HEALTH ECONOMICS
Health Econ. (2009)
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hec.1485

DYNAMIC VERSUS STATIC MODELS IN COST-EFFECTIVENESS ANALYSES OF ANTI-VIRAL DRUG THERAPY TO MITIGATE AN INFLUENZA PANDEMIC

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SUMMARY

Conventional (static) models used in health economics implicitly assume that the probability of disease exposure is constant over time and unaffected by interventions. For transmissible infectious diseases this is not realistic and another class of models is required, so-called dynamic models. This study aims to examine the differences between one dynamic and one static model, estimating the effects of therapeutic treatment with antiviral (AV) drugs during an influenza pandemic in the Netherlands. Specifically, we focus on the sensitivity of the cost-effectiveness ratios to model choice, to the assumed drug coverage, and to the value of several epidemiological factors. Therapeutic use of AV-drugs is cost-effective compared with non-intervention, irrespective of which model approach is chosen. The findings further show that: (1) the cost-effectiveness ratio according to the static model is insensitive to the size of a pandemic, whereas the ratio according to the dynamic model increases with the size of a pandemic; (2) according to the dynamic model, the cost per infection and the life-years gained per treatment are not constant but depend on the proportion of cases that are treated; and (3) the age-specific clinical attack rates affect the sensitivity of cost-effectiveness ratio to model choice. Copyright © 2009 John Wiley & Sons, Ltd.

Received 5 September 2007; Revised 29 January 2009; Accepted 20 February 2009

KEY WORDS: infectious disease; transmission; modeling choice

1. INTRODUCTION

Cost-effectiveness evaluations of health-care interventions are often based on models. Such evaluations play an important role for allocating society's scarce resources to meet the public health concerns of preventing disease, prolonging life and promoting health in the whole community (Weinstein *et al.*, 2003). The choice of an appropriate model is crucial to arrive at valid cost-effectiveness ratios (Brennan *et al.*, 2006; Kim and Goldie, 2008). Most widely used models are decision tree models and Markov models (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Bala and Mauskopf, 2006). These conventional models implicitly assume that the probability of disease exposure is unaffected by an intervention against it, and therefore the probability of exposure to the disease does not change over time. This assumed constant probability of exposure is realistic for non-transmissible diseases, and can be modeled with so-called static models.

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For transmissible infectious diseases the imposed independence between disease exposure and interventions is not realistic and another class of models is required. Interventions against transmissible diseases will not only lower the probability of the treated individual to develop illness, they also lower the exposure of the infection to others. We refer to models that take these non-linear transmission effects over time into account as dynamic models. The non-linearity arises because the probability of a susceptible being infected depends on number of infectious individuals. The best known dynamic model for spread of infection is the SEIR (Susceptible–Exposed–Infectious–Removed) model (Anderson and May, 1991; Keeling and Rohani, 2008).

Health economists involved in the evaluation of infectious diseases recognize the importance of dynamic modeling (Edmunds *et al*., 1999; Beutels *et al*., 2002; Brisson and Edmunds, 2003; Drummond *et al*., 2007). However, a general literature review of cost-effectiveness studies of vaccine programmes (Kim and Goldie, 2008) as well as disease specific reviews (Beutels, 2001; Newall *et al*., 2007; Anonychuk *et al*., 2008) reveal that only a minority of the studies on infectious diseases are based on dynamic modeling. One of these reviews presents as a general result that a decision based on cost-effectiveness ratios may depend on model choice (Beutels, 2001). Universal influenza vaccination is mentioned as a case where a dynamic model would probably be preferable to a static model; recently, one study showed that vaccination against seasonal influenza was indeed cost-effective when estimated with a dynamic model but not with a static model (Pradas-Velasco *et al*., 2008).

Dynamic models also play an important role in exploring possible strategies to contain a pandemic outbreak of influenza through controlling transmission (Ferguson *et al*., 2005; Longini *et al*., 2005; Ferguson, 2006; Germann *et al*., 2006; Lipsitch *et al*., 2007). As it is doubtful whether there will be an effective vaccine available during a first wave of an influenza pandemic, the proposed strategy in the Netherlands is to treat all individuals suffering from influenza-like illness (ILI) with oseltamivir, an antiviral (AV) drug (Health Council of the Netherlands, 2005).

Vaccination and AV therapy affect viral transmission in different ways. With vaccination, virus can only be transmitted by an individual if this individual is exposed and not immunized, either due to incomplete coverage or to an imperfect vaccine. With AV therapy, virus can be transmitted by any individual after this individual is exposed and before the therapy takes effect. Therapeutic treatment reduces viral transmission only if therapy is started soon after the onset of symptoms (Mäkelä *et al*., 2000; Stiver, 2003). This difference has important consequences for the virus transmission dynamics, and it implies that results derived from a dynamic model for a vaccine-based intervention do not carry over to results for an AV-drug intervention.

