105 deaths in a population of approximately 4.2 million people [18].

Israel has a population of approximately 6.7 million and the estimated healthcare costs for an uncontrolled pandemic were estimated as €41.2 million and € 389.1 million for the total economy (i.e., including production losses) [14].

Interventions

Antiviral drug treatment & stockpiling

Four of the reviewed articles explicitly estimated the cost–effectiveness of stockpiling antiviral drugs. In general, for the four countries (Israel [14], the UK [25], Singapore [18] and The Netherlands [20]), the authors conclude that stockpiling is cost effective if it was intended for the treatment of symptomatic individuals. It was also indicated that, under specific circumstances, prophylactic use of stockpiles might also be cost effective, for example, if prophylaxis was targeted at those with a high risk of complications [14]. The forth study estimated the cost–effectiveness of stockpiling antiviral drugs for prophylaxis for the USA. This study explicitly aimed to include all costs related to stockpiling and delivery to be reflected in the price of the drugs [24]. They concluded that targeted antiviral prophylaxis is the most effective single strategy and could, potentially, be cost saving.

Table 3. Unit costs, 2008 prices.

Study (year)	Country	Cost items (€)						
		Physician visit	*Medication (antibiotics or nonspecified)*	*Vaccination*	*AVD therapeutic*	*AVD prophylactic*	*OTC drugs*	*Hospitalization*
Balicer *et al* (2005)	Isreal	34			7 for 5 days	5 for 7 days		236 per day
Doyle *et al* (2006)	France			6 per dose	10 per course	7 per course		
Hak *et al* (2006)	The Netherlands	22	10					5811 per episode
Lee *et al* (2006)	Singapore	21			16 per course	12 per week		182 per day
Lugnér and Postma (2009)	The Netherlands	21	7		16 per course		6	382 per day
Lugnér *et al* (2009)	The Netherlands	21	7		16 per course		6	382 per day
Medema *et al* (2004)	Developed countries	43		20				392 per day
Meltzer *et al* (1999)	USA	290–442		15				3250–7389 per episode
Sander *et al* (2009)	USA	68	3–6	12	17 per course		4	2141–4824 per episode
Siddiqui and Edmunds* (2008)	UK	48			46 per course			1096 per episode

*Cost to the emergency department of €117.
AVD: Antiviral drug; ICU: Intensive care unit; OTC: Over the counter.

More specifically, Balicer *et al.* estimated the benefit–cost ratios of therapeutic use and of prophylaxis of the stockpiled antiviral drugs [14]. If benefits, expressed in monetary units, exceeded the costs for stockpiling and delivery, the intervention would be cost saving. Benefits counted involved avoided healthcare costs and avoided workdays lost (indirect costs, excluding indirect costs due to premature death). A number of strategies were investigated, including therapeutic, pre- or post-exposure prophylactic use for the total population or for high-risk groups only (those with increased risks of complications). Therapeutic use of antiviral drugs for all patients and for high-risk patients only, as well as postexposure prophylaxis (short-term involving 7 days) were all cost saving when both direct and indirect costs were included. Long-term pre-exposure prophylaxis (50 days) was not cost saving, neither was it cost saving when indirect costs were included. The most cost-saving option would be therapeutic treatment of high-risk patients. The recommendation put forward in the article is to consider providing therapeutic treatment to all patients, combining this with postexposure prophylaxis to close contacts of the patients [14].

Siddiqui and Edmunds investigated stockpiling of antiviral drugs being used for treatment either with or without near-patient testing for influenza [25]. In the test-and-treat scenario, individuals with influenza-like illness would only be treated if the test was positive for influenza. Again, the authors investigated two scenarios, one with death rates similar to the pandemics of 1957 and 1968, and one with death rates comparable to the 1918 pandemic. Treatment of illness was cost effective from the National Health Service's perspective for both pandemic scenarios, according to national cost–effectiveness thresholds, at €19,810 and €2700 per QALY, respectively. The option to first test all influenza-like illness cases was not deemed to be cost effective, although one scenario was approximately GB£1000 (€1400) above the most cited threshold of GB£30,000 per QALY (€37,800).

Table 3. Unit costs, 2008 prices (cont.).

