Cost Effectiveness of Oseltamivir Treatment for Patients with Influenza-Like Illness Who Are at Increased Risk for Serious Complications of Influenza

Illustration for The Netherlands

Maarten J. Postma,[1] *Annoesjka Novak*,[2] *Huib W.K.F.H. Scheijbeler*,[1,3] *Marlene Gyldmark*,[4] *Marianne L.L. van Genugten*[5] and *Jan C. Wilschut*[6]

1 Groningen Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, The Netherlands
2 Roche Nederland BV, Woerden, The Netherlands
3 M-TAG, a division of IMS Health Economics and Outcomes Research, London, UK
4 Roche Basel, Basel, Switzerland
5 Mapi Values, Houten, The Netherlands
6 University Medical Center Groningen, Department of Medical Microbiology, Molecular Virology Section, University of Groningen, Groningen, The Netherlands

Abstract

Background: Oseltamivir is effective in the treatment of influenza. Utilisation in The Netherlands is limited, but increasing.

Objective: To estimate the cost effectiveness of oseltamivir treatment (vs symptom relief only) for patients with influenza-like illness (ILI) who are at increased risk for serious complications of influenza.

Methods: A cost-effectiveness analysis was used, building on a previously developed model (decision tree) that was applied for evaluating influenza vaccination and pandemic preparedness plans. Three patient subgroups were assessed (elderly patients [aged ≥65 years] without chronic disease, elderly patients with chronic disease, and chronically ill, non-elderly patients). Inputs for the model were taken from various sources including a meta-analysis. A societal perspective was adopted and costs were expressed in € per life-year gained (year 2003 values). Life-years lost were discounted at 4% in accordance with Dutch guidelines. Deterministic and probabilistic sensitivity analyses were employed to assess the robustness of the results.

Results: For chronically ill patients with ILI, visits to the GP for oseltamivir treatment were cost saving. For non-chronically ill elderly patients, incremental cost-effectiveness was estimated at €1759 per life-year gained. Cost savings and favourable cost effectiveness were robust in a deterministic and stochastic sensitivity analysis.

Conclusion: Our model-based analysis suggests that at-risk people presenting with ILI to a GP could be offered oseltamivir at favourable cost effectiveness or even cost savings in the Dutch setting compared with symptom relief with analgesics only.

Influenza is a common infectious disease with a characteristic annual recurrence pattern. Mostly, annual epidemics are self-limiting and well controlled by preceding vaccination campaigns. These campaigns are generally directed at groups at increased risk, such as the elderly and the chronically ill (e.g. patients with diabetes mellitus, heart diseases, renal dysfunction and respiratory diseases). There have been several studies on the economic impacts of influenza vaccination for the elderly and other at-risk groups.[1-4] In the majority of these studies, the outcome is that vaccination of these groups is cost saving, or at least provides a favourable pharmacoeconomic profile in terms of cost effectiveness. As such, vaccination of groups at increased risk remains the cornerstone of influenza management at the population level.

However, and despite the effectiveness of annual vaccination, even contained influenza epidemics may result in significant morbidity and mortality, in particular among groups at increased risk. This arises because of influenza cases among non-vaccinated individuals (with coverage never being 100%) and breakthrough infections occurring after vaccination (with efficacy well below 100%, particularly in the elderly). To avert complications such as hospitalisations, other infections (possibly requiring antibacterials) and deaths, treatment of influenza infections with one of the available drugs is increasingly being considered;[5] this is also the case in The

Netherlands,[6] despite the fact that the newer influenza antivirals are not reimbursed for patients.

Available drugs that have proven to be effective against complications can be categorised in two classes: (i) the hydrochlorides, amantadine and rimantadine; and (ii) the neuraminidase inhibitors, zanamivir and oseltamivir, which recently came on the market. The action of amantadine and rimantadine is limited to viruses of type A only. Furthermore, these drugs have exhibited resistance problems and are associated with significant adverse effects.[7] The UK National Institute for Health and Clinical Excellence (NICE) does not recommend the use of amantadine.[7] Zanamivir is effective in the treatment of influenza A and B, but it has to be administered by inhalation or intranasally;[8,9] use in The Netherlands is very limited.[6]

Oseltamivir is a new oral neuraminidase inhibitor that is effective in the treatment of both influenza A and B.[10-12] It is recommended for influenza-like illness (ILI) during epidemic periods (i.e. during periods with the influenza virus circulating in the population), to maximise the likelihood that symptoms are indeed caused by an influenza infection and not by a related virus or a bacterial infection rendering similar symptoms. The dosage is 75mg twice daily for 5 successive days and has to be started within 48 hours of the first symptoms.[12] Oseltamivir is administered as the prodrug oseltamivir phosphate, which is converted in the liver to oseltamivir carboxylate, the active drug.