The question is whether a dynamic model would be prefereable to a static model for estimating the effects of large scale use of AV-drugs for use in cost-effectiveness analyses (Lynd *et al*., 2005). To our knowledge, no study has yet used dynamic models that account for the reduced transmission due to AV-drugs in a cost-effectiveness analysis.

This study aims to fill this gap, and more specifically, it aims to examine the differences between the cost-effectiveness ratios of therapeutic AV-drug to mitigate an influenza pandemic as calculated by a dynamic and a static model. Estimates of costs and effects of therapeutic treatment with AV-drugs are compared with a non-intervention scenario during a first wave of an influenza pandemic in the Netherlands. The sensitivity of both modeling approaches is assessed for several epidemiologic factors and aspects of drug use.

2. METHODS

We estimate the cost-effectiveness, expressed as the incremental cost-effectiveness ratio, of therapeutic treatment with AV-drugs compared with non-intervention, resulting in a cost per life-year gained due to the intervention. We do this with one dynamic model and one static model and investigate how the

DOI: 10.1002/hec

cost-effectiveness ratios differ between these model approaches. In short, the static approach estimates the effects of AV treatment as proportional to assumed number of individuals with ILI during a pandemic. The dynamic approach goes beyond this and estimates the number of individuals with ILI based on the characteristics of the virus and the contact structure in the population, and the effect on transmission of AV therapy. The structure of the cost-effectiveness calculations is the same for both approaches (Figure 1).

2.1. Models

2.1.1. Static model. The static model is a decision tree model. The population is partitioned into six age groups, and each age group is split into low-risk and high-risk groups. The model calculates the health-care consumption due to treatment and complications proportionally to the assumed number of infected or symptomatic individuals. This means that there is a specific probability attached to each 'chance node' in the decision tree, and the health-care consumption depends on number of infected individuals (Figure 1). Interventions affect only the treated individual's mortality risk and health-care consumption.

2.1.2. Dynamic model. The dynamic model is based on the age-structured SEIR-type of models (*susceptible–exposed–infected–removed*). This type of model describes the transmission of the disease, where the compartments represent number of individuals in each state at a certain point in time. Our model includes one additional compartment 'recovering' (G), where individuals still can consume health care due to complications (hospitalizations), but are no longer infectious to other people, and therefore are no longer part of the transmission process (Figure 2). Non-symptomatic individuals are also able to spread the virus. The population is partitioned into six age groups and two risk groups (Mylius *et al.*, 2008).

The key epidemiological parameters in the model include the contact rates among and within age groups, the length of the infectious period and the 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.

The cumulative numbers of individuals that enter the various compartments after one pandemic wave were used for the cost-effectiveness calculations. Appendix A shows the model equations.

2.1.3. Parameterization of the models. At the start of the first pandemic wave, the whole population is at risk of getting infected since we assume that the population lacks immunity against a pandemic virus, i.e. everyone is susceptible. The population size is 16 357 992 people (population of the Netherlands in 2007). Hospitalization and death rates are age and risk-group dependent (Baltussen *et al.*, 1998; Sprenger *et al.*, 1993). High-risk groups include immunocompromised individuals, people with chronic respiratory diseases, and all people older than 65 years in nursing homes.

We assume that 80% of individuals with ILI will use AV-drugs during the first wave.[1] This assumption is further considered in the sensitivity analysis. Therapeutic treatment is assumed to start within 48 h of the onset of symptoms. Using AV-drugs leads to a 50% reduction of health-care resource use due to complications, and a 50% reduction in deaths (Stiver, 2003; Kaiser *et al.*, 2003). Outpatient health-care utilization is based on opinions from an expert panel (van Genugten *et al.*, 2003).

The attack rate in an influenza pandemic remains unknown until the epidemic has passed. In the three pandemics during the last century the clinical attack rates (CAR) have been estimated to be around 25–30% (Nguyen-Van-Tam and Hampson, 2003). During these three pandemics the CAR has not been evenly distributed over age groups. To facilitate the comparison between the two approaches,

[1]Assumption based on estimates from national experts involved in pandemic preparedness.

