



## Reviews of Economic Evaluations relating to Influenza

### **Economic evaluation of influenza pandemic mitigation strategies in the United States using a stochastic microsimulation transmission model**

Sander B, Nizam A, Garrison Jr L P, Postma M J, Halloran E, Longini Jr I M; *Value in Health* 2009; 12(2):226-233

**Study Question:** A discrete-time stochastic micro-simulation model was constructed to compare the economic impact of no intervention with 16 single and combination strategies from the societal perspective. Single prophylactic strategies included pre-vaccination, antiviral post-exposure prophylaxis (in combination with treatment of the index case), and school closure. The main outcome measures were quality-adjusted life years (QALYs) gained, cases and deaths. Effects were discounted at an annual rate of 3%. Sensitivity analysis was performed to test the robustness of the cost-effectiveness ratios. A number of key variables were tested including mortality, school closure, and probability of a pandemic.

**Patient Group:** People who may be at risk of becoming infected with influenza were considered for the present analysis. The age groups are children 0-4 years old, children 5-18 years old, younger adults (19-64 years old), and older adults ( $\geq 65$  years). Younger adults are further stratified into high and low risk. High-risk adults have underlying chronic conditions (e.g. cardiovascular, respiratory, or metabolic disease), which increase their risk for bronchitis, pneumonia, hospitalizations, and mortality.

**Key Results:** Study findings showed that all interventions reduce the illness attack rate, morbidity, and mortality. Many interventions are also cost saving compared with no interventions. The authors found that stockpiling targeted antiviral prophylaxis (TAP) is cost saving in the event of a pandemic, and will avoid loss of life. Full targeted antiviral prophylaxis (FTAP) is the most effective single strategy, reducing the attack rate by 54%. If a low-efficacy vaccine is available and administered before the onset of the pandemic. Adding school closure provides the greatest benefit and is likely to be an attractive strategy if transmission and mortality rates are high. Pre-vaccinating 70% of the population is expected to reduce the number of cases by 48% and is the second least costly strategy. The incremental cost-utility ratio for FTAP plus school closure, and vaccination plus school closure compared to FTAP, assuming a higher case fatality rate of 5%, reduces from US\$48,500 per QALY to US\$18,500 per QALY gained, making these strategies more attractive at higher mortality rates. The higher the attack rate, the more worthwhile are interventions providing broad coverage, such as school closure, FTAP and pre-vaccination.

### **Cost-effectiveness and value of information analyses of neuraminidase inhibitors for the treatment of influenza**

Wailoo A J, Sutton A J, Cooper N J, Turner D A, Abrams K R, Brennan A, Nicholson J G.; *Value in Health* 2008; 11(2):160-171

**Study Question:** Using a decision model, the aim of the study was to assess the cost-effectiveness of alternative strategies for the treatment of suspected influenza in otherwise healthy adults and to identify future research priorities using value of information analysis. The interventions examined were amantadine, zanamivir, and oseltamivir and the comparator was no treatment. Probabilistic



sensitivity analysis using Monte Carlo simulation was conducted, with expected value of perfect information for the entire model and for individual parameters being calculated. The setting was community in the UK, and the perspective adopted in the economic analysis was that of the UK National Health Service (NHS).

**Patient Group:** The study group used in the model comprised individuals in the community with suspected influenza. The analysis was restricted to males and females aged between 12 and 65 years.

**Key Results:** The baseline results showed that, based on mean costs (UK pounds) and effects, zanamivir is dominated by oseltamivir (less costly and more effective). The incremental cost-effectiveness ratio for amantadine (compared with no treatment) was £11,000 and £44,000 per quality-adjusted life year (QALY) for oseltamivir (compared with amantadine). The results of the probabilistic sensitivity analysis indicated that the probability that amantadine is cost-effective at a willingness to pay of £30,000 per QALY is 0.74, falling to 0.49 at £20,000 per QALY. Global expected value of perfect information (EVPI) is £2 million over 15 years if a willingness to pay threshold of £30,000 per QALY is assumed rising to £9.6 million at £45,000 per QALY. EVPI for only one parameter exceeds £500,000 at £30,000 per QALY: the quality of life for untreated influenza. The authors conclude that at traditionally accepted values of willingness to pay for health benefits, it is unlikely that additional research would be an efficient use of scarce resources. The only exception to this, they argue, would be to examine the health-related quality of life impact of influenza in an untreated patient group. If a higher threshold value were acceptable, there is a small group of parameters that may warrant further investigation. These would, however, require comparative and potentially expensive research studies.

### **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**

Postma M J, Novak A, Scheijbeler H W, Gyldmark M, van Genugten M L, Wilschut J C; *Pharmacoeconomics* 2007; 25(6):497-509

**Study Question:** To estimate the cost effectiveness of oseltamivir treatment (versus symptom and pain relief using over the counter analgesic drugs) for patients with influenza-like illness (ILI) who are at increased risk for serious complications of influenza. Three patient subgroups are assessed (elderly patients [aged  $\geq$  65 years] without chronic disease, elderly patients with chronic disease and chronically ill, non-elderly patients). Decision analytical modelling is employed, with the analysis being conducted from both the health care system and societal perspectives.

**Patient Group:** A hypothetical cohort of 100,000 patients with influenza-like illness (ILI) visiting a general practitioner (GP) within 48 hours after the symptoms emerged.

**Key Results:** General practitioner (GP) visits for oseltamivir treatment were cost saving for chronically ill patients with influenza-like illness (ILI). The incremental cost per life year gained for non-chronically ill elderly patients was estimated at Euros 1759. Cost savings and favourable cost effectiveness were robust to both deterministic and stochastic sensitivity analyses. In conclusions, the authors suggest that in the Dutch situation, treatment with oseltamivir of people at increased risk may well be cost effective compared with symptom relief only.



## Post-exposure influenza prophylaxis with oseltamivir: cost effectiveness and cost utility in families in the UK

Sander B, Hayden F G, Gyldmark M, Garrison L P Jnr; *PharmacoEconomics* 2006; 24(4):373-386

**Study Question:** The neuraminidase inhibitor oseltamivir effectively prevents influenza A and B virus infection and has been shown to also be effective when used for post-exposure prophylaxis (PEP). However, considerable uncertainty exists surrounding current estimates of cost-effectiveness ratios for oseltamivir. Thus, the aim of this study was to assess the cost effectiveness and cost utility of preventing post-exposure influenza infection using oseltamivir from a healthcare payer's perspective in the UK. In order to do this, a simulation model was developed to predict morbidity and mortality due to influenza and to compare oseltamivir PEP with no prophylaxis within families with members aged  $\geq 13$  years. Two scenarios were tested: 1) comparison of patients receiving PEP versus patients not receiving PEP and not being treated with oseltamivir should they become infected; and 2) comparison of patients receiving PEP versus patients not receiving PEP but being treated with oseltamivir should they become infected.