This active metabolite selectively inhibits the neuraminidase of the influenza virus. NICE recommends oseltamivir for the treatment of groups at increased risk in the UK. This recommendation is based in part on an estimated favourable cost effectiveness of treatment with oseltamivir compared with symptom relief only for such populations.[6]

This study aims to validly estimate the cost effectiveness of oseltamivir treatment for individuals at increased risk (adolescents and adults with chronic disease, and the elderly) in the context of the healthcare system in The Netherlands, but also from a broader societal perspective that includes costs of production losses. Our analysis is specifically relevant in light of (i) the increasing use of oseltamivir in The Netherlands; and (ii) the recent introduction of mandatory pharmacoeconomic analyses for drug reimbursement applications in The Netherlands,[13] in particular for those drugs that claim to have an 'added value' compared with already existing treatments.
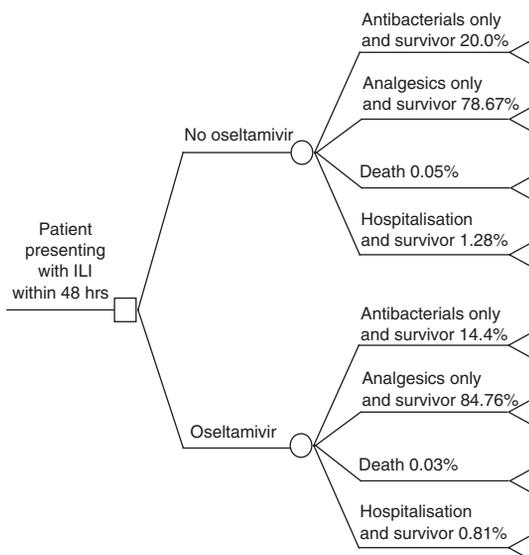
With respect to the latter, we note that an incremental cost-effectiveness analysis is now required in The Netherlands, in which the new drug is to be compared with a valid comparator; in this article we compare oseltamivir with conventional symptom and pain relief using over-the-counter (OTC) analgesic drugs.

Methods

General Design

We developed a simulation model in MS Excel™ that compared the costs and effects of treating high-risk (HR) groups with oseltamivir versus symptomatic treatment, such as the application of analgesics for the relief of malaise, fever and pain. Our cost-effectiveness model was based on concepts developed in two earlier studies.[14,15] In one study, we investigated the cost effectiveness of vaccinating the elderly in The Netherlands[14] and in the other study, we assessed the economic implications of pandemic influenza for The Netherlands.[15] Mathematical expressions and data handling used in these studies were elaborated further to develop the current study. To be in accordance with the available clinical trials on oseltamivir (in particular the specific subgroups identified in those trials)[5] and the available data in The Netherlands,[14,15] cost effectiveness was estimated for three separate subgroups, all at increased risk for influenza complications:

- elderly patients (aged ≥65 years) without chronic disease (low risk [LR]);
- elderly patients with chronic disease (HR);
- chronically ill, non-elderly patients (HR; adults and children aged >12 years or adolescents).

The basic structure of the model is summarised as a decision tree in figure 1 (designed using DATA 3.5, TreeAge Software Inc.).

Fig. 1. Schematic representation of the model as a decision tree (illustrated for high-risk adults), different probabilities apply to different branches according to specifications in tables I and II. **ILI** = influenza-like illness.

Table I. Clinical parameters for oseltamivir and placebo; data from a re-analysis of a meta-analysis[5] and an individual clinical trial[12]

Clinical parameter	Oseltamivir	Placebo	RR	Distribution (mean, SD)
Deaths (n)[a] [5]	10 (605)[b]	16 (601)[b]	0.62	Lognormal (−0.48, 0.40)
Patients hospitalised (n)[5]	12 (605)[b]	19 (601)[b]	0.63	Lognormal (−0.47, 0.36)
Patients receiving antibacterials (n)[5]	69 (605)[b]	95 (601)[b]	0.72*	Lognormal (−0.33, 0.15)
Hours lost[12]	173 (25,200)[c]	230 (25 080)[c]	0.75*	Lognormal (−0.29, 0.10)
ALOS[5]	7.17 (63)[d]	7.82 (112)[d]	0.92	Normal (7.17, 0.43)[d] Normal (7.82, 0.36)[e]

a   RR for incidence of pneumonia was used as proxy for the RR of death.
b   Total number of patients.
c   Total number of patient-hours.
d   Oseltamivir.
e   Placebo.
ALOS = average length of stay; **RR** = relative risk; * indicates statistical significance (95% level).

The Model

The model was developed to relate the costs of oseltamivir to both health gains of the treatment and savings on complications that were averted by the treatment. Thus, three dimensions were integrated into the cost-effectiveness estimate: (i) costs of oseltamivir; (ii) savings on complications; and (iii) life-years gained due to averted mortality. Net costs were calculated as costs of treatment minus savings on averted complications. Both direct medical savings (related to averted hospitalisations or use of antibacterials) and indirect savings related to averted production losses (for chronically ill, non-elderly patients) were included. The number of life-years gained was based on national age- and gender-specific death rate distributions for influenza-related causes combined with assumed effectiveness of oseltamivir. The incremental cost-effectiveness ratio (ICER) was defined as the net costs divided by the life-years gained. The ICER was calculated in the base case (most likely values for parameters) and sensitivity analysis and reflects the comparison between oseltamivir and symptom-relief treatment only.

