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Economic evaluations of neuraminidase inhibitors to control influenza.

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Title: Review of economic evaluations of neuraminidase inhibitors to control influenza.

Short running title: Economic evaluations of neuraminidase inhibitors in adults

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Summary: Up to 10% of individuals present influenza-like illness each year. Neuraminidase inhibitors reduce significantly the median duration of flu symptoms by 1.38 days and median time to return to normal activities by 0.9 days in adults. This review presents the economic evaluations of neuraminidase inhibitors in adults. Choice of key parameter estimates in cost-effectiveness or cost-benefit models were sensitive to the perspective of analysis: health-care payer or societal, including productivity gains. This review discusses among other key parameters the proportion of influenza-like illness due to the influenza virus (targeted by neuraminidase inhibitors and flu vaccine) and the measure of health benefits by either QALYs gained or willingness-to-pay for a day of symptoms averted. Overall, neuraminidase inhibitors are worth their costs and do not challenge annual flu vaccination, but should be seen as a complementary option to reduce the burden of influenza.

Key words: influenza; neuraminidase inhibitors; zanamivir; oseltamivir; cost-effectiveness analysis; cost-benefit analysis; QALY; indirect costs; adults.

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INTRODUCTION

This brief overview presents three key points that play a major role in the economic evaluation of strategies based on antiviral drugs to prevent and control influenza. First, influenza-like illness (ILI) is usually defined as an acute febrile illness with symptoms of coughing, myalgia, headache or sore throat. However, influenza viruses are not the sole infectious agents responsible for ILI, and the proportion of ILI accounted for by influenza viruses varies greatly across the studies, i.e. from 15 to 70%. Second the burden of influenza in the community depends on the virulence of the circulating strains and the characteristics of the population, either at-risk for medical complications or otherwise healthy. Third, annual flu vaccination is a consensual and recommended strategy among the at-risk population, and strategies based on antiviral drugs may not challenge those based on vaccination, at least in the at-risk population.

Influenza-positive rates in individuals suffering from ILI

A number of infectious agents can be responsible for ILI, including influenza viruses, adenoviruses, respiratory syncytial viruses, rhinoviruses, parainfluenza viruses, *Mycoplasma pneumoniae* and the *Legionella spirella* species.[1] There are various laboratory diagnostic methods to identify influenza viruses.[2] The following diagnostic methods are here presented in decreasing order of time it takes to see results: serology (2 weeks), viral isolation by culture (3-10 days), RT-PCR (Reverse Transcriptase Polymerase Chain Reaction, 1-2 days) and Immunofluorescence or influenza Enzyme-Immuno-Assay (a couple of hours). The proportion of influenza-positive patients depends on several factors including the “true” level of influenza infections in the eligible population (patients suffering from ILI), the collection of specimens sent for identification and the method(s) used for diagnosis. This proportion will increase with testing

of patients during flu epidemics, the use of a specific clinical case definition for ILI and sensitive diagnostic methods such as RT-PCR on good quality samples.[2] When an influenza virus was identified by viral culture, the proportion of influenza-positive patients younger than 65 years and seeking medical advice for ILI varied between 16 and 29% in surveillance data,[3-5] but reached 40% in one epidemiologic survey when a more specific clinical case definition of influenza was used.[6] When the collection of specimens was limited to unvaccinated patients and, above all, during flu epidemics, this proportion increased substantially, i.e. from 46% to 62% in clinical trials of neuraminidase inhibitors.[7-11] When influenza virus was identified by viral culture plus another diagnostic method (serology or RT-PCR), an even higher proportion of influenza virus infections was found among patients in clinical trials of neuraminidase inhibitors (up to 71% [9] and 77%, [12] respectively).

On the other hand, the proportion of patients with ILI seeking medical advice varies greatly across health care systems. The average population consulting with ILI over 10 winters (1987-96) was estimated at 0.85% in the UK, where the National Health Service recommends to avoid medical advice during flu epidemics.[13] It was estimated at 50% in a recent French National prospective survey, in which it correlated strongly with the severity of symptoms, i.e. when patients could benefit the most from antiviral drugs.[14] Assuming that the proportion of influenza-positive infections is similar between patients currently seeking medical advice and those who are not, the burden of influenza is much greater than currently estimated, and it could be reduced significantly by extended strategies to prevent and control influenza.