DOI: 10.1002/hec

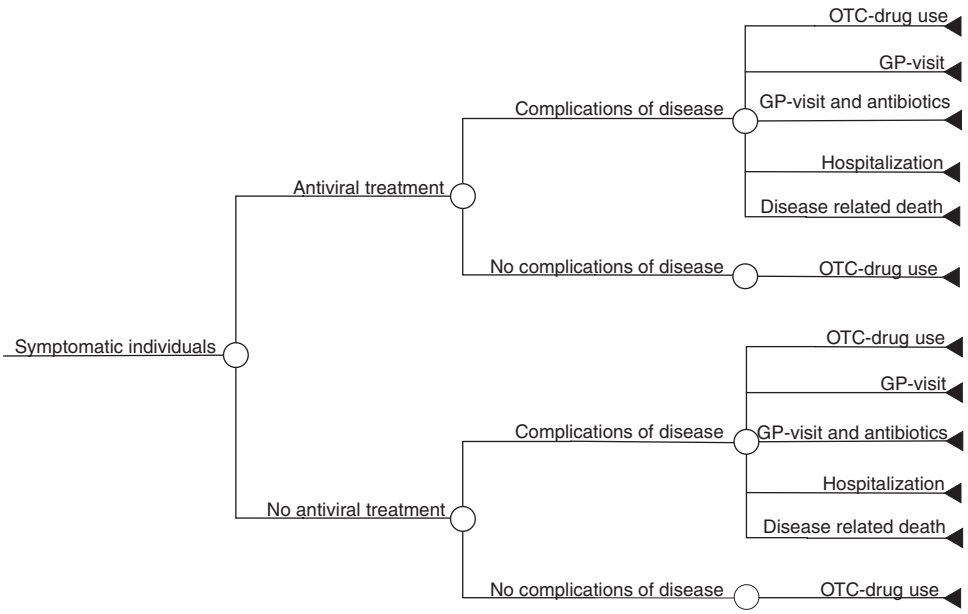

Figure 1. Structure for static model and cost-effectiveness calculations.

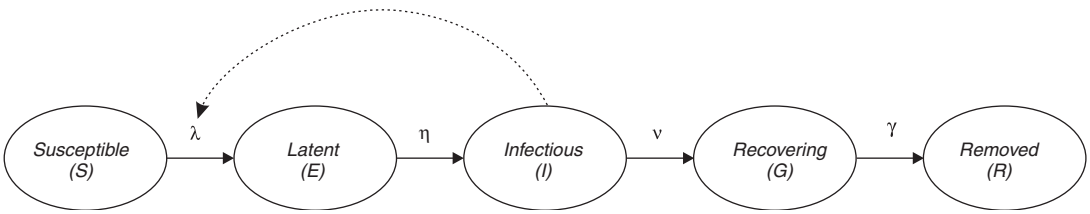

Figure 2. Schematic illustration of the dynamic disease model. *Note*: λ = rate of becoming infected (force of infection), η = rate of becoming infectious, ν = the rate of losing infectiousness, γ = rate of recovery or death. See Appendix A for further details

we modeled the prevalence of ILI in the static model as the overall CAR predicted by our dynamic model (38%) in the base-case scenario.

The transmission is dependent on contacts between susceptible and infected individuals. We use contact patterns between and within age groups derived from self-reported social contact data (Wallinga *et al.*, 2006). The durations of latent and infectious periods are based on observational data from a Japanese household study (Hirotsu *et al.*, 2004). These are calibrated such that the generation interval (defined as the expected duration between the point in time when one individual is being infected by influenza virus and the point in time when that individual is infecting someone else) matches the observed value of 2.85 days (Wallinga and Lipsitch, 2007). A key epidemiological variable is the basic reproduction number, R_0, which describes how many secondary cases of infections are caused by one primary case in a susceptible population (see e.g. Keeling and Rohani, 2008, p. 20). The R_0 estimate (1.73) is based on data from the Asian Flu in 1957 (Wallinga *et al.*, 2006). Of all infected individuals, 60% develop clinical symptoms (Jordan *et al.*, 1958; Fukuda *et al.*, 2004). We further assume that the clinical course of the pandemic virus reflects that of a seasonal influenza virus.

DOI: 10.1002/hec

We perform sensitivity analyses to investigate the influence of various parameters. For both models we assume the impact of therapy under the assumptions that 60 and 70% of the population will follow AV-drug treatment (rather than 80% in the base case). For both models we assume different attack rates implying different sizes of the pandemic, expressed as CAR of 25 and 50% (rather than 38% in the base case). These attack rates correspond to a value of R_0 of 1.37 and 2.44, respectively. In addition we provide an alternative comparison between approaches by adjusting the static model using the age-specific attack rates that are predicted by the dynamic model, rather than assuming an overall CAR.