Cost items (€)				Comment	Ref.
ICU	*Administration costs*	*Stockpiling test*	*Production losses*		
			53 per day	Physician visits include prescription drugs and diagnostic tests. Future costs discounted 3%	[14]
				Two doses of the vaccine was assumed	[15]
				Cost per death (2591) is estimated as costs for general practitioner, specialist, first aid, diagnostics, intensive care, general ward and ambulance	[17]
			57–88 depending on age	Number of lost days at work differs depending on severity of disease	[18]
1790/day			36 per h	Antiviral drug course is 10 days. Future costs discounted 4%, life-years gained 1.5%	[19]
1790/day			36 per h	Antiviral drug course is 10 days. Included annual storage costs and opportunity costs rate of 4%. Stockpiling base-case 30 years	[20]
				Life-years gained discounted 5%. Vaccination includes administration cost	[21]
	5		63–97 per day	Physician visits and hospitalizations include medication and production losses, and vary depending on age	[22]
	7 per vaccination		673 per week	Hospitalization cost depends on diagnosis. Production losses slightly higher for teachers. Two doses vaccine was needed. 20% added to costs of the antiviral drug and vaccine to incorporate distribution and storage costs	[24]
	23 per course or test	1 per test or course		Antiviral drug treatment includes administration cost. Stockpiling base-case 30 years. Future costs and benefits discounted 3.5%	[25]

*Cost to the emergency department of €117.
AVD: Antiviral drug; ICU: Intensive care unit; OTC: Over the counter.

One article investigated the cost–effectiveness of stockpiling for prophylaxis in Singapore and showed that the longer the duration of prophylaxis is, the higher the cost–effectiveness ratios [18]. In particular, costs per life saved increase from €1.20 million for 6 weeks of prophylaxis to €2.40 million for maximum prophylaxis (24 weeks). Costs per life saved was relevantly reduced if prophylaxis would be targeted at high-risk groups and/or those aged older than 65 years. Treatment of symptomatic individuals was shown to be cost saving for all age and risk groups.

The cost–effectiveness of stockpiling antiviral drugs in The Netherlands has also been estimated in relation to the risk of a pandemic outbreak [20]. If the risk of an outbreak is above 9%, keeping and renewing the stock during 30 years would be cost effective, including production losses. If only healthcare costs are included, the risk would have to be approximately 23–27% for the stockpiling investment to be cost effective. These calculations are based on the estimates of Lugnér *et al.* [19] and, thus, are based on the same dynamic model [30]. Apart from the costs in that previous study, storing, stock turnover and opportunity costs are added [20].

Two articles estimate the cost–effectiveness of antiviral drug therapy without explicitly including any stockpiling costs [15,19]. Doyle *et al.* investigated the French preparedness plan and estimated that therapeutic treatment of the whole population with antiviral drugs would cost €900 per avoided hospitalization and €3700 per avoided death during two pandemic waves, each lasting 10 weeks [15]. The second concluded that treatment of symptomatic cases would be cost effective, at an incremental cost–effectiveness ratio of €1700 per life-year gained [19].

Vaccination

Meltzer *et al.* were the first to publish research on the costs and cost–effectiveness of interventions against pandemic influenza [22]. Their aim was specifically to investigate the economic

Table 4. Studies of pandemic influenza mitigation strategies.

Study (year)	Country	Topic	Model approach	Strategies	Outcome measure	Summary of findings	Ref.
Mylius *et al* (2008)	The Netherlands	Vaccination strategies	Dynamic SEIR model	Vaccination of high-risk groups or high-transmission groups	Number of deaths, hospitalizations and influenza-like illness	If vaccination before the peak, target at those groups with high-transmission potentials	[30]
Longini *et al* (2004)	USA	Prophylaxis AVD compared with vaccination	Discrete time stochastic simulation	Targeted prophylaxis AVD to identified contacts, vaccination before influenza season	Number of influenza cases	Targeted prophylaxis has significant effects on slowing spread of influenza, 80% prophylaxis for 6–8 weeks is almost as effective as vaccinating the entire population	[2]
Van Genugten *et al* (2003)	The Netherlands	Vaccination and AVD strategies, scenario approach	Decision model (static)	Vaccination of risk groups or total population, pneumococcal vaccination of high-risk groups, antiviral drug therapy	Hospitalizations and deaths prevented	Vaccination prevents highest number of hospitalizations and deaths	[31]