The starting point for the model was a cohort of patients with ILI visiting a GP within 48 hours after the symptoms emerged, distinguished for each subgroup. As diagnostic tests are not generally used, this cohort actually consists of a mixture of both truly influenza-infected and non-influenza-infected patients. A meta-analysis, which analysed the efficacy of oseltamivir treatment in different subgroups (based on several clinical trials), reported a typical rate of approximately 65% of influenza-positive patients in such a cohort visiting the GP.[5]

The modelled cohort was first evaluated on costs of complications and deaths (and related life-years lost) in the absence of oseltamivir treatment (symptomatic treatment only), with efficacy from the placebo arms inserted in the model. Second, the cohort was evaluated with oseltamivir treatment and efficacy taken from the active arms of the trials in the meta-analysis. The difference provided the estimate of the savings on complications and health gains in terms of life-years gained; these were subsequently inserted in the ICER. Implicitly, it was assumed that effectiveness at the population level resembles efficacy from the trials, given the short duration of the regimen and the mild toxicity profile of oseltamivir.[10-12]

Data were taken from several sources, including the above-mentioned meta-analysis,[5] previous studies,[14,15] national statistics and expert opinions.[16] Based on available data, base-case values were estimated and, if possible, probability distributions were elaborated in order to perform a probabilistic sensitivity analysis or Monte Carlo simulation

on those parameters with high uncertainty around the base case (using @RISK by Palisade). In addition, deterministic sensitivity analyses were performed for selected variables unsuited for a probabilistic analysis, for example, the discount rate.

Clinical Parameters for Oseltamivir

Direct and indirect savings and averted deaths were based on effectiveness estimates of oseltamivir treatment for patients with ILI. Effectiveness on hospitalisation, antibacterial use and death was derived from the published meta-analysis[5] (differences in other medications and follow-up physician visits were not investigated in the oseltamivir trials). To estimate relative risks (RRs) for the whole group of patients with ILI (both infected and non-infected) and being at increased risk (elderly and/or being HR), a re-analysis had to be performed on the published data in Kaiser et al.[5] as the results for those groups individually were not specified. This re-analysis was directly performed on the published materials by extracting and/or adding the appropriate numbers from the paper and calculating the respective RR according to its definition, inclusive

confidence intervals assuming a lognormal distribution for any RR. As a further breakdown in efficacy estimates was impossible, effectiveness was assumed to be similar for all three above-specified subgroups and was subsequently formally inserted in the model as (1 – RR). Effectiveness for indirect savings (averted production losses) was based on Treanor et al.,[12] relating the time to return to normal activity (measured in hours) to total hours under treatment with oseltamivir (by intention to treat; i.e. 5 days).

Table I lists the numbers of patients in the meta-analysis with ILI at increased risk (HR adolescents and adults and all elderly patients) and the observed event rates, estimated mean RRs and estimated distributions for RRs to be used in the probabilistic analysis (lognormal distribution[17,18]). Additionally, the potential reduction in average length of stay (ALOS) due to oseltamivir treatment compared with placebo was estimated, and is also shown in table I (Normal distributions assumed for both treatment arms, based on the central limit theorem). As shown in table I, on average, oseltamivir reduces ALOS by

Table II. Estimated influenza-related hospitalisations and deaths per 100 000 partly vaccinated, unprotected and influenza-like illness (ILI) populations[14,15,20-23]

Parameter	Per 100 000 partly vaccinated population	Per 100 000 unprotected population	Per 100 000 patients with ILI
High-risk adolescents and adults			
Pneumonia hospitalisation	72	88	926
Other influenza-related hospitalisation	28	34	358
Total influenza-related hospitalisation	*100*	*122*	*1284*
Influenza-related deaths	4	5	51
High-risk elderly patients			
Pneumonia hospitalisation	175	245	3182
Other influenza-related hospitalisation	10	14	182
Total influenza-related hospitalisation	*185*	*259*	*3364*
Influenza-related deaths	93	130	1688
Low-risk elderly patients			
Pneumonia hospitalisation	38	43	558
Other influenza-related hospitalisation	2	2	26
Total influenza-related hospitalisation	*40*	*45*	*584*
Influenza-related deaths	22	25	321

Table III. Assumptions on resource use and costs: in the base case and in the probabilistic (assuming Uniform distributions in these cases[29]) and/or sensitivity analyses

Resource	Base case	Probabilistic/sensitivity analyses
Average length of hospital stay (days)		
pneumonia	13	
other	7.4	
Probability of an inpatient day at ICU (%)	5	0
Patients receiving an antibacterial prescription (%)	20	Uniform (10, 30)
Working days during illness	5	Uniform (4, 6)
Days of absenteeism	1.5	Uniform (1, 2)
Days with reduced productivity	3.5	Difference between working days during illness and days of absenteeism
Reduced productivity (%)	50	Uniform (30, 70)
Extra GP visits for oseltamivir prescription (%)	0	50
Unit costs (€; year 2003 values)		
non-ICU inpatient day	359	
ICU inpatient day	1684	
antibacterial prescription	14.16	
loss of day of work	224	
initial GP visit	20.70 (23[a])	
oseltamivir prescription	28.75	

a   Inclusive of over-the-counter medication.

8% compared with placebo or symptomatic treatment (mean RR = 0.92).

As certain complications of ILI, such as hospitalisations, are infrequent, statistically significant deviations of the RRs from 1 were not always achieved in the pooled estimates from the meta-analysis (see table I; hospitalisation). The use of probability distributions in the probabilistic analysis accounts for this uncertainty in the estimated RRs. This approach has also been taken, for example, to account for the uncertainty in the effectiveness of pneumococcal vaccination on invasive disease. Conducting studies to significantly show such effects requires unrealistically high numbers of patients.[19]

Additionally, a deterministic sensitivity analysis was directed at those effectiveness estimates that failed to be statistically significant (mortality, hospitalisation and ALOS), investigating proportional effects on the outcome of percentage changes in these parameters.