**Patient Group:** Families with members  $\geq 13$  years. Two scenarios were tested: 1) comparison of patients receiving post-exposure prophylaxis (PEP) versus patients not receiving PEP and not being treated with oseltamivir should they become infected; and 2) comparison of patients receiving PEP versus patients not receiving PEP but being treated with oseltamivir should they become infected.

**Key Results:** Post-exposure prophylaxis (PEP) with oseltamivir results in reduced morbidity (e.g. fewer influenza cases) and associated reductions in complications, hospitalisations and mortality due to influenza. When comparing oseltamivir PEP with no prophylaxis for contact attack rates of 8%, 12% and 30%, the mean costs per quality adjusted life year (QALY) gained for scenario one were estimated at £29,938, £18,697 and £5,403, respectively; the mean costs per case avoided were £467, £293 and £84, respectively. The corresponding results for scenario two were £52,202, £31,610 and £9,688 per QALY gained. Sensitivity analyses illustrate the large economic impact of the mechanism by which contacts access the drug. Based on these findings, the authors conclude that PEP with oseltamivir is likely to be a cost-effective strategy for family contacts in the UK from a healthcare payer perspective when influenza-like illness contact attack rates are 8% or higher and the only treatment given is usual care.

## A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population

Lin J-T, Yu X-Z, Cui D-J, Chen X-Y, Zhu J-H, Wang Y-Z, Wu X-D; *Current Medical Research and Opinion* 2006; 22(1):75-82

**Study Question:** In high-risk patients, influenza is associated with increased risk of complications and death. Oseltamivir has been shown to be effective against influenza virus types A and B in adults and children. However, reports on the effects of oseltamivir in high-risk patients are lacking. Thus, the aim of this multicentre (carried out at nine university tertiary teaching hospitals), randomised, controlled trial was to evaluate the efficacy and safety of oseltamivir treatment in a population at high risk for influenza. Patients were randomised using the block randomisation method whereby numbers were allocated by the admitting physician according to the sequence of enrolment. Analysis was carried out on an intention-to-treat basis.

**Patient Group:** 118 Chinese patients with chronic respiratory diseases (chronic bronchitis, obstructive emphysema, bronchial asthma or bronchiectasis) or chronic cardiac disease were recruited to the study. Laboratory tests showed 56 patients to be influenza-infected (fever  $\geq 37.8$



degrees C and at least two of seven symptoms) and they were randomly assigned to receive oral oseltamivir 75mg twice daily for five days (oseltamivir group; n=27), or symptomatic treatment (control group; n=29) within 48 hours after symptom onset. There were no significant differences between the two groups in terms of baseline characteristics. Patients were excluded if they had a high suspicion of bacterial infection (based on signs, symptoms, leukocyte count  $>10.0 \times 10^9/L$  or neutrophil granulocyte level  $\geq 0.8\%$ ). Pregnant or nursing women were also excluded, as were patients with a history of alcohol or drug abuse and those who had been vaccinated for influenza within 12 months prior to the start of the study.

**Key Results:** The aim of this multicentre (carried out at nine university tertiary teaching hospitals), randomised, controlled trial was to evaluate the efficacy and safety of oseltamivir treatment in a population at high risk for influenza. Patients were randomised using the block randomisation method whereby numbers were allocated by the admitting physician according to the sequence of enrolment. Analysis was carried out on an intention-to-treat basis. Relative to symptomatic treatment, oseltamivir significantly reduced the duration of influenza symptoms by 36.8% (174 hours versus 110 hours;  $p=0.0479$ ), and the severity by 43.1% ( $p=0.0002$ ). In addition, oseltamivir significantly reduced the duration of fever by 45.2% (104 hrs versus 57 hours;  $p=0.0051$ ), and the time to return to baseline health status by five days ( $p=0.0011$ ). The incidence of complications (11% versus 45%;  $p=0.0053$ ) and antibiotic use (37% versus 69%;  $p=0.0167$ ) were also significantly lower in the oseltamivir group compared with the control group. The cost of treating influenza and its complications was lower in the oseltamivir group, but this difference did not reach statistical significance (US\$70.98 +/- US\$55.99 in the oseltamivir group versus US\$95.16 +/- US\$92.01 in the control group;  $p=0.2462$ ). Based on these findings, the authors conclude that oseltamivir is effective and well tolerated in high-risk patients with chronic respiratory or cardiac diseases. It can reduce the duration and severity of influenza symptoms and decrease the incidence of secondary complications and antibiotic use, without increasing the total medical cost. The currency exchanges rate during the period November 2002 to February 2003 was US\$1 = 8.27 China Yuan Renminbi (CNY).

## **Economics of neuraminidase inhibitor stockpiling for pandemic influenza, Singapore**

Lee V J, Phua K H, Chen M I, Chow A, Ma S, Goh K T, Leo Y S; *Emerging Infectious Diseases* 2006; 12(1):95-10

**Study Question:** A decision analysis model was developed to compare strategies for stockpiling neuraminidase inhibitors to treat and prevent influenza in Singapore. Three strategies were compared: supportive management (no action), early treatment of clinical influenza with oseltamivir (treatment only), and prophylaxis in addition to early treatment (prophylaxis). Oseltamivir was selected because of its safety profile and available data on influenza prophylaxis and treatment. Direct and indirect costs were considered as well as costs of death.

**Patient Group:** Individuals with influenza in Singapore were considered for the present analysis.

**Key Results:** Study findings show that the best overall economic benefit is on the treatment-only strategy. If no action were taken during a pandemic, the mean number of simulated deaths in Singapore would be 1,105, with mean hospital days of 23,098. The optimal treatment stockpile is 40% to 60%; 40% maximises economic benefits while 60% maximises treatment benefits. The mean economic cost would exceed \$1.43 billion Singapore dollars and 78% of all deaths would occur in groups at high risk. Increasing the duration of prophylaxis increased lives saved. Lives saved from



prophylaxis compared to treatment increased significantly only after prophylaxis of more than 4 weeks and increased steadily until 20 weeks; costs per life saved also improved.

### **Antiviral agents for influenza: a comparison of cost-effectiveness data**

Lynd L D, Goeree R, O'Brien B J; *PharmacoEconomics 2005; 23(11):1083-1106*

**Study Question:** The majority of the economic burden of influenza-related illness is attributable to indirect costs as a result of lost productivity. There are currently four antiviral drugs available for the treatment of influenza: two ion channel blockers, amantadine and rimantadine; and two neuraminidase inhibitors, zanamivir and oseltamivir. The aim of this paper was to review the studies evaluating the cost-effectiveness of currently available antiviral treatment and prophylaxis management strategies for influenza. Published studies that reported both costs and effectiveness of influenza management were extracted using MEDLINE, pre-MEDLINE and EMBASE. Fifteen studies met the inclusion criteria, with 14 based on decision-analytic modelling and one economic analysis performed alongside a clinical trial. Analyses were undertaken from both the societal and payer perspectives.