2.2. Health-care consumption and costs

Health-care consumption includes outpatient health-care utilization (over the counter drugs, visits to general practitioner (GP) and antibiotic prescriptions due to influenza-related complications), hospitalizations, and costs for therapeutic intervention with AV-drugs. The AV-drugs are distributed through the ordinary health-care system. A prescription can be collected at the pharmacy after a telephone consultation with the GP. The societal perspective is taken into account by estimating production losses according to the friction cost method. This is an alternative to the human capital approach to value productivity losses (Brouwer and Koopmanschap, 2005; Rothermich and Pathak, 1999); our choice is based on the Dutch guidelines for pharmacoeconomic research (Oostenbrink *et al*., 2004).

We discount life-years by 1.5%, following the Dutch guidelines (CVZ, 2006). Costs are not discounted, since these are assumed to arise within 1 year. Unit costs of direct medical costs and production losses were collected from different sources and expressed in 2005 prices. Assumptions, unit costs for the cost-effectiveness analysis and sources are presented in Appendix B.

3. RESULTS

According to the dynamic model, about 10.4 million people of the 16.4 million Dutch inhabitants would be infected during an influenza pandemic of which 6.2 million would have ILI. The pandemic would result in around 9000 deaths if left uncontrolled. According to the static model, number of deaths would be 1.4 times higher. In both approaches these numbers would be about 40% lower when patients with ILI are treated with AV-drugs. We combined these results with estimates on health-care utilization to investigate the cost-effectiveness of AV-drug therapy when estimated with the different model approaches. Both models provided favorable and almost identical incremental cost-effectiveness ratios when including health-care costs only: €1695 (static model) and 1637 (dynamic model) per life-year gained, and intervention becomes cost-saving when including productivity loss (Table I).

We further investigated the sensitivity of the models to changes in assumptions (Figure 3). The impact of a different policy goal was examined through lowering the percentage of the population that would use AV-drugs. With lower use of AV-drugs the difference between the models became bigger. Furthermore, the dynamic model provided a higher cost-effectiveness ratio than the static model when use of AV-drugs was lower than the base assumption of 80%. Evidently, higher use of AV-drugs reduces the transmission, making the estimates approaching each other.

The impact of changing the size of the epidemic, expressed as changing the CAR, did not change the cost-effectiveness ratio in the static model. This is explained by the fact that both costs and effects are proportional to the number of infected individuals, and therefore the ratio of costs and effects remains unaffected by the number of infected individuals. Contrary to this, the cost-effectiveness ratio of the dynamic model was very sensitive to these changes in size. For a CAR of 50% the relation between the ratios from the different models switched, the cost-effectiveness ratio from the dynamic model became higher (€2556 per life-year gained) than that of the static (€1695 per life-year gained).

Next, we investigated the impact on the static model of the age-specific attack rates derived from the dynamic model when analyzing the uncontrolled pandemic. The cost-effectiveness ratio calculated with

DOI: 10.1002/hec

Table I. Results from cost-effectiveness models of therapeutic treatment of pandemic influenza. Costs in thousands Euro 2005

	Static model				Dynamic model			
	Non-intervention		Therapeutic antiviral drugs		Non-intervention		Therapeutic antiviral drugs	
	Number	Cost (€)	Number	Cost (€)	Number	Cost (€)	Number	Cost (€)
Infected	—	—	—	—	10 369 872	—	8 594 056	—
Influenza like illness	6 221 923		6 221 923	—	6 221 923	—	5 156 433	—
Direct costs								
GP-telephone calls	0	0	4 977 538	51 737	0	0	4 125 147	42 877
Antiviral drugs	0	0	4 977 538	105 026	0	0	4 125 147	87 041
GP-visits due to complications	1 555 481	32 336	933 288	19 401	1 555 481	32 336	773 465	16 079
Antibiotics	466 644	5968	279 987	3580	466 644	5968	232 040	2968
OTC drugs	4 977 538	30 735	4 977 538	30 735	4 977 538	30 735	4 125 147	25 472
Hospitalization	29 256	134 389	17 553	80 634	22 941	105 384	13 851	63 625
Total direct costs		203 428		291 114		174 422		238 061
Effects								
Number of deaths	12 362		7417		9012		5 362	
Life years lost	143 297		85 978		108 309		64 938	
Life years lost discounted[a]	129 351		77 610		96 795		57 912	
Production losses								
Due to ILI		1 208 442		685 172		1 235 487		579 599
Due to prod reduction		1 170 944		43 221		1 214 232		37 238
Due to death		3534		2120		3665		2275
Total production losses		2 382 920		730 513		2 453 384		619 111
Cost-effectiveness ratio (using incremental direct costs, and discounted life-years gained)	€ 1695 per life-year gained				€ 1637 per life-year gained			

[a]1.5% discount rate.