Epidemiology and Burden of Illness of Influenza

Baseline values on epidemiology and burden of illness to be reduced with the above effectiveness parameters were primarily derived from previous research and completed with additional novel analyses. For elderly populations, information was available from Postma et al.[14] on rates of influenza-related hospitalisation and deaths in this population. For HR adolescents and adults, similar data were available from the original publications from which the data on the elderly were drawn.[14,20,21] These population-based data were transformed into hospitalisation and death rates for patients with ILI (table II). This transformation involved three steps:

- specification of hospitalisation and death rates for the specified subgroups at the population level (for hospitalisation, separate estimates for influenza and influenza-related pneumonias were available[14,15,20,21]);
- correction with appropriate coverage of vaccination and estimated vaccine efficacy to derive

similar rates per unprotected population (coverage rates were 23% for HR adolescents and adults, 51% for HR elderly patients and 20% for LR elderly patients;[15] estimated vaccine effectiveness was 80% for non-elderly patients and 56% for elderly patients[22,23]);

- calculation of these rates per group of patients with ILI using the attack rates of ILI in unprotected populations as estimated for The Netherlands (9.5% for non-elderly patients and 7.7% for elderly patients[15]).

Life-years lost were based on the estimated death rates in table II and remaining life expectancies from national statistics. In particular, for the elderly, previous estimates were updated using an increase in life expectancy of 2% per year,[24] resulting in life-years lost per influenza-related death of a HR elderly patient at 5 years, and at 7.7 years for an LR elderly patient.[14,25] For adolescents and adults, remaining life expectancies (2003 levels) were directly estimated from age and sex distributions of 239 reported influenza-related deaths between 1996 and 2003.[25] This resulted in an average of 28.2 life-years lost per influenza-related death in this sub-group of HR adolescents and adult patients. Life-years lost were discounted at 4% according to the Dutch guideline[26] (and at 1.5% and 0% in the deterministic sensitivity analysis[26,27]).

The average length of hospitalisation was estimated to be 13 days for pneumonia and 7.4 days for other influenza-related hospitalisations (2002 levels).[28] The probability of an inpatient day being spent in the ICU was assumed to be 5%, based on an estimated 7% for pneumonia[29] and a lower assumed percentage for other influenza-related admissions (investigated in the sensitivity analysis).

No reliable data concerning work absenteeism due to influenza were available for The Netherlands.[30] We conservatively assumed that patients with influenza had an average of 1.5 days of absenteeism (range: 1–2).[31-34] Loss of efficiency was included for ill individuals going to work despite their illness. The average duration of illness due to influenza has been previously estimated to be 4–10 days.[32,35] We conservatively assumed 5 days of illness on average during working days (including absenteeism days; range: 4–6).[28] In the base case, we assumed an efficiency loss of 50% (range: 30–70%) during those days with illness but without absenteeism.[36]

Outpatient medication is used to alleviate symptoms of influenza, prevent complications and improve a patient's quality of life. Two groups of drugs were considered. Antibacterials may be prescribed to prevent/treat other (bacterial) infections. OTC medication, such as analgesics, may be taken to

Table IV. Outcomes for symptom relief only and oseltamivir, life-years gained (LYG) through oseltamivir treatment in the base case per 100 000 patients

Treatment group	Deaths (n)	Life-years lost	Hospitalisations (n)	Production loss (days)	LYG
High-risk adolescents and adults					
Symptom relief	51	886	1 284	325 000	
Oseltamivir	32	550	806	243 292	336
High-risk elderly patients					
Symptom relief	1 688	7 815	3 364	NA	
Oseltamivir	1 048	4 852	2 110	NA	2 963
Low-risk elderly patients					
Symptom relief	321	2 177	584	NA	
Oseltamivir	199	1 352	367	NA	825

NA = not applicable.

Table V. Costs (€ × 1000; year 2003 values) for symptom relief only and oseltamivir, net costs (negatives indicate savings) for oseltamivir treatment, and the incremental cost-effectiveness ratio (ICER), expressed as net costs per life-year gained (see for life-years gained), in the base case per 100 000 patients

Treatment group	Total	Outpatient costs[a]	Hospital costs	Costs of production loss	Net costs	ICER
High-risk adolescents and adults						
Symptom relief	54 668	2 583	6 247	45 838		
Oseltamivir	43 288	5 379	3 595	34 314	−11 380	Dominant
High-risk elderly patients						
Symptom relief	20 730	2 583	18 147	NA		
Oseltamivir	15 823	5 379	10 444	NA	−4 907	Dominant
Low-risk elderly patients						
Symptom relief	5 749	2 583	3 166	NA		
Oseltamivir	7 201	5 379	1 822	NA	1 452	1 759

a   Includes the costs of OTC medication and the initial GP visit (indicative figure of €23 used for the combination of both), antibacterial medication and (if applicable) oseltamivir (€28.70 per prescription).