AVD: Antiviral drug; SEIR: Susceptible, exposed, infectious, removed (compartmental dynamic model).

impact of vaccine-based interventions in the USA. As one of the early models, the model was static, without taking the spread of disease explicitly into account. They used age-specific attack rates based on the 1918, 1928–29 and 1957 epidemics and pandemics. The economic impact was measured as the net returns, defined as the value of avoided outcomes (that is, avoided costs) minus the cost of vaccination. The vaccine effectiveness varied between age groups. A high vaccine–effectiveness scenario entailed effectiveness of 0.40–0.70 for different health outcomes and healthcare consumption, whereas a low-effectiveness vaccine was of 0.30–0.55. Estimations were made using attack rates between 15 and 35%, analyzed in increments of 5%. With an effective coverage of 40% of the population (and a vaccine price of €21 per dose, including administration costs and costs for treating side effects, one dose per person, high vaccine effectiveness), there would be net savings of vaccination. For higher coverage, at almost three-times as high vaccination costs and a relatively low attack rate at 15%, net returns were estimated to possibly become negative.

Sander *et al.* estimated that a low-efficacy vaccine for 70% of the population would result in 48% less cases, which would be a less costly strategy than to do nothing [24]. The low-efficacy vaccine entails that the efficacy for susceptibility to infection was 0.30 and 0.50 for infectiousness. As opposed to the previous study, this result was based on a dynamic model. Compared with no intervention, vaccination would save 130 QALY per 1000 population in the USA. In combination with closing schools, vaccination would cost approximately €35,030 per QALY gained compared with full targeted antiviral prophylaxis alone.

Medema *et al.* estimated the cost–effectiveness of different vaccine production technologies (egg based vs cell culture) [21]. Using slightly unconventional health-economic terminologies, they estimated various outcomes for the two different vaccine production techniques and for one no-intervention scenario: the number of influenza cases, outpatient visits, hospitalizations, deaths and discounted year per life lost. These estimates are combined with the costs for resources used. Cost–effectiveness was estimated at €4800 per life-year gained; however, it remains unclear which options were compared to arrive at this number.

The cost per avoided influenza case in France was estimated at €90 if there were two doses of vaccine per person available for the population of 59.6 million [15]. Avoiding one hospitalization (death) would cost €2100 (€9000) if vaccination were to be considered for the total population [15].

Social distancing

Three articles discuss the economic effects of social distancing [16,23,24].

In the USA, closing schools are assumed to cost 2.5 days productivity losses per week for parents that must stay at home (for children <12 years of age) and 5 days per week for teachers and other professionals [24]. Schools were assumed to be closed for 26 weeks. The simulations include the effect of reduced transmission. The extra costs would be €1.85 million per 1000 population, achieving a reduced attack rate of 39% instead of 50% if schools remain open. QALYs gained were estimated at 69 per 1000 of the population.

Sadique *et al.* estimated the costs due to school closure during a pandemic in the UK [23]. Estimates showed that approximately 16% of the workforce also represents the main caregivers and are, therefore, likely to be absent if children have to stay home. Furthermore, since mostly women were expected to be the main caregiver, the health and social work sector would be highly affected owing to the high proportion of women in these sectors. The costs in the base scenario (mostly women taking care of children under the age of 16 years) would be approximately €1.22 million per week. There are no estimates presented on the effects on the transmission of closing schools.

Epstein *et al.* showed that, in order to significantly reduce the total number of influenza cases worldwide, at least 95% of air travel would have to be cancelled [16]. At this level of reduction in travel, the delay of a few weeks in the initial spread of the epidemic may have huge effects on the cumulative numbers of cases. The costs are based on estimations from the effects on travel restrictions after the terrorist attacks of 11 September 2001. Costs for the USA were estimated to be €68–73 billion per year. Adding impacts on labor, the total of €73 billion would rise further to approximately €77 billion, costs being 0.8–0.9% of the USA gross national product. The authors label this "far from ruinous" for the US economy. No costs to the rest of the world's economy or countries likely to lose tourism and other productive activities were included.