DOI: 10.1002/hec

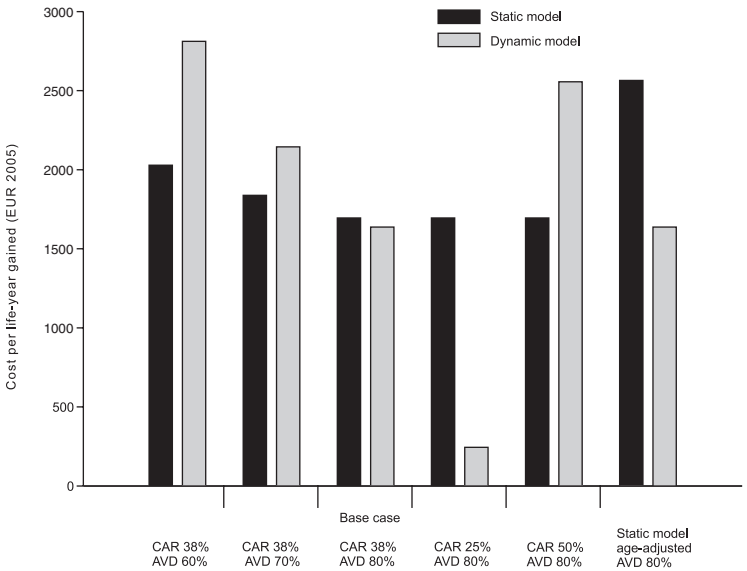

Figure 3. Cost-effectiveness ratios of the static and dynamic model for different assumptions about the clinical attack rate (CAR) with 80% of people with influenza-like illness using antiviral drugs, and for different assumptions about the percentage of persons with influenza-like illness using antiviral drugs (AVD)

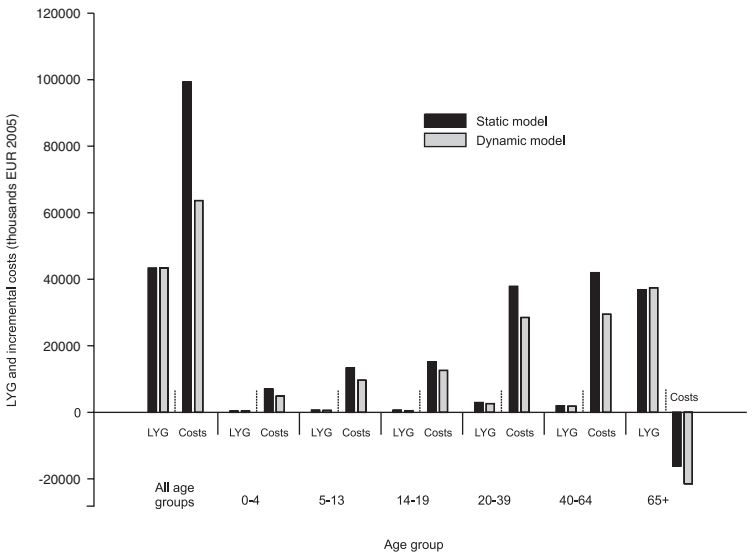

Figure 4. Life-years gained (LYG) and incremental costs between AV-therapy and non-intervention, age-adjusted static model and dynamic model. Life-years gained are not discounted in order to show an unbiased picture of the transmission effect

the static model increased to €2564 per life-year gained and thus became higher than that of the dynamic model. Number of life-years gained between non-intervention en AV therapy now became nearly identical in the two model approaches. The remaining difference between the two ratios is due to the effect of reduced transmission (Figure 4).

DOI: 10.1002/hec

4. DISCUSSION

We estimated the epidemic size, health-care utilization and costs, as well as production losses of an influenza pandemic with two different models, one dynamic and one static. For both models we evaluated a scenario for an uncontrolled pandemic and an intervention scenario with therapeutic use of AV-drugs in a Dutch setting. We find that therapeutic use of AV-drugs during an influenza pandemic is cost-effective compared with a non-intervention scenario. This result is robust in the sense that it does not depend on the model (static or dynamic) that is used for the estimates, and in the sense that it does not change when less AV-drugs are used than planned, or when attack rates are higher than anticipated. All cost-effectiveness ratios are below the (unofficial) threshold of €20 000 per life-year gained that seems to be applied in the Netherlands.

It is tempting to assert that the robustness of our finding implies that model choice is unimportant for economic underpinning of pandemic planning. We believe that such an assertion would be misguided. Even though both the static and the dynamic model conclude that the intervention is cost-effective, there are a number of differences between the two model approaches that are crucial in planning for an influenza pandemic. Below we list four key differences.

First, the two modeling approaches do differ in the expected cost-effectiveness ratios for most scenarios. If a different threshold for cost-effectiveness would be applied, the outcome may differ between the models.