**Patient Group:** Patients taking antiviral agents for influenza, both as treatment and as a prophylactic management strategy. The study population taken from the studies include healthy adults, adults at risk of influenza-related adverse outcomes, institutionalised and non-institutionalised elderly and children

**Key Results:** The only dominant strategy relative to standard care was vaccination of the institutionalised elderly. All other strategies in all populations were both more costly and more effective than standard care. Depending on the population and the perspective, the incremental cost-effectiveness ratios (ICERs) for antiviral treatment strategies ranged from \$US5, 000 per quality adjusted life year (QALY) for amantadine in test-and-treat studies to >\$US400, 000 per QALY for zanamivir or oseltamivir treatment in children. Sensitivity analyses in all studies consistently reported a strong influence of the population prevalence or diagnostic accuracy of influenza on the cost-effectiveness of all strategies. Based on these findings, the authors conclude that given the variation in the ICERs of antiviral treatment and prophylaxis, the uncertainty around many model parameters, and the dynamic nature of influenza from year to year, antiviral treatment or prophylaxis for influenza is likely to be more cost effective in specific populations at specific times during the influenza season, and during influenza seasons when the population prevalence reaches epidemic levels or there is mismatch between the vaccine and the circulating virus.

### **Influenza treatment with neuraminidase inhibitors: cost-effectiveness and cost-utility in healthy adults in the United Kingdom**

Sander B, Gyldmark M, Hayden F G, Morris J, Mueller E, Bergemann R; *European Journal of Health Economics 2005; 6(3):244-252*

**Study Question:** To assess the cost-effectiveness and cost-utility of treating influenza with neuraminidase inhibitors (oseltamivir and zanamivir) from a health care payer's and societal perspective in the United Kingdom. This was done through a decision-analysis model incorporating first- and second-order Monte Carlo simulation

**Patient Group:** Healthy adult population aged 13 to 64 years.

**Key Results:** The authors' assessed the cost-effectiveness and cost-utility of treating influenza with neuraminidase inhibitors (oseltamivir and zanamivir) from a health care payer's and societal perspective in the United Kingdom. From the healthcare payer perspective oseltamivir is associated



with greater overall benefits than zanamivir and usual care, greater mean expected cost per patient than usual care, and lower mean expected cost per patient than zanamivir. Cost differences between zanamivir and are due mainly to the higher price of zanamivir but also to a higher rate of pneumonia (zanamivir). Treatment with either neuraminidase inhibitor results in reduced morbidity and faster return to normal activities. However, oseltamivir dominates zanamivir in cost-utility analysis due to its lower costs. Comparing oseltamivir with usual care, the costs are £14.36 (minimum £10.69 and maximum £17.67) per day of normal activity gained and £5,600 (minimum £1,403, maximum: usual care dominant) per quality-adjusted life-year gained from the healthcare payer perspective. Oseltamivir dominates usual care from the societal perspective. Under sensitivity analysis for the National Health Service (NHS) perspective the analyses show that the results are very sensitive to the level of diagnostic certainty assumed. As the level of diagnostic certainty is reduced the incremental cost-effectiveness for oseltamivir increase. Oseltamivir remains cost-effective from the healthcare payers perspective at a threshold of 30,000 per quality adjusted life year (QALY) gained and dominant from the societal perspective even assuming 34% diagnostic certainty. In multiway sensitivity analysis omitting all effects related to hospitalizations, complications and mortality and assuming a low diagnostic certainty rate of 34% oseltamivir is still cost-effective from the NHS point of view and dominates usual care from the societal point of view. Discounting has only a small impact on the results, as does the lower work loss assumed in sensitivity analysis. The authors conclude that treatment with oseltamivir is a cost-effective strategy for otherwise healthy adults in the UK from both the healthcare payer and societal perspective.

### **Economic evaluation of oseltamivir phosphate for postexposure prophylaxis of influenza in long-term care facilities**

Risebrough N A, Bowles S K, Simor A E, McGeer A, Oh P I; *Journal of the American Geriatric Society* 2005; 53(3):444-451

**Study Question:** A decision analysis model was constructed to compare the cost-effectiveness of oseltamivir used for postexposure prophylaxis in long-term care facilities with that of amantadine postexposure prophylaxis and no prophylaxis, from a single government-payer perspective. The model was developed with a 30-day time frame. The analysis began at the start of an influenza season to permit the inclusion of amantadine dose calculation costs accrued at the beginning of each influenza season. The following comparators were considered: no prophylaxis, amantadine postexposure prophylaxis, and oseltamivir postexposure prophylaxis. The primary outcome measure was the occurrence of influenza-like illness, defined as fever plus at least one of the following symptoms: cough, rhinorrhea, nasal congestion, and sore throat.

**Patient Group:** A hypothetical cohort of elderly persons living in a Canadian long-term care facility who received influenza vaccination was considered for the present analysis.

**Key Results:** Study findings showed that prophylaxis strategies were less expensive and provided better outcomes than no prophylaxis. Compared with no prophylaxis, implementing a postexposure prophylaxis strategy would save between Can\$2,109 and Can\$3,357 per 100 patients in medical care costs and prevent between 2.8 and 4.2 influenza-like illness cases per 100 patients over a 30-year period. Oseltamivir postexposure prophylaxis was less expensive than amantadine postexposure prophylaxis (saved Can\$1,248 per 100 patients), with marginally better clinical outcomes. The cost saving was due to reduced costs associated with influenza-like illness complications. Sensitivity analysis of the efficacy of the prophylaxis strategies varied from approximately 60% to 90% relative risk reduction compared with placebo based on ranges from clinical trials and observational studies.



Overall sensitivity analysis results supported the robustness of these conclusions and the adoption of postexposure prophylaxis strategies.

## Impact on health outcome and costs of influenza treatment

Sander B, Gyldmark M, Aultman R, Aoki F Y; *Journal of Medical Economics* 2004; 7:67-83

**Study Question:** The study evaluates health outcomes and costs to the health care payer of treating influenza with oseltamivir compared with usual care in a high-risk population in the UK. The authors used a decision analytic model based on published data from 6 randomised double blind studies conducted in high risk populations.

**Patient Group:** Adults aged 13 to 64 years with co-morbidities, or adults aged 65 years or over.

**Key Results:** The main objective of this study was to evaluate health outcomes and costs to the healthcare payer of treating influenza with oseltamivir in a high-risk population. Oseltamivir is cost-effective in both the cost-effectiveness simulation and cost-utility simulation. The mean cost per day gained to return to normal activity is £3, and per quality adjusted life year (QALY) gained is £225. Sensitivity analysis (both uni and multivariate) showed that lowering diagnostic accuracy or prescribing oseltamivir too late in 10% of the patients affected the conclusion. Treatment with oseltamivir compared to usual care in high-risk patients was cost-effective. Under more conservative scenarios it remained cost-effective, with a cost-utility ratio of £17,873 per QALY. The results of the sensitivity analysis indicate that the result is robust. Compared to previous studies the ratio is more favourable, but this is explained by the use of QALYs rather than other quality of life (QoL) measures. The authors conclude that treatment with oseltamivir has favourable cost-effectiveness ratios even under conservative assumptions.