Transmission & healthcare utilization models

The four economic evaluations based on dynamic models included in this review [16,19,20,24] are based on earlier published transmission models for the specific situations in the USA [2] and The Netherlands [30]. As such, these studies had a major impact on developing the methodologies for modeling influenza pandemics and economic consequences, without presenting formal cost–effectiveness estimations. Another study that has had a large impact on both the dynamic model development and the cost–effectiveness calculations for The Netherlands was developed by van Genugten *et al.* [31]. The article, published in *Emerging Infectious Diseases*, investigated the healthcare needs during a pandemic but did not include any formal cost–effectiveness calculations [31]. Notably, van Genugten *et al.* were the only researchers who included pneumococcal vaccination as an explicit strategy to control the impacts of pandemic influenza. Recently, and also in the light of new, more effective pneumococcal vaccines now being available, this strategy has received renewed interest [32]. For the comprehensiveness of this review, these studies are summarized in Table 4.

Discussion

From this review on published cost–effectiveness studies of interventions to mitigate an influenza pandemic, it can be concluded that many interventions have been estimated to be cost effective. Notably, the dynamic models taking a reduction of transmission explicitly into account provide lower cost–effectiveness ratios than the static decision-tree type of models. In particular, the dynamic type of modeling allows for the indirect effects of herd protection from interventions – for example, vaccination – to be taken into account, and further enhance the benefits of these interventions. This implies a greater reduction in healthcare consumption, illness and deaths owing to these reduced transmission potentials in the calculations. Specifically, for the USA and The Netherlands, where both types of models have been used to estimate the effects of control measurements, this phenomenon that dynamic models come up with more favorable cost–effectiveness can be seen [19,24].

The stockpiling of antiviral drugs was generally found to be highly cost effective, for example, if using the stockpile for treatment of symptomatic cases [14,18,20,24]. In one specific study using dynamic modeling [24], the use of the stockpile in large-scale, targeted, antiviral prophylaxis was identified as the most effective single strategy, providing both QALY gains and cost savings.

The expectation is that a vaccine against the new, now circulating influenza A/H1N1 virus will be available shortly. With a very well-matched vaccine, thus, highly effective (potentially approaching 100%), and a high coverage, the transmission can be expected to be even more contained than what is assumed in the models reviewed in this article. This, of course, assumes a high compliance to a national vaccination program. These models were often developed with the threat of an avian influenza virus, with no highly effective vaccination expected to be available before the peak of the epidemic (e.g., 30% was used for a badly matching vaccine). In light of the new influenza A/H1N1 virus, these models may, thus, underestimate the effect of vaccination and, subsequently, the cost–effectiveness of this intervention. Notably, these models are based on previous pandemics and characteristics of seasonal influenza. The novel influenza has, until now, showed a slightly different attack rate; in particular, children and young adults seem to be the most vulnerable groups for the infection [33], whereas a seasonal influenza normally attacks older age groups harder, with higher probabilities for complications.

One study linked the closing of schools explicitly to reduced transmission [24]. Even with the very long closing-time assumed (i.e., during the whole of the pandemic period of 26 weeks), the cost per QALY gained is reasonable, illustrating the huge effect of the reduced transmission. A more specific policy would be to close schools for a much shorter period, somewhere before the peak of the pandemic. That would reduce the costs substantially, but the effect on transmission would probably be almost as high, since school children contribute the most to the spread, especially before the peak [30]. Of course, reopening the schools should not result in a resurgence of the pandemic and merely causes the initial peak to shift rather than to decline or even disappear.

The recent pandemic alert issued by the WHO did not include any recommendations on the restriction of international travel. The effect in reduced transmission of such a restriction is relatively small, whereas the high cost due to reduced world trade and tourism is substantial. Moreover, at this stage of the A/H1N1 pandemic, morbidity and mortality caused by the virus still seems relatively mild. Most models included in this review assume case–fatality rates similar to seasonal influenza but a few of them present sensitivity analyses using higher rates based on the devastating 1918–1919 Spanish influenza outbreak [14,22,25].

We conclude that the choice of an appropriate model is crucial to arrive at valid cost–effectiveness ratios [13]. Health economists involved in the evaluation of infectious diseases recognize the importance of dynamic modeling [8,9,34,35]. However, a general literature review of cost–effectiveness studies of vaccine programs [7], as well as disease-specific reviews [36–39], reveal that only a minority of the economic evaluations of infectious diseases' control is based on dynamic modeling. In this review, the same appears to hold true for cost–effectiveness analyses in pandemic influenza control. To further enhance validity of the approaches, we recommend that further research is directed toward linking dynamic epidemiological models for pandemic spread with economic outcomes, considering the full impacts on national economies, including direct, indirect, medical and nonmedical costs.