Second, the two modeling approaches do differ in their ability to describe how the infection attack rates may change over different age and risk groups. In the static model it is not possible to know the precise distribution of attack rate over various age and risk groups unless the age-stratified attack rate is given *a priori* for each scenario. In contrast, in the dynamic model the distribution is consistently inferred for each scenario from a single global infection attack rate in the uncontrolled scenario. We have shown that for influenza, where different age and risk groups contribute differently to disease burden and costs, the changing infection attack rates over the groups are extremely important. This finding significantly extends earlier comparisons of modeling approaches to assess the cost-effectiveness of influenza control (Pradas-Velasco *et al.*, 2008).

Third, the two modeling approaches do differ in their sensitivity of the expected cost-effectiveness ratio to changes in infection attack rate. The static model suggests that the cost-effectiveness ratio is insensitive to the infection attack rate, and hence there seems to be no uncertainty about the cost-effectiveness ratio even though there is a large uncertainty about the infection attack rate of a future pandemic. In contrast, the dynamic model suggests that cost-effectiveness ratios are sensitive to the infection attack rate, and hence the large uncertainty about the infection attack rate of a future pandemic implies that we actually cannot be completely certain about the cost-effectiveness ratio.

Fourth, a more general aspect is that the two modeling approaches do differ in their ability to deal with the possibility of eradicating a disease. A welfare economic argument to use dynamic models is provided by Geoffard and Philipson (1997). They show that the welfare effects of eradication of a disease by means of vaccination only can be investigated by taking the dynamic externalities into account. They argue that the most important welfare effects are the avoided, costly prevention efforts for future generations, an aspect that is not accounted for in a static analysis. For example, the economic benefits of measles eradication in the USA were estimated taking into account a force of infection that decreased over time, even if the model did not describe the actual transmission (Miller *et al.*, 1998). The point is that using a force of infection that changes over time takes us beyond the framework of static models.

To understand the similarities and differences between the static and the dynamic modeling approaches, it is convenient to think of a static model as a specific, albeit unrealistic, case of a dynamic model. This special case arises when the initial proportion of susceptible individuals in each group would be equal to the final infection attack rate in that group, and when all susceptible individuals are infected instantaneously by the first influenza case. The latter condition requires the unrealistic assumption that the reproductive number R_0 would be very high. This argument leads us to expect that

DOI: 10.1002/hec

a static model performs equally well as a dynamic model if the disease is characterized by a high value for R_0 (Edmunds *et al*., 1999). We note that this is not the case for pandemic influenza (e.g. Wallinga and Lipsitch, 2007); hence we have no guarantee that static and dynamic models for pandemic influenza result in similar outcomes.

Considering the static model as a specific, unrealistic case of an dynamic model with a very high value for the reproductive number, helps to understand that in this case an intervention may reduce the initial proportion of susceptible individuals or may reduce the consequences of infection, but may not reduce the effective reproductive number or the probability of a susceptible being infected. That is, a static model cannot account for a reduced risk of infection for a susceptible individual that results from an intervention aimed at another individual (the so-called herd immunity effect). This has been noticed before. For example, Welte *et al*. (2005) showed how a static model of chlamydia screening could lead to inefficient conclusions, resulting in targeting wrong groups for screening.

It is tempting to assert that a static model always provides a conservative estimate of the cost-effectiveness since it does not account for herd immunity and therefore underestimates the health effects. However, such an assertion is not always tenable. Brisson and Edmunds (2006) showed that vaccination against varicella-zoster virus in children could cause more disease in older individuals, such that vaccination would result in a loss in QALY. Here we show that for the specific case of mitigating an influenza pandemic using AV-drugs the herd immunity not only impacts the health effects and health-care utilization, but also the demand for AV-drugs and related costs.

As in any other scenario study we have made a few simplifying assumptions that should be addressed. Throughout this study we have assumed the effectiveness of AV-drug therapy to remain constant. The effectiveness might decrease if the pandemic influenza virus develops resistance against the AV-drugs. AV-drug resistance often leads to a loss of transmissibility in the virus, and model studies have shown that the threat of an emerging resistant virus that is less transmissible should not discourage the use of AV-drugs, at least not at intermediate levels of use (Lipsitch *et al*., 2007). Throughout this study we have assumed that individual behavior remains unaffected by the ongoing pandemic. However, pessimistic expectations about an epidemic could also influence people's beliefs about the future epidemic, even leading to more risky behavior (Auld, 2003). Individual, voluntary measures such as avoiding public transportation and staying home from work would also influence the transmission (Sadique *et al*., 2007).