## Antiviral therapy for influenza: a clinical and economic comparative review

Schmidt A C; *Drugs* 2004; 64(18): 2031-2046

**Study Question:** This study reviews the literature concerning antiviral therapy for influenza, reviewing the clinical evidence for efficacy, and briefly summarising information on the economics of such actions. A PubMed search is undertaken using generic drug names and the term influenza, and additional information is used from drug companies.

**Patient Group:** No patient group given

**Key Results:** Each year influenza epidemics cause a considerable burden of disease. Vaccination against influenza A and B viruses has been and remains the cornerstone of influenza prevention, but antiviral therapy can serve as an important adjunct to vaccination in controlling the impact of the disease. This study, a literature review, concerns the efficacy and economics of antiviral therapy for influenza. The author states two classes of drugs as being licensed in a number of countries. The M2 ion channel blockers/amantadanes (amantadine and rimantadine)- inhibitors of influenza A virus replication, and neuraminidase inhibitors (zanamivir and oseltamivir), active against influenza A and B. These drugs shorten the course of influenza by one day and relieve symptoms. There is said to be uncertainty if therapy reduces complications and hospitalisation. Economic evidence is not consistent, due to differences in methodology and no consensus on probabilities concerning risks and outcomes. England and Germany recommend neuraminidase inhibitors for high-risk individuals, for example those over 65 years or under two years and those with chronic cardiovascular, pulmonary or renal disease, diabetes mellitus or immunosuppression. There is no agreement on recommendations for healthy patients and the availability of safe and effective antiviral therapy options should be kept in mind by the practising clinician. More specific recommendations and



policy formulation will depend on additional efficacy data that include frequency of complications and hospitalisation as outcome measures.

## **Effect of influenza treatment with oseltamivir on health outcome and costs in otherwise healthy children**

Reisinger K, Greene G, Aultman R, Sander B, Gyldmark M; *Clinical Drug Investigation 2004; 24(7):395-407*

**Study Question:** An economic model was developed to evaluate the effect of influenza treatment on health outcome and costs in otherwise healthy children. Oseltamivir treatment was evaluated. First and second order Monte Carlo simulation was performed to correct for the uncertainty surrounding input variables (e.g., time to return to normal activity, hospitalization rates, complications and mortality). Direct costs were considered for the present analysis. The main outcome measure was quality-adjusted life years (QALYs). Sensitivity analysis was performed to test the robustness of the cost-effectiveness ratios.

**Patient Group:** A total of 698 otherwise healthy 1-12 years presenting 48 hours of illness onset and having an oral/otic temperature  $\geq 37.8$  degrees Celsius and at least one respiratory syndrome were considered for the present analysis.

**Key Results:** The objective of this study was to evaluate the effect of treating children with influenza with oseltamivir on health outcomes and costs to healthcare payers. Study findings show that oseltamivir is effective in reducing the duration of influenza illness as measured by return to normal health and activity in otherwise healthy children. The reduction in duration of illness was 2 days and represents a 40% faster return to normal health and activity for children aged 1-12 years. In children 1-5 years, the treatment effect was even greater, with a 2.4 day (48%) reduction in duration of illness with incremental cost-utility rates of £11,173 per quality-adjusted life year (QALY) and oseltamivir being dominant compared with usual care. Most cost-utility ratios remained less than £30,000 per QALY even in conservative scenarios.

## **Oseltamivir for treatment of influenza in healthy adults: pooled trial evidence and cost-effectiveness model for Canada**

O'Brien B J, Goeree R, Blackhouse G, Smieja M, Loeb M; *Value in Health 2003; 6(2):116-125*

**Study Question:** Influenza is a common viral respiratory infection that is associated with significant morbidity. Oseltamivir (Tamiflu) is a neuraminidase inhibitor - a new class of antiviral treatment for influenza where efficacy and safety has been established but cost-effectiveness is unknown. The aim of this decision analytic study was to estimate the costs and effectiveness of two treatment scenarios for empiric management of otherwise healthy nonelderly patients presenting with influenza-like illness (ILI) to primary care physicians in Canada: 1) where oseltamivir is reimbursed and on formulary for prescription; and 2) where oseltamivir is not on formulary.

**Patient Group:** Otherwise healthy nonelderly patients (n=2,288), aged 16-64 yrs, presenting with influenza-like illness (ILI) to primary care physicians in Canada. Patients had no comorbid conditions and no prior influenza vaccination. Patients were randomised to one of two treatment scenarios: (1) where oseltamivir is reimbursed and on formulary for prescription; and (2) where oseltamivir is not on formulary.

**Key Results:** Influenza was confirmed in 1,575 (69%) patients and oseltamivir treatment reduced the mean time to symptom alleviation by 1.08 days (6.83 vs 5.75 days; 95% CI 0.58-1.59). Infected patients treated with oseltamivir had higher utility scores than placebo patients over the 7 days of



follow-up ( $p < 0.05$ ). Cost per influenza-day averted with oseltamivir on formulary is \$49 (95% CI 31-107) and the cost per QALY is \$57,863 (95% CI \$48,919-\$70,149). Results are sensitive to the percentage of patients presenting to their physician beyond 48 hours from symptom onset who get oseltamivir and the prevalence of influenza among patients presenting with ILI. Based on these findings, the authors conclude that oseltamivir for treatment of patients with ILI is potentially cost-effective if clinical diagnostic specificity for influenza observed in clinical trials is applicable to routine practice. More population-based information on the prevalence of influenza among early (<48 hours) presenters with ILI would be valuable.

### **Management of influenza symptoms in healthy adults**

Rothberg M, He S, Rose D; *Journal of General Internal Medicine 2003; 18(10): 808-815*

**Study Question:** This paper makes use of decision analysis to assess the cost effectiveness of rapid testing and antiviral therapy for health adult patients under 65 years of age with influenza symptoms. Data are in the main form previously published sources. Outcome measures include quality adjusted life expectancy. Treatment included amantadine, rimantadine, oseltamivir, or zanamivir.

**Patient Group:** Healthy adults under 65 with influenza symptoms.

**Key Results:** This study uses decision analysis to assess the cost effectiveness of rapid testing and antiviral therapy for health adult patients with influenza symptoms. For base case analysis not giving antiviral therapy is the most expensive and least effective strategy, costing \$471 per patient including lost work time. Amantadine treatment increases life expectancy by 0.0014 quality adjusted life years (QALYs) while saving \$108 per patient relative to no treatment with antivirals. Zanamivir adds 0.0002 QALYs at an incremental cost of \$31 dollars, or \$133,000 per QALY saved. All other strategies, including testing, are less effective and more expensive. The model is sensitive to the probability of infection with influenza, proportion of type B influenza, the relative efficacy of drugs, and the value of a workday lost.

### **Bedside rapid flu test and zanamivir prescription in healthy working adults: a cost-benefit analysis**

Schwarzinger M, Housset B, Carrat F; *Pharmacoeconomics 2003; 21(3):215-224*

**Study Question:** To estimate the economic effects of implementing rapid flu tests (RFT) and zanamivir among unvaccinated healthy working adults who consult within 2 days of the onset of influenza-like symptoms. The strategies were: RFT and conditional zanamivir prescription; systematic zanamivir prescription without RFT and; neither RFT nor zanamivir. This was done through a decision analysis to perform a cost-benefit analysis from a societal perspective.