Expert commentary

For properly analyzing interventions in infectious diseases, dynamic models are more and more seen as being warranted. The health economic analyses of pandemic influenza that are based on dynamic modeling have all been published in the last couple of years. This might be related to the large interest in possible containment and mitigation of pandemic influenza that emerged in the last decade, partly owing to the development of new antiviral therapies against influenza and vaccine developments. The possibility of slowing down pandemics by the therapeutic and prophylactic use of these drugs led to modeling efforts in the area of mathematical epidemiology, subsequently followed by interest in analyses on the economic justification of stockpiling antiviral drugs and vaccines to be prepared for the event of an outbreak. In addition, social-distancing measures (e.g., school closures and air-travel restrictions) have been investigated in this respect.

One recent study combines all these aspects in one health-economic analysis: investigating various (combinations of) control strategies, applying a dynamic model and – in the meantime – justifying antiviral stockpiling [24]. This study was extensive in its accounting for both direct medical costs and indirect costs for lost production. Various interventions, including social distancing and pharmaceutical interventions, were investigated, including a wide range of options for targeted antiviral prophylaxis, such as targeting household members only, or targeting work and school contacts as well, both with availability of antiviral treatment for 25 or 50% of the population. In addition, prevaccinating 70% of the population with a low-efficacy vaccine was investigated. Full targeted antiviral prophylaxis was identified as the most effective single strategy providing QALY gains and cost savings. Further findings indicated that prevaccination, if combined with school closure, dominated over both to do nothing and school closure alone (lower net costs and more QALYs gained). In addition, the combination of prevaccination and school closure provided extra QALYs if compared with full targeted antiviral prophylaxis but at the expense of extra net costs. In particular, costs per QALY gained were approximately €36,500 for the combination compared with full targeted antiviral prophylaxis. This study was, however, targeted solely in a USA-type setting. Comprehensive assessments for other country settings are required.

Five-year view

In general, we expect that, for health economic assessments, more and more dynamic models will be used in the future, not only in the field of (pandemic) influenza but for most infectious diseases. The collaboration between health economists and mathematical modelers is crucial in that respect. For a long time, dynamic models have been seen as too complex and as being too extensive in their demand for data. Yet, information on various aspects is becoming available – for example, on explicit contact pattern in populations and various types of costs for infectious diseases. Therefore, arguments that lack information on transmission, epidemiology and economics of specific infectious diseases as reason not to develop a dynamic model rapidly lose their validity. In addition, the availability and free access to user-friendly software aids to this development. In the coming years, we recommend the intensification of linking dynamic epidemiological models for infectious diseases' spread with economic outcomes, further enhancing the validity of the approaches in cost–effectiveness of infectious disease control, including pandemic influenza.

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Key issues

- Dynamic models that describe the transmission of infectious diseases are often vital to make valid estimates of cost–effectiveness of interventions for controlling these infectious diseases. Control of pandemic influenza poses no exception to this.
- Yet, many models that have been developed to date for analyzing pandemic influenza control measures have been static rather than dynamic models.
- Such static models generally suggest (slightly) less-favorable cost–effectiveness than dynamic models.
- The spread of an influenza virus with pandemic potential in a totally susceptible population can be huge; this enhances the cost–effectiveness profile of various interventions, including antiviral treatment, prophylaxis, vaccination (also with a less effective vaccine) and social-distancing measures.
- Dynamic models can indicate how nonpharmaceutical interventions, such as school closures, can delay or flatten the peak of a pandemic, allowing more time to develop a vaccine that, in many cases, is estimated to be cost effective.
- Stockpiling of antiviral drugs – for use of either treatment or prophylaxis – is consistently estimated to be highly cost effective or even cost saving. It is widely accepted to be the most effective single strategy.
- Vaccination with a low-efficacy vaccine and school closure can be cost effective in addition to use of stockpiled antiviral drugs.
- To further enhance the validity of the approaches, we recommend that further research is directed toward linking dynamic epidemiological models for pandemic spread with economic outcomes, considering the full impacts on national economies, including direct, indirect, medical and nonmedical costs.

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