A dynamic model is most useful for prediction of cost-effectiveness of infectious disease control measures, provided that there is sufficient data to parameterize such a model, if interest is in both direct and indirect effects of interventions. If the interest is only in direct effects, for example when we know an intervention has no impact on the transmission of the infectious agent, a static model may suffice. But in general the indirect effect of reduced transmission is a gain, not only for the treated individual, but also for the whole population, providing a significant public health benefit. The non-linear disease dynamics that cause these indirect effects of interventions needs to be recognized (Brandeau *et al*., 2003). In the specific case of pandemic influenza, we require information on the expected effects and costs of interventions, both the direct and indirect, as well as the sensitivity of these expectations to our assumptions (see e.g. Duintjer Tebbens *et al*., 2008). Whereas dynamic models make explicit that our estimates for cost-effectiveness depend on the assumed size of an epidemic, static models implicitly assume that the assumed epidemic size is irrelevant. For decisions about an appropriate size of a stockpile of AV-drugs in order to be able to mitigate a pandemic these differences may be vital. We argue that for pandemic preparedness planning static models have a limited use.

ACKNOWLEDGEMENTS

We thank two anonymous referees for their useful comments on our manuscript.

DOI: 10.1002/hec

APPENDIX A: THE DYNAMIC MODEL

The dynamic model is formulated as a set of ordinary differential equations. The population is divided into six age groups and two risk groups. The frequency of contacts between individuals is dependent on their age groups. The variables $S_{a,r}$, $E_{a,r}$, $I_{a,r}$, $G_{a,r}$ and $R_{a,r}$ denote number of susceptible, latent (*or exposed*), infectious, recovering and removed (immune or dead, meaning that these individuals cannot re-enter the susceptible compartment) individuals in age/risk group *a,r*. The parameter γ represents rate of becoming infected, η represents the rate of becoming infectious, v the rate of losing infectiousness, and γ denotes the rate of recovery or death, all measured in days.

The model equations assume that the durations of exposed and infectious periods follow a realistic gamma distribution (Wearing *et al.*, 2005). Technically, this is accomplished by splitting up both exposed and infectious compartments in n_E and n_I consecutive stages, respectively. The average time spent in each consecutive stage is $1/\eta$ for exposed individuals, and the total exposed period is therefore n_E/η; the average time spent in each consecutive stage is $1/v$ for infectious individuals, and the total infectious period is therefore n_I/v (Table AI). Values of n_E and n_I, η and v are chosen such that the generation interval for influenza matches observed average of 2.85 days (Wallinga and Lipsitch, 2007).

$$\frac{\mathrm{d}S_{a,r}}{\mathrm{d}t} = -\lambda_{a,r} S_{a,r}$$

$$\frac{\mathrm{d}E^{(0)}_{a,r}}{\mathrm{d}t} = \lambda_{a,r} S_{a,r} - \eta E^{(0)}_{a,r}$$

$$\frac{\mathrm{d}E^{(i)}_{a,r}}{\mathrm{d}t} = \eta E^{(i-1)}_{a,r} - \eta E^{(i)}_{a,r}$$

$$\frac{\mathrm{d}I^{(0)}_{a,r}}{\mathrm{d}t} = \eta E^{(n_E)}_{a,r} - v I^{(0)}_{a,r}$$

$$\frac{\mathrm{d}I^{(j)}_{a,r}}{\mathrm{d}t} = v I^{(j-1)}_{a,r} - v I^{(j)}_{a,r}$$

$$\frac{\mathrm{d}G_{a,r}}{\mathrm{d}t} = v I^{(n_I)}_{a,r} - \gamma G_{a,r}$$

$$\frac{\mathrm{d}R_{a,r}}{\mathrm{d}t} = \gamma G_{a,r}$$

where the superscripts i and j ($i \in \{1, \ldots, n_E\}$ and $j \in \{1, \ldots, n_I\}$) denote the stage numbers.

The hazard rate for a susceptible individual of becoming infected in age/risk group *a,r* is described by $\lambda_{a,r} = q \sum_b c_{a,b} \sum_s I_{b,s}$, where a and b are age groups and r and s are risk groups. The parameters $c_{a,b}$ describe the contact rate between individuals in age groups a and b (Table AII). The infectivity parameter q was chosen such that $R_0 = 1.73$ (Wallinga *et al.*, 2006).

In the cost-effectiveness calculations we use the cumulative number of infections, hospitalizations and deaths after one pandemic wave as calculated by this model.