Variability of the burden of influenza according to year and risk for medical complications

Virulence of circulating strains

The frequent antigenic changes (or antigenic drift) due to point mutations during viral replication may explain the occurrence of influenza epidemics each year and the possible recurrence of influenza infection in individuals. The virulence of the circulating strains is assessed by morbidity and mortality indicators, such as the total number of ILI or the peak-incidence of ILI as provided by surveillance systems (<http://oms2.b3e.jussieu.fr/flunet/>), [15] and the excess of hospitalizations and deaths during influenza seasons. All influenza seasons were judged mild to moderate worldwide during the last decade, as compared to those that followed the first circulation of the H3N2 strain in 1968.

Distribution of the adult population according to risk for medical complications

The burden of influenza depends on the characteristics of the population regarding the risk of developing medical complications from influenza. In the at-risk population, influenza infection can lead to hospitalizations and deaths with significant effect on both health outcomes and medical costs (and intangible costs of premature death, if valued). In the otherwise healthy population, influenza infection remains a common infectious disease and the burden of influenza is then driven by indirect costs of lost work days and a consequent drop in productivity, as well as the direct costs of physician visits and antibiotic use. About 60% of the population of a developed country is between 18 and 65 years of age, the vast majority of whom are otherwise healthy individuals. Accordingly, the otherwise healthy adults bear most of the economic burden of influenza.

The at-risk population includes, in most developed countries: individuals aged >65 years (i.e. individuals aged >70 years account for 90% of influenza-related deaths); residents of nursing homes and other chronic-care facilities that house individuals of any age who have chronic medical conditions; adults and children who have chronic disorders of the pulmonary or cardiovascular system, including asthma; adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression.[16] The US Advisory Committee on Immunization Practices recommended recently the annual vaccination of individuals aged 50-64 to increase the low vaccination rate among individuals with high-risk conditions (a quarter of this age group),[17] and encouraged the annual vaccination of children aged 6-23 months because they are at increased risk for influenza-related hospitalizations.[18]

A consensual strategy: annual flu vaccination in the at-risk population

Annual flu vaccination in the at-risk population

A consensual strategy in developed countries is the annual flu vaccination of the at-risk population. A meta-analysis showed that influenza vaccination in individuals aged > 65 years reduced hospitalization risk by 50% and mortality risk by 68%.[19] Moreover, annual vaccination is a cost-saving strategy in the at-risk population where the costs are above all medical costs.[20,21] Annual vaccination has enjoyed a steady growth in uptake in all developed countries and is viewed as a successful public health initiative.[22]

None of the four antiviral drugs specific for influenza infection, i.e. amantadine, rimantadine, zanamivir, and oseltamivir, has been, as of yet, demonstrated to be effective in preventing serious influenza-related complications in the at-risk population (bacterial or viral pneumonia or exacerbation of chronic diseases or hospitalizations or deaths).[23,24] However, antiviral drugs have shown a preventive efficacy similar to vaccination on the one hand,[25,26] and the vaccination coverage rate depends dramatically on at-risk sub-populations, on the other hand, i.e. over 60% in individuals aged 65 years and older to 30% in individuals aged 18-64 with high-risk conditions.[18] Accordingly chemoprophylaxis with antiviral drugs may be a relevant strategy in the unvaccinated at-risk population, either during flu epidemics or when a household contact is suffering from ILI.[27,28] However, chemoprophylaxis should remain a second best option according to a recent economic study showing that vaccination was more cost-effective than chemoprophylaxis during flu epidemics in the elderly population.[29]

Annual flu vaccination in the otherwise healthy population

In the otherwise healthy population, options to prevent and control influenza are directed towards the reduction of indirect costs of lost work days and consequent drops in productivity that account for most of the burden of influenza. The extension of annual flu vaccination to the otherwise healthy population and treatment by antiviral drugs are therefore competing strategies in this population. Economic evaluations of annual flu vaccinations of otherwise healthy adults have shown since 1995 that annual flu vaccination was a cost-saving strategy when performed at the workplace.[30-34] Difficulties in comparing the benefits of annual flu vaccination and antiviral drugs are discussed in the Expert opinion chapter (see below).