**Patient Group:** Unvaccinated healthy working adults (<65 years) who consult within 2 days of the onset of influenza-like symptoms with at least two symptoms of myalgia, cough, headache or sore throat.

**Key Results:** During influenza epidemics, systematic zanamivir prescription provided the best health outcome (0.81 influenza days averted) and minimised societal costs (reduced by US\$29.80 per person compared with no zanamivir). Rapid flu tests (RFT) with conditional zanamivir averted 0.65 influenza days and saved US\$14.40 per person. Restricting the perspective to that of the healthcare payer, the medical costs associated with no zanamivir were US\$88.70 per patient consulting with influenza-like illness and increased to US\$125.50 with systematic zanamivir and US\$127.60 with RFT with zanamivir. During influenza epidemics, the systematic zanamivir strategy was more cost



saving than the RFT with zanamivir strategy in all sensitivity analyses, though savings were greatest with no zanamivir when daily earnings were at or below US\$74.30. The most cost-saving strategy also depended on the proportion of influenza-positive patients. When the proportion of influenza-positive patients was under 39%, the no zanamivir strategy yielded the greatest societal savings; otherwise, systematic zanamivir was the dominant strategy. Medical costs associated with no zanamivir were US\$88.70 per patient consulting with influenza-like illness and increased to US\$125.50 with systematic zanamivir and to US\$127.60 with RFT and conditional zanamivir. The authors conclude that due to poor sensitivity of current RFT, systematic zanamivir prescription without RFT for unvaccinated healthy working adults should be recommended during influenza epidemics.

### **Cost-effectiveness of newer treatment strategies for influenza**

Smith K J, Roberts M S; *The American Journal of Medicine* 2002; 113:300-307

**Study Question:** Recent advances in the diagnosis and treatment of influenza, such as rapid testing and neuraminidase inhibitor therapy, are available, but their place in clinical practice and their cost-effectiveness have not been determined. Thus, the aim of this study, using a decision model, was to estimate the cost-effectiveness of these newer interventions by comparing several influenza management strategies. The analysis was carried out from both a third-party payer and a societal perspective.

**Patient Group:** Patients with influenza

**Key Results:** In the baseline analysis, testing strategies are more expensive and less effective than treatment strategies. Amantadine costs US\$9.06 per illness day avoided or US\$11.60 per quality-adjusted day gained. Compared with amantadine, zanamivir costs US\$198 per illness day avoided or US\$185 per quality adjusted day gained, whereas oseltamivir costs US\$252 per illness day avoided or US\$235 per quality-adjusted day gained. In elderly patients who require reduced dosage, rimantadine costs US\$128 per quality-adjusted day gained compared with amantadine. In younger patients, amantadine is favoured if the likelihood of influenza A is >67%; otherwise, neuraminidase inhibitors are favoured. Testing strategies are more costly and less effective when the influenza probability is >30%. No testing or treatment is favoured if the influenza probability is <32% and the influenza utility is >0.77. In elderly patients, amantadine is favoured over rimantadine if the utility of medication side effects is >0.94. Based on these findings, the authors conclude that antiviral treatment of influenza without rapid testing is reasonable economically in febrile patients with typical symptoms during influenza season. The choice of antiviral agent depends on age, the likelihood of influenza A, and the willingness to pay per quality-adjusted day gained.

### **Economic analysis of influenza vaccination and antiviral treatment for healthy working adults**

Lee P Y, Matchar D B, Clements D A, Huber J, Hamilton J D, Peterson E D; *Annals of Internal Medicine* 2002; 137(4):225-231

**Study Question:** Physicians have several treatment options for influenza, including vaccination and various antiviral therapies. However, the optimal influenza prevention and treatment strategy is unknown. The aim of this cost-benefit study, using a decision model, was to compare the relative health values of contemporary treatment strategies for influenza in a healthy sample of working adults. Eight treatment options were assessed based on the possible combinations of vaccination



and antiviral therapy (rimantadine, oseltamivir, or zanamivir or no treatment) should infection develop. The analysis was carried out from a societal perspective.

**Patient Group:** Healthy employed adults 18 to 50 years of age, without any significant comorbid conditions, receiving either influenza vaccination or nonvaccination and antiviral therapy.

**Key Results:** In the base-case analysis, all strategies for influenza vaccination had a higher net benefit than the nonvaccination strategies. Vaccination and use of rimantadine, the most cost-beneficial strategy, was \$30.97 more cost-beneficial than nonvaccination and no use of antiviral medication. The health benefits of most antiviral treatments equalled or exceeded their costs for most scenarios. The choice of the most cost-beneficial antiviral strategy was sensitive to the prevalence of influenza B and to the comparative workdays gained by each antiviral therapy. Based on these findings, the authors conclude that vaccination is cost-beneficial in most influenza seasons in healthy working adults. Although the benefits of antiviral therapy for persons with influenza infection appear to justify its cost, head-to-head trials of the various antiviral therapies are needed to determine the optimal treatment strategy.

### **An assessment of oseltamivir for the treatment of suspected influenza**

Husereau D R, Brady B, McGeer A; *Canadian Coordinating Office for Health Technology Assessment 2002; 7:1-12*

**Study Question:** Oseltamivir has been approved for the treatment of uncomplicated, acute illness due to influenza in adults who have been symptomatic for no more than two days. However, the clinical and economic impact of a oseltamivir for the treatment of influenza is not known. The objectives of this assessment are (1) to assess and quantify the efficacy and effectiveness of oseltamivir in individuals who are suspected of having influenza; and (2) to assess the cost-effectiveness (study perspective government payer in Canada, only direct medical costs were included) of treating suspected influenza with oseltamivir in a primary care setting where standard treatment is no active medical intervention.

**Patient Group:** 2 populations were assessed 1) healthy population 2) those at risk of developing influenza

**Key Results:** The meta-analysis reviewed evidence from 6 trials with 1735 participants of which 469 individuals were individuals at risk for developing complications. Oseltamivir treatment resulted in an absolute reduction of 1% (95% CI [- 2%] to 3%) and 2% (95% CI [- 5%] to 8%) for a combined outcome of death, hospitalization, and complications of illness in otherwise-healthy and at-risk individuals suspected of having influenza, respectively. Taken separately the results for these three outcomes were similarly small and statistically insignificant. Oseltamivir reduced the median time to return to normal activity by 57 hrs (95% CI: 2.4 hrs to 111.6 hrs) when compared with placebo. A decision analytic model was used to compare the health outcomes, resource use, and costs associated with treating suspected influenza with oseltamivir to symptomatic relief medication only. Two populations were assessed separately; the otherwise healthy population of 18 to 65 year olds and those at risk of developing influenza-related complications. In a healthy population using a base case diagnostic accuracy of 35%, and a 50% diagnostic accuracy if there are substantial numbers of late presenting patients treated inappropriately with oseltamivir, the cost per QALY was \$119 500. The cost per QALY was less than \$50,000 assuming a 68% diagnosis, few inappropriately-treated late presenting patients, and optimistic assumptions about the clinical effectiveness of oseltamivir. It was concluded that there is insufficient evidence that oseltamivir reduces complications, hospitalizations and/or death in individuals suspected of having influenza. The economic analysis



suggests that, from a government payer perspective, oseltamivir is unlikely to be cost-effective for treating suspected influenza in otherwise healthy adults.