NA = not applicable; **OTC** = over the counter.

alleviate severe headaches, other painful symptoms and fever. The percentage of patients receiving prescriptions for antibacterials from GPs has been estimated at 20% in the base case[16] (range: 10–30%). In our analysis, we assumed that oseltamivir did not affect the use of OTC drugs. Similarly, no positive effect of oseltamivir on potential subsequent GP visits was assumed. We present results for an assumed €23 for the initial GP visit and OTC medication. These costs are similar for cases of both symptom relief only and oseltamivir treatment, and therefore do not influence the outcomes of the incremental analysis.

Table III lists all assumptions on resource utilisation and costs.

Valuing the Savings of Oseltamivir Treatment

The savings of oseltamivir treatment are the monetary costs related to the burden of illness that was averted due to treatment. Monetary valuing was performed according to the costing guidelines for pharmacoeconomic research in The Netherlands,[26,37,38] specifying national average estimated cost prices rather than tariffs or prices reflecting local situations (table III). Price levels of 2003 were

applied and, again according to the guidelines, value added taxes were included.

For valuing reductions in production losses due to absenteeism and reduced efficiency, we used the approach developed within the framework of the Dutch guidelines for pharmacoeconomic research, labelled the friction costing approach.[26,37] One typical feature of the Dutch approach relates to the inclusion of an elasticity of production losses to work-time losses at 0.8 (i.e. 20% of absenteeism does not result in production loss). Thus, one day of averted production loss was valued at €224, taking the sex and age distribution of the workforce into account.[37] Furthermore, it was accounted for that 63% of the non-elderly HR population was part of the workforce (of those aged 13–64 years).[25] No indirect savings for the elderly were included.

Costs of Oseltamivir Treatment

The costs of a full course of oseltamivir treatment was estimated at €22.30, based on the recommended daily dose of 150mg for 5 days.[38] Additionally, the pharmacist's fee of €6.45 was added per prescription.[38] No extra costs for the GP visit were inserted in the base case, as it was assumed that the patients involved visited the GP anyway for their

illness. In the deterministic sensitivity analysis, we investigated what the effect would be if 50% of patients with ILI presenting in general practice actively sought an oseltamivir prescription, and would not have visited the GP otherwise (costs of a GP visit: €20.70[37]). Correspondingly, no indirect costs of production losses were assumed for getting the oseltamivir prescription in the baseline. In the deterministic sensitivity analysis, 1 hour of production loss was assumed for those 50% of patients actively seeking an oseltamivir prescription at €17.64 (= 224 × 0.63/8).

Additionally, the starting point assumption of our model – that 100% of patients would seek oseltamivir treatment within 48 hours of the start of the symptoms – was investigated in the sensitivity analysis. This conservatively assumed that beyond 48 hours no benefits of oseltamivir treatment could be expected.

Adverse events of oseltamivir comprise primarily nausea.[10,12] Intake of the drug with some food averts the nausea reaction,[39] and no costs for adverse events were inserted in the model.

Results

In the base case, for 100 000 patients with ILI, oseltamivir treatment was estimated to avert 19, 640 and 122 deaths for HR adolescents and adults, HR elderly patients and LR elderly patients, respectively (table IV lists all relevant outcomes). This corresponded to life-years gained for these respective groups of 336, 2963 and 825. Net costs for oseltamivir treatment for the respective groups were −€11 380 000, −€4 907 000 and €1 452 000, re-

spectively (table V). Obviously, negative net costs indicate net savings and indicate dominance for oseltamivir versus symptomatic treatment (dominance = net savings in combination with health gains). For LR elderly patients, the ICER was estimated at €1759 per life-year gained.

The probabilistic sensitivity analysis revealed probabilities for dominance of oseltamivir over symptomatic treatment at 88% for HR adolescents and adults and 76% for HR elderly patients. For LR elderly patients, a probability of 95% was estimated for the ICER to be below €9338 per life-year gained.

The deterministic sensitivity analysis revealed that excluding indirect costs switches the dominant position of oseltamivir treatment in HR adolescents and adults into slight costs per life-year gained, compared with symptomatic treatment (table VI). Results for the elderly are obviously not influenced. In the base case, the Dutch guideline for discounting both money and health at 4% was applied.[37] As mentioned, application of a lower discount rate is currently in discussion and often recommended.[40] Discounting of life-years at 1.5% reduced net costs per life-year gained down to €1626 for LR elderly patients, and at 0% further down to €1548. Assuming an extra GP visit for 50% of patients with ILI, and 1 hour of production loss for non-elderly patients, the ICER increased to €2975 per life-year gained for LR elderly patients, whereas dominance remains for both other groups. Finally, the assumption that all inpatient days were non-ICU had only minor effects on cost effectiveness.