Strategies to prevent and control influenza, including rapid diagnostic tests in the otherwise healthy population

The extension of annual flu vaccination to the otherwise healthy population and treatment by antiviral drugs represent two opposite strategies in terms of population involvement to maximize effectiveness. The effectiveness of annual vaccination is maximal when the vaccination coverage rate is 100%, whereas the effectiveness of antiviral drugs is maximal when antiviral drugs are selectively given to patients with ILI, i.e. when the probability of influenza infection is at its highest. Rapid Flu Tests that increase positive predictive values for diagnosing influenza infection are suitable for point-of-care use in physicians' offices. Their development was concomitant to those of neuraminidase inhibitors (Biota's FLU OIA®, and Roche's Influenza A/B Rapid Test®). In this economic review, we focused on strategies involving neuraminidase inhibitors and possibly Rapid Flu Tests to control influenza in the otherwise healthy population.

PHARMACOLOGY, EFFICACY, AND SAFETY OF NEURAMINIDASE INHIBITORS

Pharmacology of neuraminidase inhibitors

Orthomyxovirus influenza is a membrane-enveloped RNA virus containing surface-expressed proteins, i.e. hemagglutinin, neuraminidase (NA) and ion-channel M2 proteins. NA is a highly conserved protein with nearly the same amino-acid sequence and three-dimensional structure in influenza A and B strains. Neuraminidase inhibitors (NA-inhibitors) are rationally designed small molecules that bind tightly to NA and stop the influenza virus from spreading and infecting new cells, and thus slow the rate of infection.[35]

As shown in **Table 1** there are two marketed NA-inhibitors, i.e. zanamivir (Relenza®) and oseltamivir (Tamiflu®), and peramivir is on the board with expected marketing in 2003, if the ongoing randomized clinical trial confirms its promising laboratory features.[36-39] For decades, two antiviral drugs inhibiting the ion-channel M2 proteins, i.e. amantadine and rimantadine, have been used to treat influenza infection. NA-inhibitors have several advantages over ion-channel M2 inhibitors: activity against influenza B viruses, absence of serious side effects, and lower rates of resistance development both in vitro and in vivo.[18,35] Moreover ion-channel M2 inhibitors are rarely used in some developed countries, or even removed from the pharmacopoeia (e.g. rimantadine in France).

Efficacy and safety of neuraminidase inhibitors

According to a meta-analysis of clinical trials of zanamivir, 10 mg zanamivir inhaled twice daily reduced significantly, in intention-to-treat analysis, the median duration of flu symptoms by 1.38

days [CI95%, 0.84 to 1.93], the median time to become afebrile by 0.50 days [CI95%, 0.23 to 0.77], and the median time to return to normal activities by 0.90 days [CI95%, 0.19 to 1.61].[40] Similar results were found in the clinical trials of 75 mg oseltamivir taken orally twice daily.[10,11,41]

In the previous meta-analysis of clinical trials, 10 mg zanamivir inhaled twice daily showed no significant increase in side effects compared to a placebo.[40] However zanamivir is not recommended for treatment of patients with underlying airway disease due to the risk of serious adverse effects,[42] and because its efficacy has not been demonstrated in this population. With 75 mg oseltamivir taken twice daily, nausea and vomiting were reported more frequently (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among those individuals receiving a placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%).[18,25] A limited number of adults enrolled in clinical trials of oseltamivir discontinued treatment because of adverse effects.[18]

Zanamivir and oseltamivir have all been approved in 2002 in those developed countries that account for 85% of the world pharmaceutical market, although this approval occurred at different times (see **Table 1**). Several factors are likely to affect the choice of NA-inhibitors in relation to patient compliance: the route of administration, the number of administrations per day, adverse effects and the price. To the extent that oseltamivir (Tamiflu®) leads the world market of NA-inhibitors despite its higher cost and increased adverse effects, we may guess that it is related to its oral route of administration, which is much more convenient than inhaled zanamivir.[43] It may also be linked to a more aggressive advertising campaign (e.g. Roche won the 2000 Australian Direct Marketing Association award, the first time a pharmaceutical company has

walked away with this honor). If the current clinical trial confirms the efficacy of peramivir, peramivir taken orally once daily could challenge other NA-inhibitors.