### **Spotlight on zanamivir in influenza**

Cheer S M, Wagstaff A J; *American Journal of Respiratory and Critical Care Medicine* 2002; 1(2):147-152

**Study Question:** To review the evidence on pharmacoeconomic considerations regarding the use of zanamivir in treating and preventing influenza A and B. Reference is made to five published studies.

**Patient Group:** Patients with influenza and people at risk of contracting influenza

**Key Results:** Zanamivir is a potent competitive inhibitor of the neuraminidase glycoprotein, which is essential in the infective cycle of influenza A and B viruses. The limited evidence suggests that zanamivir is more cost effective than oseltamivir in flu patients (incremental costs per symptom free day gained were \$US22.58 and \$US38.51 respectively). Zanamivir also appeared cost effective when cost per quality adjusted life year (QALY) comparisons were made for zanamivir treatment compared to no active treatment. The authors suggest that prospective cost-effectiveness analyses and investigations of efficacy in preventing serious complications of influenza, particularly in high-risk patients, are required.

### **Economic evaluation of strategies for the control and management of influenza in Europe**

Scuffham P A, West P A; *Vaccine* 2002; 20:2562-2578

**Study Question:** To compare the cost-effectiveness of different strategies for the control and management of influenza for the elderly populations in three European countries (England, Wales, France and Germany). A "no intervention" scenario was compared with six control strategies: opportunistic vaccination (passive recruitment), comprehensive vaccination programmes (active recruitment), 4 week's chemoprophylaxis course using neuraminidase inhibitors (NIs), 4 weeks chemoprophylaxis course using ion-channel inhibitors (ICIs), early treatment with NIs, and early treatment with ICIs. Modelling techniques were used and a health care financier perspective adopted.

**Patient Group:** The elderly population of the three study countries (aged 65 years and over in the UK and France and aged 60 years and over in Germany)

**Key Results:** For the same population coverage in all 3 countries opportunistic vaccination (OppVac) averted 2.9 times more total days of morbidity compared with comprehensive strategy (ChemoNI) and 4.5 times more morbidity days averted (MDAs) compared with ChemoICI. Compared with early treatment strategies, chemoprophylaxis offers better health gains in reduced cases, hospitalisations, deaths and days of morbidity. Health gains from neuraminidase inhibitors (NIs) used for either chemoprophylaxis or early treatment are greater than the health gains from ion-channel inhibitors (ICIs). For an elderly population of 10,000, ChemoNI for 4 weeks costs almost 700,000 Euros for 41% coverage in Germany, 730,000 Euros for 33.4% coverage in England and Wales and 800,000 Euros for 61% coverage in France. ChemoICI costs between 13.3 and 18.5% of the costs for a ChemoNI strategy and an OppVac strategy costs between 5.3% and 9.3% of ChemoNI. In all 3 countries the greatest reduction in estimated medical care costs come from vaccination strategies. The reduction in medical costs from OppVac were 2.5 times greater than the reduction in costs from ChemoNI, 4.0 times greater compared with ChemoICI and 8.0 times greater compared with early treatment strategies. Vaccination strategies in England and Wales were the only strategies where benefits were



greater than costs (benefit cost ratio (BCR) >1). The costs of vaccination strategies in Germany and France outweighed the cost-savings from reduced medical care. For Germany both vaccination strategies had greater returns on investment compared with other strategies. For every Euro spent in Germany on opportunistic vaccination, 0.56 Euros would be gained from reduced medical care costs. In France this was 0.77 Euros for each Euro invested. The return from chemoprophylaxis strategies ranged from 0.02 to 0.14 for every Euro invested, with BCRs for ChemoICI strategies 3.5 times greater than for ChemoNI. Early treatment strategies were a better investment compared with chemoprophylaxis strategies in France and Germany. Treatment strategies with ICI (TreatICI) resulted in the greatest BCR for France, more than vaccination and chemoprophylaxis strategies. For France, when MDAs excluded deaths, the ICER for CompVac (14.8 Euros) was greater than TreatICI (8.8 Euros). Although ICIs cost less than NIs, ICIs were assumed to be clinically less effective (1.0 MDA versus 1.2 MDA for NIs). Early treatment strategies using ICIs were more cost-effective in all three countries. ChemoICI was more cost-effective than early treatment strategies in Germany and England and Wales, but was the least cost-effective strategy in France. The cost per MDA from ChemoNI was less than the cost per MDA from early treatment in England and Wales. Compared with changes in all other factors, vaccination strategies were most sensitive to change in the price of the vaccine. Results for England and Wales were sensitive to changes in the discount rate, but not so in Germany. The attack rate for clinically symptomatic ILI was the factor with the greatest uncertainty. Chemoprophylaxis strategies were most sensitive to the timing of the programme, the price of the antiviral, the antiviral dose and the assumed years of potential life lost (YPLL). Early treatment strategies were highly sensitive to the GP consultation rates and the percentage of those consultations that occur within 2 days of developing clinical symptoms. The authors conclude that vaccination strategies were the most cost-effective. Chemoprophylaxis strategies were highly expensive even under assumptions of optimal timing. Early treatment strategies with antivirals substantially increased demand for GP services and were more expensive than prevention through vaccination.

## Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults

Muennig P A, Khan K; *Clinical Infectious Diseases* 2001; 33:1879-1885

**Study Question:** At present, there is uncertainty regarding whether influenza-like illness in healthy adults is best managed by preventive efforts that use the trivalent influenza vaccine, administration of neuraminidase inhibitors at the onset of illness, or recommendation of supportive care alone at the onset of illness. The aim of this study was to conduct a cost-effectiveness analysis to examine these three strategies for managing influenza-like illness. The analysis was carried out from a societal perspective.

**Patient Group:** Healthy adults residing in the USA in 1997, 15 to 65 years of age, with influenza-like illness (ILI) who receive either trivalent influenza vaccine, neuraminidase inhibitors at onset of illness, or recommendation of supportive care alone at the onset of illness. ILI is defined here as subjectively determined fever or a measured temperature  $\geq 37.7^{\circ}\text{C}$  plus a cough or sore throat (the World Health Organisation (WHO) definition)

**Key Results:** Vaccination with inactivated trivalent vaccine would save approximately US\$25 per person while resulting in a net gain of approximately 3.2 quality-adjusted hours relative to providing treatment with the neuraminidase inhibitor oseltamivir. Treatment with oseltamivir was associated with an incremental cost-effectiveness of approximately US\$27,619 per quality adjusted life year (QALY) gained relative to providing supportive care. In descending order, the model was most



sensitive to the following variables: incidence of influenza-like illness (ILI), transportation costs, caregiver costs, the cost of a medical visit in the vaccination arm and the cost of the influenza vaccine. Vaccination remained the dominant strategy when each of these variables was tested over the range of plausible values of each parameter. Based on these findings, the authors conclude that vaccination is cost saving relative to providing either treatment with oseltamivir or providing supportive care alone.