Table VI. Incremental cost-effectiveness ratio in net costs (€; year 2003 values) per life-year gained of oseltamivir treatment for patients with influenza-like illness visiting a GP within 48 hours after the first symptoms, in the base case and deterministic sensitivity analysis

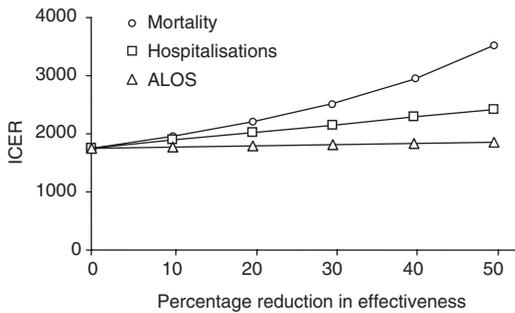| Patient group	Base case	Excluding indirect savings	Discount rate for life-years 1.5% (0%)	Extra GP visit for 50%	All inpatient days non-ICU
High-risk adolescents and adults	Dominant	429	Dominant	Dominant	Dominant
High-risk elderly patients	Dominant	Dominant	Dominant	Dominant	Dominant
Low-risk elderly patients	1759	1759	1626 (1548)	2975	2012

Fig. 2. Incremental cost-effectiveness ratio (ICER) in net costs per life-year gained (€, year 2003 values) for oseltamivir treatment in low-risk elderly patients as a result of varying effectiveness of oseltamivir on mortality, hospitalisation and average length of stay (ALOS), expressed as percentage reductions from base-case effectiveness estimates (38% for mortality, 37% for admissions and 8% for ALOS). For high-risk groups, dominance persists over the whole range of percentage reductions investigated.

A further deterministic sensitivity analysis was directed at percentage changes in effectiveness of oseltamivir in reducing mortality (38% in base case), hospitalisation (37% in base case) and ALOS (8% in base case). For example, a 50% reduction (to 19%) in the effectiveness of oseltamivir on mortality resulted in an increase in the ICER to €3518 per life-year gained for LR elderly patients. With maximum reductions in effectiveness investigated in this univariate analysis at 50%, all alternatives for LR elderly patients remained below €4000 (figure 2; with reductions in mortality being the most influential), whereas dominance of oseltamivir over symptomatic treatment persisted for both the HR adolescents and adults and the HR elderly patients (not shown).

Figure 3 shows a sensitivity analysis of our starting assumption that 100% of patients presenting at the GP would be within 48 hours of symptom onset for LR elderly patients. Cost effectiveness seems to remain within acceptable limits. For HR groups, the dominance of oseltamivir over symptom relief only remains in all options investigated, except for HR elderly patients at 75% being beyond 48 hours late (€1255 per life-year gained).

Discussion

Compared with symptom relief only, oseltamivir treatment appears cost saving for HR elderly patients and HR adolescents and adults (if, for the latter, averted production losses are included in the analysis) who present with ILI symptoms to a GP in The Netherlands. Probabilistic and deterministic sensitivity analyses show the robustness of the potential for cost savings in these groups. For LR elderly patients, the ICER ranges in deterministic sensitivity analysis from €1548 to €4043 per life-year gained, with an estimated 95% probability to be below €9338 per life-year gained in the probabilistic analysis.

The analysis is based on an extensive meta-analysis of studies on oseltamivir treatment, published resource use data, national statistics, expert opinions and Dutch cost prices and probability distributions for core parameters. From the meta-analysis, estimates for RRs of oseltamivir compared with placebo were taken, inclusive of their uncertainty.[5,41] In the probabilistic analysis, the full uncertainty in the effectiveness parameters was taken into account, inclusive of potential risk increases instead of reductions. In doing so, probabilistic analysis enables estimation of cost effectiveness in situations where showing statistical significance for infrequently oc-
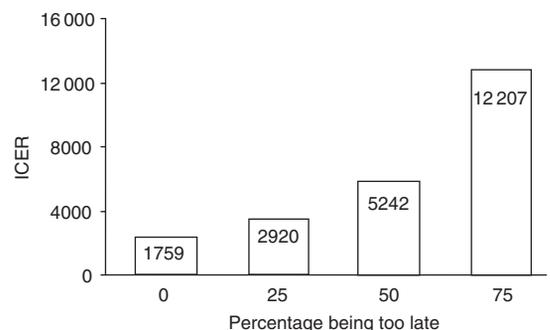

Fig. 3. Incremental cost-effectiveness ratio (ICER) [€, year 2003 values] for varying percentage of patients being prescribed oseltamivir too late; i.e. beyond 48 hours after symptom onset (0% in the base case); note that for prescriptions that are too late, no effectiveness was assumed.

curring complications (hospitalisation, death) is not achieved.

Several parameters, although not included in the probabilistic analysis, do merit discussion. Our model has been developed during the last decade and has been used to underpin decisions to extend influenza vaccination from elderly patients with chronic disease alone to all elderly patients in preparedness for pandemic influenza.[14,15] In particular, with respect to the latter, previous economic analyses justified storage of oseltamivir as preparedness for the pandemic.[15,42] Recent cohort and case-control analyses have even indicated higher influenza-related death rates than those used in our model[43,44] and higher hospitalisation rates.[44] Inclusion of such results would further improve the pharmacoeconomic profile of oseltamivir in the groups investigated here. Therefore, the results of our analysis could be considered as conservative estimates. Furthermore, our model compared oseltamivir treatment with symptomatic treatment using primarily analgesics. We assumed that the use of oseltamivir would not influence the use of this class of drugs, despite the fact that oseltamivir results in a more rapid return to normal activity. Obviously, this is another assumption that results in a conservative estimate of the cost effectiveness of oseltamivir treatment compared with symptomatic treatment. Similarly, no reduction in follow-up GP visits was conservatively assumed for oseltamivir treatment. Finally, we note that already some analyses are available for oseltamivir treatment of influenza inclusive of the indirect effects on slowing down the spread of the virus in the population, beyond having the benefits in the index case only.[45] Again, this argument would also render our analysis a rather conservative one.