One of the strong appeals of NA-inhibitors is their lower rates of resistance development as compared to ion-channel M2 inhibitors. Drug resistance conferred due to changes in the NA active site could be monitored by NA inhibition assays. In vitro, NA substitutions were acquired in zanamivir-selected viruses at residues 119 (A/N2, B) and 292 (A/N2 and A/N9), in oseltamivir-selected viruses at residues 274 (A/N1) and 292 (A/N2) and in peramivir-selected viruses at residue 292 (A/N2). In vivo, NA substitutions were acquired in zanamivir-selected mutants at residue 152 (B), in oseltamivir-selected mutants at residues 119 (A/N2), 198 (B), 274 (A/N1) and 292 (A/N2). NA substitutions were often accompanied by impairment of virus infectivity and virulence in animal models. Emergence of viruses with NA substitutions is uncommon in drug-treated humans, and the development of influenza viruses resistant to NA-inhibitors in influenza-positive patients is very low or not observed in immuno-competent adults.[18,44]

ECONOMIC EVALUATIONS OF NEURAMINIDASE INHIBITORS TO CONTROL INFLUENZA IN OTHERWISE HEALTHY ADULTS

This review is limited to economic studies performed in otherwise healthy adults without taking into consideration the therapeutic options including ion-channel M2 inhibitors (see above). Our search procedure included all economic studies (with comparison of costs and benefits of at least two strategies to control influenza) published until October 2002 and selected on PUBMED by the following terms: "neuraminidase inhibitor", "zanamivir", "oseltamivir", "adult", "cost-

effectiveness analysis", "cost-benefit analysis",[45] and relevant economic studies referenced in previous, selected papers.

Table 2 shows the 10 economic studies with evaluation of NA-inhibitors in adults.[29,34,40,46-52] Four studies looked for the benefits of Rapid Flu Testing,[49-52] three studies focused on head-to-head comparison of NA-inhibitors to annual flu vaccination,[29,34,48] and three were interested in the implementation of zanamivir from the health-care payer perspective.[40,46,47] All studies were based on decision trees and evaluated either the cost-effectiveness of interventions,[29,40,46-49,52] or the cost-benefit of interventions.[34,50,51] Sensitivity analyses were performed in all economic studies since base-case parameters incorporated into the decision tree were often uncertain. Several options for analyzing parameter uncertainty were taken in the models, i.e. one-way sensitivity analysis,[29,40,46,52] multi-way sensitivity analysis,[47,50,51] and probabilistic sensitivity analysis using Monte Carlo simulation with triangular distribution of the parameters.[34,48,49]

In economic studies, NA-inhibitors result in 1) health benefits measured by days of flu symptoms avoided, Quality-Adjusted Life Years (QALYs) gained or intangible benefits measured by the willingness-to-pay for one day of flu symptoms averted; 2) reduction of medical costs by decreasing secondary infectious complications and related antibiotic use,[53] and over-the-counter drugs (acetaminophen and cough treatments) consumption;[7] and 3) reduction in indirect costs.[54] Productivity gains were all measured in the human capital approach with a lost work day averted valued at the median earnings for one day.[55]

As shown in **Table 2**, vaccination dominated NA-inhibitors in head-to-head comparisons (i.e. vaccination that led to greater health benefits and that was less expensive), and systematic treatment by NA-inhibitors of patients consulting with ILI dominated a selective drug prescribing strategy based on Rapid Flu Test results during flu epidemics. With the health care payer perspective that includes only medical costs, NA-inhibitors were not cost-effective in otherwise healthy adults, but the cost-effectiveness ratio decreased substantially when all adults, including the at-risk population, were included. With the societal perspective that incorporates all costs, regardless of who incurs these costs, NA-inhibitors were shown to be worth their cost during flu epidemics when NA-inhibitors were considered separately from vaccination.

Some model parameters played a key role in the results found in the base case analysis, as shown by their major influence in sensitivity analysis: the inclusion of patients at-risk for influenza complications with possible hospitalization, the proportion of ILI due to influenza viruses targeted by NA-inhibitors and vaccination (i.e. this doubled from 34%[40] to 70%[46]), the measure of health benefits in terms of "QALYs" per day (i.e. from 0.133/365[49] to 0.442/365[46]), and, in case of flu vaccination evaluation, the ILI attack rate and the match of vaccine strains to the circulating influenza viruses. The influence of these latter parameters was consistently found in other economic evaluations of annual influenza vaccination of otherwise healthy adults.[30-32] For instance, when the ILI attack rate decreased from 15% to 5%, individual net benefits provided by vaccination were divided by 8 (US\$ 32 to 4),[33] or it was no longer associated with net benefits under a threshold of 6.3%.[34]

EXPERT OPINION

Incentives to pay for NA-inhibitors

The US Panel on Cost-Effectiveness in Health and Medicine and other leading health economists have recommended that economic evaluation should be performed from a societal perspective that incorporates all costs regardless of who incurs the costs.[55,56] However, it seems justifiable to underline the different incentives to pay for NA-inhibitors from particular perspectives, i.e. the health-care payer, the firms, and the patients with ILI.