## **Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment**

Husereau D R, Brady B, McGeer A; *Canadian Coordinating Office for Health Technology Assessment 2001; 21:1-46*

**Study Question:** The authors evaluated the cost-effectiveness of oseltamivir in the treatment of suspected influenza. A decision analytic model was used for a cost-utility study. Utilities for the "influenza-outpatient" health state was based on data collected for CCOHTA's Zanamivir Report from a sample of 11 healthy adults who were asked to assume they had moderately-severe influenza and then completed the Health Utilities Index Mark 3. The base case analysis assumed there were no late presenters. A one-way sensitivity analysis was performed. The perspective was that of the government in Canada.

**Patient Group:** Patients with suspected influenza

**Key Results:** The utility study showed that the "influenza-outpatient" mean score was 0.636. For flu-related hospitalization the utility was assumed to be 0.35. For the healthy population expected unit costs are \$53.20 for oseltamivir, \$15 for antibacterial medication, \$23 for physician visits and \$500 x 4.4 days for hospital. Total cost for a flu-positive patient in the healthy population was \$84.44 and for a flu-negative patient \$85.08 when both patients were treated with oseltamivir. Using standard treatment the total cost for both a flu-positive and flu-negative patient in the healthy population was \$31.88. In the at-risk population unit costs were: \$53.20 for oseltamivir, \$15 for antibacterial medication, \$23 for physician visits and \$500 x 6.3 for hospital. For the at-risk population the cost of flu-positive patients was \$130.52. Cost of flu-positive patients \$145.48 and for standard treatment cost of flu-positive and flu-negative patients \$92.28. The cost-effectiveness of oseltamivir was very sensitive to the diagnostic accuracy as the drug only works for those infected with influenza. For a diagnostic accuracy of 14%, 35%, 50% and 68% respectively that incremental cost per patient was \$53.11, \$52.98, \$52.88 and \$52.76. The incremental symptom days avoided per patient was 0.18, 0.44, 0.64 and 0.86. The incremental cost per day of symptoms avoided were \$299, \$119, \$83 and \$61 respectively. The incremental QALYs gained per patient were 0.00018, 0.00044, 0.00063 and 0.00086 respectively. The incremental cost per QALY gained was \$299,500, \$119,500, \$83,500 and \$61,300 respectively. Results of the base case and sensitivity analysis showed that at a diagnostic accuracy of 35% and below the incremental cost per QALY was above \$100,000. For a diagnostic accuracy of 50% the incremental cost per QALY ranged from \$77,000-\$84,000. However if 25% of patients are treated outside the 48-hour window of effectiveness the incremental cost per QALY is above \$100,000. Results only proved oseltamivir to have an incremental cost per QALY below \$50,000 with 68% diagnostic accuracy, few inappropriately-treated late presenting patients and optimistic assumptions above the clinical effectiveness of oseltamivir.



## Cost-effectiveness analysis of inhaled zanamivir in the treatment of Influenza A and B in high-risk patients.

Griffin A D, Perry A S, Fleming D M; *Pharmacoeconomics 2001; 19(3):293-301*

**Study Question:** Modelling within a meta-analysis including six studies was performed to assess the cost-effectiveness of inhaled zanamivir in the treatment of Influenza A and B in high-risk patients. The study setting was the United Kingdom.

**Patient Group:** Influenza A and B high-risk patients

**Key Results:** A total of 2,751 patients were recruited into the 6 studies and received zanamivir 10mg twice daily or placebo. Of these, 321 high-risk patients were included in the analysis (154 zanamivir, 167 placebo). Patients were considered high-risk if they had chronic respiratory disease (including asthma and COPD); significant cardiovascular disease (excluding patients with hypertension as the sole diagnosis); were immunocompromised; or were  $\geq 65$  years of age with or without underlying medical conditions. In addition, two studies included patients with diabetes mellitus. The effectiveness measures used in the analysis were time to return to normal activities, time to alleviation of symptoms and incidence of complications, which were compared across three scenarios: (1) base case; (2) sensitivity analysis excluding serious adverse event; and (3) sensitivity analysis excluding one hospitalised patient. Figures given in parentheses are confidence intervals. In scenario (1) (including rare inpatient hospitalisation), the time taken to return to normal activities was 11.96 days (10.64, 13.28) in the placebo group vs. 9.48 days (8.26, 10.70) for the zanamivir population, an incremental effect of 2.48 days (0.68, 4.27). The incremental cost-effectiveness ratio (ICER) was £18.14 (£1, £85). Scenario (2) did not alter the effectiveness results; however the ICER fell to £9.50 (£5, £39). Scenario (3) indicated that zanamivir was more effective than placebo [11.96 days (10.64, 13.28) vs. 9.44 days (8.22, 10.67)]. The ICER again fell to £8.61 (£3, £43). Time to alleviation of symptoms in Scenario (1) was 9.09 days (7.96, 10.21) vs. 7.05 days (6.09, 8.01) in the placebo and zanamivir groups, respectively. The incremental effect was 2.03 days (0.56, 3.51), whilst the ICER was £22.08 (£0, £97). Scenario (2) did again did not alter the effectiveness results; however the ICER fell to £11.56 (£6, £43). Scenario (3) showed that zanamivir was more effective than placebo [9.09 days (7.96, 10.21) vs. 7.02 days (6.06, 7.99)]. The ICER was lower at £10.50 (-£3, £49). The incidence of complications in all three scenarios was the same for both placebo [25% (18%, 31%)] and zanamivir [16% (10%, 21%)]. However, the ICER was £501 (-£94, £3234), £262 (£90, £1574) and £245 (£84, £1,736) in scenarios 1, 2 and 3 respectively. The cost per QALY was estimated to be £3,920 (£7,490 including hospitalisation costs). Using cost-effectiveness acceptability curves illustrates that there is a 90% certainty that zanamivir would be cost effective (excluding inpatient costs) if the ceiling ratio for a QALY was £8,000 and a 95% certainty that zanamivir would be cost effective if the ceiling ratio was £11,500 per QALY. The evaluation demonstrates that significant health benefits can be obtained with zanamivir therapy in high-risk patients, with cost effectiveness point estimates (excluding inpatient costs) of £9.50 per day of normal activities gained, £11.56 per symptom free day, £262 per complication averted and approximately £3,900 per QALY.