Table AI. Parameter and their values in the dynamic model

Parameter		Value
n_E/η	Mean exposed period	1.95 day
n_I/v	Mean infectious period	1.60 day
$1/\gamma$	Mean recovery period	7.00 day

DOI: 10.1002/hec

Table AII. Normalized age-specific contact matrix C (Wallinga *et al*., 2006)

	0–4	5–12	13–19	20–39	40–64	65+
0–4	1.000	0.186	0.105	0.204	0.094	0.068
5–12	0.186	1.232	0.145	0.157	0.092	0.052
13–19	0.105	0.145	1.549	0.350	0.259	0.103
20–39	0.204	0.157	0.350	0.410	0.268	0.136
40–64	0.094	0.092	0.259	0.268	0.228	0.123
65+	0.068	0.052	0.103	0.136	0.123	0.349

Table BI. Assumptions in the static and dynamic models

		Age group					
		0–4	5–13	14–19	20–39	40–64	65+
Population		16 357 992					
Proportion of total population	high risk	0.0014	0.0023	0.0020	0.0162	0.0215	0.0506
	low risk	0.0577	0.0951	0.0835	0.2478	0.3278	0.0942
Remaining life years (average in age group)		75.79	69.34	62.01	48.10	28.75	10.67
Proportion ILI[a] of infected		0.60	0.60	0.60	0.60	0.60	0.60
Probabilities given ILI							
OTC drugs		0.80	0.80	0.80	0.80	0.80	0.80
GP-visits due to complications		0.25	0.25	0.25	0.25	0.25	0.25
Antibiotics due to complications		0.30	0.30	0.30	0.30	0.30	0.30
Probabilities given infection							
Probability of hospitalization	high risk	$8.70*10^{-3}$	$8.70*10^{-3}$	$8.70*10^{-3}$	$1.29*10^{-2}$	$1.29*10^{-2}$	$3.36*10^{-2}$
	low risk	$3.45*10^{-5}$	$3.45*10^{-5}$	$3.45*10^{-5}$	$4.31*10^{-5}$	$4.31*10^{-5}$	$5.85*10^{-3}$
Probability of death	high risk	$3.44*10^{-4}$	$3.44*10^{-4}$	$3.44*10^{-4}$	$5.11*10^{-4}$	$5.11*10^{-4}$	$1.69*10^{-2}$
	low risk	$1.47*10^{-5}$	$1.47*10^{-5}$	$1.47*10^{-5}$	$1.83*10^{-5}$	$1.83*10^{-5}$	$3.21*10^{-3}$

[a]ILI = influenza-like illness.

APPENDIX B: ASSUMPTIONS REGARDING COST-EFFECTIVENESS ANALYSIS OF INTERVENTION VERSUS NON-INTERVENTION

Both the static and the dynamic model use the same assumptions regarding population structure and health-care consumption (Table BI).

In the cost-effectiveness analysis unit costs and other economic parameters are collected from different sources (Table BII).

For productivity loss due to death, the friction cost method counts a friction period after which the person is replaced and the productivity is resumed. This friction period is estimated to 22 weeks during which production is lost. A productivity elasticity of 0.8 is calculated for these losses, meaning that sick leave results in a loss of 80% of the production value (in stead of a proportional 100% loss of production value). The assumptions about the productivity elasticity were originally made in the development of the friction cost method, and are based on Dutch labor market studies (Koopmanschap *et al*., 1995). The length of the friction period is based on estimated vacancy length in the Netherlands in 2002 (Oostenbrink *et al*., 2004). The production value is estimated as the average salary among the working population aged 20–64 years, adjusted for participation in the workforce (62% of the population aged 15–64), assuming an 8 h work day (CBS) (Table BII).

DOI: 10.1002/hec

Table BII. Unit costs and production losses, assumptions

	Euro 2005	Source
Direct costs		
General practitioner visits	20.39	Oostenbrink *et al.* (2004)
Antiviral drugs	15.00	Authors assumption[a]
Antibiotics	6.56	Postma *et al.* (2005)
Over-the-counter drugs	6.06	Postma *et al.* (2005)
Hospitalization, normal care	362.58	Oostenbrink *et al.* (2004)
Intensive care, intensive care	1699.67	Oostenbrink *et al.* (2004)
Number of days in hospital	8	van Genugten *et al.* (2003)
Assumptions production losses		
Absenteeism due to ILI[b] (days)	1.5	Postma *et al.* (2005)
Reduced productivity due to ILI	50%	Postma *et al.* (2005)
Reduced productivity (days)	3.5	Postma *et al.* (2005)
Absenteeism due to ILI-child age 0–14 years (days)	1.2	Pisu *et al.* (2005)
Working days per year	160	Oostenbrink *et al.* (2004)
Working hours per year	1540	Oostenbrink *et al.* (2004)
Proportion working population of total population (2005)	62.6%	CBS (www.statline.nl)
Average cost per working hour (age 15–64)	EUR 34.15	Oostenbrink *et al.* (2004)

[a]Assumption based on estimates from national experts involved in pandemic preparedness.
[b]ILI = influenza-like illness.

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