The meta-analysis on effectiveness[5] was limited to people aged ≥13 years, which provided the main rationale for limiting our analysis to this age group. However, some information is available on the treatment of children aged from 1 to 12 years from a randomised, double-blind, placebo-controlled study in such children with fever and cough or coryza (n = 695; it turned out that 65% had influenza). Oseltamivir treatment significantly reduced antibacterial prescriptions and otitis media episodes.[46] Recently, this finding has also been extended with a pharmacoeconomic evaluation.[47]

Previous pharmacoeconomic evaluations in groups of increased risk investigated oseltamivir treatment compared with symptom relief in Canada, Japan, the UK and US.[48-51] One study lacks (i) extensive reporting of methods allowing full appreciation of their approach and (ii) first-face validity as better cost effectiveness for healthy adults than for risk groups was estimated.[48] Our results are in line with the other three economic evaluations.[49-51] All these studies found close to cost-saving results, with costs per QALY at only a few hundred $US or £ or a maximum of $US3000. Marginally less favourable results than from our study – indicating cost-saving potentials in many options – can be explained primarily from relatively higher oseltamivir costs up to almost $US60 and lower hospitalisation costs down to just over $US1000, compared with our price at €22.30 (an exclusive pharmacist's fee) and approximately €5000, respectively. As our costing reflects the Dutch guideline procedure for pharmacoeconomic analyses, no variation in these costings should be applied.[26,37] Also NICE concluded that "the evidence indicated that, when influenza, is circulating, it would be both clinically effective and *cost effective* for at-risk people with ILI to be treated with … oseltamivir if they can begin their course of medication within 48 hours of the appearance of symptoms."[6]

Study Limitations

The major limitation of this study is the absence of evidence on the effect of oseltamivir on influenza-related deaths. In this study we assumed that the

risk reduction for pneumonia (reported in Kaiser et al.[5]) was the same as that for the number of influenza-related deaths. Further research is warranted on this effect; however, as the number of influenza-related deaths is relatively small, it may require studies with huge numbers of participants to evidence such an effect on mortality.

Conclusions

The Dutch threshold for cost effectiveness has been suggested at €20 000 per life-year gained.[52] Therefore, we conclude that, in the Dutch situation, treatment with oseltamivir of people at increased risk may well be cost effective compared with symptom relief only: either cost savings are suggested or cost effectiveness is estimated well below the threshold. The relevance of our findings is enhanced by recent developments in The Netherlands. In particular, as of 1 January 2005, new drugs claiming added value have to show a favourable cost effectiveness to be eligible for reimbursement.[53]

Acknowledgements

References

1. Postma MJ, Baltussen R, Heijnen M-LA, et al. Pharmacoeconomics of influenza vaccination in the elderly: reviewing the available evidence. Drugs Aging 2000; 17 Suppl. 3: 217-27
2. Postma MJ, Baltussen R, Wilschut JC. A synthesis of further evidence for favourable cost-effectiveness of elderly influenza vaccination. Expert Rev Pharmacoeconomics Outcomes Res 2006; 6: 215-27
3. Nichol KL, Goodman M. The health and economic benefits of influenza vaccination for healthy and at-risk persons aged 65 to 74 years. Pharmacoeconomics 1999; 16 Suppl. 1: 63-71
4. Wood SC, Nguyen VH, Schmidt C. Economic evaluations of influenza vaccination in the elderly: impact on public health policy. Dis Manage Health Outcomes 2000; 8: 273-85
5. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003; 163: 1667-72
6. Stichting Farmaceutische Kengetallen [online]. Available from URL: http://www.sfk.nl [Accessed 2005 Nov 12]
7. National Institute for Clinical Excellence (NICE). Guidance on the use of zanamivir, oseltamivir and amantadine for treatment of influenza: technology appraisal guidance no. 58. London: NICE, 2003
8. MIST Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet 1998; 352: 1877-81
9. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. J Infect Dis 1999; 180: 254-61
10. Nicholson KG, Aoki FY, Osterhaus ADME, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Lancet 2000; 355: 1845-50
11. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999; 341: 1336-43
12. Treanor JT, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza; a randomized controlled trial. JAMA 2000; 283: 1016-24
13. Rutten F. Health technology assessment and policy from the economic perspective. Int J Technol Assessment Health Care 2004; 20: 67-70
14. Postma MJ, Bos JM, van Gennep M, et al. Economic evaluation of influenza vaccination: assessment for The Netherlands. Pharmacoeconomics 1999; 16 Suppl. 1: 33-40
15. Van Genugten MLL, Heijnen M-LA, Jager JC. Pandemic influenza and healthcare demand in The Netherlands: scenario analysis. Emerg Infect Dis 2003; 9: 531-8
16. National Institute of Public Health and the Environment. Meeting of Dutch experts on influenza. 2001 Jul 2; Bilthoven
17. Hennekens CH, Buring JE. Epidemiology in medicine. Philadelphia (PA): Lippincott, Williams & Wilkins, 1987
18. Doubilet P, Begg CB, Weinstein MC, et al. Probabilistic sensitivity analysis using Monte Carlo simulation. Med Decis Making 1985; 5: 157-77
19. Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine: part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. Eur J Epidemiol 2004; 19: 365-75
20. Baltussen RMPM, Reinders A, Sprenger MJW, et al. Estimating influenza-related hospitalisation in The Netherlands. Epidemiol Infect 1998; 121: 129-38
21. Sprenger MJW, Mulder PGH, Beyer WEP, et al. Impact of influenza on mortality in relation to age and underlying diseases, 1967–1989. Int J Epidemiol 1993; 22: 333-9
22. Cox NJ, Subbarao K. Influenza. Lancet 1999; 354: 1277-82
23. Couch RB. Prevention and treatment of influenza. NEJM 2000; 343: 1778-87
24. Central Bureau of Statistics of The Netherlands [online]. Available at URL: http://www.cbs.nl [Accessed 2005 Nov 12]