## Fast track appraisal of zanamivir (relenza): summary of evidence

National Institute for Clinical Excellence (NICE); *NHS R and D Health Technology Assessment Programme 2001; 1-11*

**Study Question:** Two measures are currently used within the National Health Service (NHS) to reduce the impact of flu: immunisation by vaccines and antiviral prophylaxis/therapy with amantadine. The aim of this report is to provide a summary of the evidence used in the fast track



appraisal of zanamivir (Relenza) undertaken by the National Institute of Clinical Excellence. Zanamivir is the first of a new class of selective influenza virus neuraminidase inhibitors. The evidence is based on a systematic review of the literature using a number of electronic bibliographic databases. Studies were included if they were of randomised clinical trial (RCT) design and compared zanamivir treatment to placebo or current therapy in adult patients with influenza A or B infections (three trials met inclusion/exclusion criteria - all Glaxo Wellcome phase III trials). Also included is a submission on zanamivir from its manufacturer, Glaxo Wellcome. No published economic evaluations of zanamivir were identified and thus a model for the cost effectiveness and budget impact of zanamivir was presented in the industry submission. The report is part of the NHS R & D Health and Technology Assessment programme.

**Patient Group:** 1,588 patients (813 in active groups and 775 in placebo groups), aged >12 yrs, with influenza A or B infections, taken from three randomised clinical trials (RCTs)

**Key Results:** A median reduction of one day (95% CI: 0.5 to 1.5 days) in the time to alleviation of symptoms with zanamivir was reported in the pooled intention to treat population. In both the intention to treat, influenza positive and high-risk populations, the reduction in symptom alleviation with zanamivir varied across the three trials. Overall, there was absolute reduction in complications with zanamivir of 7% (95% CI: 3-11%) in the intention to treat population. In the high-risk population, there was, overall, an absolute reduction in complications of 13%, although in the North American trial, the level of complications actually increased by 9%. The industry submission states that the direct costs to the health service of zanamivir, using modelling, will be £18.52 per 5-day course of treatment (less than the anticipated cost of £24). The lower cost prediction is the result of a reduction in antibiotic costs, GP consultation costs and inpatient cost through re-hospitalisations. It was also predicted that enhancement of productivity with zanamivir would result in an overall cost saving to society of £21.51 per patient. The incremental cost per day of symptom alleviation would be £18.52. However, the authors of this report state that such a cost-effectiveness analysis is questionable given the inconsistency in the outcome measure across studies and the large number of assumptions upon which the calculation of cost are based.

## Pharmacoeconomic model to evaluate new influenza treatments

Armstrong E P, Abarca J; *Formulary 2000; 35:169-181*

**Study Question:** Zanamivir and oseltamivir are two agents of a new class of drugs - neuraminidase inhibitors - to receive FDA approval for the treatment of influenza. Because the two agents are more expensive yet have a more favourable side effect profile than the older treatments amantadine and rimantadine, coverage decisions can be difficult to make. The aim of this paper was to present a decision-analytic model of influenza treatments, using zanamivir as the main example. The study is for illustrative purposes and all the figures included are hypothetical. The analysis was undertaken from the perspective of the managed care organisation.

**Patient Group:** Patients receiving zanamivir or oseltamivir for the treatment of uncomplicated acute illness due to influenza virus.

**Key Results:** This hypothetical study identifies a useful strategy to compare two newer treatment agents for influenza infections. Important steps are to clearly identify the treatment alternatives, structure an appropriate tree, accurately determine the resource unit consumption (and their corresponding costs) for each treatment path and carefully determine the probabilities for each chance node. This hypothetical study provides a useful approach for a health system to assess their respective clinical and economic outcomes for these two agents along with the no viral treatment path.



## **Impact of zanamivir treatment of productivity, health status and health care resource use in patients with influenza**

Aoki F Y, Fleming D M, Griffin A D, Lacey L A, Edmundson S on behalf of the Zanamivir Study Group; *Pharmacoeconomics* 2000; 17(2):187-195

**Study Question:** To assess the impact of zanamivir treatment on patient morbidity in patients with influenza. The study was a multi-centre randomised trial in 14 different countries in Europe and North America

**Patient Group:** 722 otherwise healthy patients with influenza were included in the influenza-positive population. 1256 patients in total were included in the study. Patients were randomised to treatment (2 versions) and placebo (2 versions) in the ratio 2:1. Patients with unstable chronic illness, those who were pregnant and those breast feeding were excluded.

**Key Results:** Compared with placebo, significantly fewer patients treated with zanamivir had contacts with health care professionals. In addition, zanamivir patients spent significantly fewer days if work or college/school, and showed significant improvements in productivity compared with placebo patients. Finally, the health status questionnaire revealed significant improvements in patient well-being over the first 5 days of the study in those treated with zanamivir compared with those who received placebo. The authors conclude that zanamivir treatment reduced absenteeism, improved patient productivity and well-being, and reduced the additional use of healthcare resources in patients with influenza.

## **Zanamivir for the treatment of influenza in adults: supplement to the assessment report**

NHS R & D Health Technology Assessment Programme; *NHS R and D Health Technology Assessment Programme* 2000; 1-8

**Study Question:** Since the submission of the West Midlands Development and Evaluation Service report "Zanamivir for the treatment of influenza in adults" to the National Institute of Clinical Excellence (NICE), new data from a further randomised placebo-controlled trial (NAI30008) has been received from Glaxo Wellcome UK Limited. This is the first trial specifically recruiting an at-risk population to be reported. The aim of this paper is to present an update to the original review to incorporate this new evidence. The methods used are the same as those in the original review. This report is part of the NHS R & D Health Technology Assessment Programme.

**Patient Group:** 525 patients aged 12 and over with underlying asthma and chronic obstructive pulmonary disease (COPD) presenting with influenza-like illness (fever of  $\geq 37.8^{\circ}\text{C}$  plus at least two of the following symptoms: myalgia; headache; cough; sore throat) with symptom onset  $< 36$  hours. Mean age of patients was 39.4 yrs (range, 12-88). Baseline characteristics were similar between treatment and control groups.

**Key Results:** Study NAI30008, a randomised placebo-controlled trial, produced results that are consistent with the findings of other studies for a reduction in time to alleviation of symptoms and in the use of antibiotics for complications. However, the new data confirm that the observed benefits are almost certainly a true effect and are not due to chance. Importantly, there is now more substantial data to show that zanamivir has a similar (acceptable) safety profile in at-risk adults compared to otherwise healthy adults. Feeding the new best estimates of effectiveness into the original economic model developed in the National Institute of Clinical Excellence (NICE) submission, produces a cost per quality adjusted life year (QALY) for treating influenza in at-risk adults when influenza is circulating of £31,500. This is slightly higher than in the original estimate of £27,000 per



QALY mainly because the estimated reduction in duration of symptoms is less. Glaxo Wellcome UK Limited have used a similar model to that used in the original review but their estimate of cost per QALY is £13,000. This lower estimate is due to the fact that Glaxo Wellcome UK Limited assume a higher prevalence of influenza positive adults amongst those visiting their GPs with influenza and a higher gain in utility for the difference between influenza and no influenza. However, the authors of this report believe there is a genuine uncertainty about these parameters.

**Date searched: 7<sup>th</sup> May 2009**