25. Centraal Bureau voor de Statistiek [online]. Available from URL: http://statline.cbs.nl/StatWeb [Accessed 2005 Nov 12]

26. College voor Zorgverzekeringen (CvZ). Guidelines for pharmaco-economic research. Amstelveen: CvZ, 1999

27. Klok RM, Brouwer WBF, Annemans LJP, et al. Towards a healthier discount procedure. Expert Rev Pharmacoeconomics Outcomes Res 2005; 5: 59-63

28. Prismant for Health Care, Utrecht [online]. Available at URL: http://www.prismant.nl [Accessed 2005 Nov 12]

29. Postma MJ, Heijnen M-LA, Jager JC. Cost-effectiveness analysis of pneumococcal vaccination for elderly individuals in The Netherlands. Pharmacoeconomics 2001; 19 (2): 215-22

30. Postma MJ, Jansema P, Scheijbeler HWKFH, et al. Scenarios on costs and savings of influenza treatment and prevention for Dutch healthy working adults. Vaccine 2005; 23: 5365-71

31. Nichol KL. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. Arch Intern Med 2001; 161: 749-59

32. Demichelli V, Jefferson T, Rivetti D, et al. Prevention and early treatment of influenza in healthy adults. Vaccine 2000; 18: 957-1030

33. Akazawa M, Sindelar JL, Paltiel D. Economic costs of influenza-related work absenteeism. Value Health 2003; 6: 107-15

34. Campbell DS, Rumley MH. Cost-effectiveness of the influenza vaccine in a healthy working-age population. J Occup Environ Med 1997; 39: 408-14

35. Szucs T. The socio-economic burden of influenza. J Antimicrob Chemother 1999; 44: 11-5

36. Keech M, Scott AJ, Ryan PJJ. The impact of influenza and influenza-like-illness on productivity and healthcare resource utilisation in a working population. Occup Med 1998; 48: 85-90

37. College voor Zorgverzekeraars (CvZ). Guideline prices for pharmaco-economic research. Diemen: CvZ, 2004

38. College voor Zorgverzekeringen (CvZ). Farmacotherapeutisch kompas 2002. Amstelveen: CvZ, 2002

39. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza. JAMA 1999; 282: 1240-6

40. Brouwer WBF, Niessen LW, Postma MJ, et al. Need for differential discounting of costs and health effects in cost effectiveness analyses. BMJ 2005; 331: 446-8

41. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. Value Health 2005; 8: 1-2

42. Postma MJ. Re: Tamiflu: NNT to prevent a pandemic flu death may be a million. BMJ 2005 Dec 7 [online]. Available from URL: http://www.bmj.com/cgi/eletters/331/7526/1203-b#123 247 [Accessed 2007 Apr 27]

43. Voordouw BC, van der Linden PD, Simonian S, et al. Influenza vaccination in community-dwelling elderly: impact on mortality and influenza-associated morbidity. Arch Intern Med 2003; 163: 1089-94

44. Hak E, Buskens E, van Essen GA, et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. Arch Intern Med 2005; 165: 274-80

45. Longini IM Jr, Halloran ME, Nizam A, et al. Containing pandemic influenza with antiviral agents. Am J Epidemiol 2004; 159: 623-33

46. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001; 20: 127-33

47. Reisinger K, Greene G, Aultman R, et al. Effect of influenza treatment with oseltamivir on health outcome and costs in otherwise healthy children. Clin Drug Invest 2004; 24: 395-407

48. Husereau DR, Brady B, McGeer A. An assessment of oseltamivir for the treatment of suspected influenza. Ottawa (ON): Canadian Coordinating Office for Health Technology Assessment, 2001

49. Inoue T, Watanabe K, Chonabayashi N, et al. Pharmacoeconomics of antiviral therapy for influenza in a Japanese hospital setting. Clin Drug Invest 2005; 25: 49-63

50. Sander B, Gyldmark M, Aultman R, et al. Impact on health outcome and costs of influenza treatment with oseltamivir in elderly and high-risk patients. J Med Econ 2004; 7: 67-83

51. Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. Ann Intern Med 2003; 139: 321-9

52. Bos JM, Postma MJ. Using pharmacoeconomics for policy making: is rational decision making enhanced by applying thresholds for cost-effectiveness? Expert Rev Pharmacoeconomics Outcomes Res 2004; 4: 247-50

53. Tolley K, Postma MJ. Pharmacoeconomics and market access in Europe: case studies in Scotland and The Netherlands. ISPOR Connections 2006 Oct 15; 12: 3-6

Correspondence: Professor *Maarten J. Postma*, GRIP, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.
E-mail: m.j.postma@rug.nl