From the health-care payer perspective, NA-inhibitors may be an attractive option to the extent that they could reduce very costly influenza-related hospitalizations (e.g. pneumonia therapy was estimated at US\$ 4,000 per week,[49] or hospitalization at £ 222 per day),[40] but the probability of bearing the brunt of costly medical complications is very low and has a significant implication only in the at-risk population. Interestingly, Burls et al. showed that a 6% reduction of high-risk patients hospitalized in a conservative sensitivity analysis favoring NA-inhibitors decreased the cost-effectiveness ratio slightly, dropping from £ 54,000 to £ 48,000 per QALY.[40]

From the firm's perspective, NA-inhibitors may be an attractive option to the extent that they reduce lost work days,[54] and increase the median time to return to normal activities.[40] The measurement of productivity gains by the number of lost work days averted is a conservative estimate, since it relies solely on the lack of physical presence and thus does not take into account the productivity losses that occur when a worker with ILI nonetheless comes to work.[57] In our review, four economic studies took into account indirect costs averted that generally favored NA-inhibitors.[34,49-51] However, indirect costs averted in two other economic studies represented a

half to a third of the estimates of previous studies (see **Table 2**), either because all the adult population was taken into consideration (including non-working adults),[47] or because caregiving costs were used instead of earnings.[48] Consequently, these two economic studies showed that NA-inhibitors were not cost-effective.

With the perspective of patients with ILI, NA-inhibitors may be an attractive option to the extent that they could allow patients to return to normal activities earlier (of particular interest in liberal professions), they could prevent in-house secondary transmission of influenza infection (with further reduction in indirect costs), and they marginally reduce OTC consumption. Whereas the indirect costs incurred by some patients with ILI are substantial, no economic study has evaluated strategic options specifically dedicated to patients suffering from ILI.

An issue related to the perspective of economic analysis is the type of economic study performed to evaluate NA-inhibitors, either through a cost-effectiveness analysis or cost-benefit analysis. The usual decision rule for cost-effectiveness analysis consists of comparing the cost-effectiveness ratio to a given threshold, or the cost-effectiveness of other strategies, actually funded by the health-care payer. In our opinion, a cost-benefit analysis is more fitting for the problematic of NA-inhibitors in the otherwise healthy population given the health outcomes in this population (i.e., influenza-like illness is a short-term, non-fatal disease), the lack of payment or copayment for NA-inhibitors in most developed countries, and the willingness-to-pay of patients with ILI to reduce the length and severity of flu symptoms.

Uncertainty in modeling of economic studies reviewed

According to sensitivity analyses in economic studies of NA-inhibitors, the proportion of ILI due to influenza viruses and the measure of health benefits in terms of "QALYs" per day dramatically changed the cost-effectiveness of NA-inhibitors. The base case analysis of commissioned reports provided by organizations that ought to inform health-care payers, i.e. the National Institute for Clinical Excellence (NICE) in the UK and the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) in Canada, included strikingly conservative estimates disfavoring NA-inhibitors.[40,47] The influenza-positive rate was fixed at 34% and 35%, based on surveillance data taken during flu epidemics, respectively, and the number of QALYs was extrapolated from 0.284 and 0.364 QALYs per day based on generic multi-attribute utility instruments, respectively (see **Table 2**).

Influenza-positive rates

As was reminded in the Introduction, influenza-positive rate depends crucially on several factors, including the method(s) used for diagnosis. Pooled results from randomized clinical trials of zanamivir, including 1033 patients with ILI, showed that influenza was identified in 56% of the cases by viral isolation, in 61% by serology and in 71% by RT-PCR, but the results from the three methods were shown to agree in only 67% of patients with ILI.[2] Surveillance data on influenza-positive rates usually rely on viral isolation and should be considered as low estimates during flu epidemics. On the other hand, clinical trials were selective of their patient populations and in practice, influenza-positive rates should be considered as high estimates during flu epidemics. In our opinion, the effectiveness of NA-inhibitors would be best assessed by surveillance systems that are based on similar methods for diagnosis than those used in

randomized clinical trials, although economic constraints could limit the use of a combination of two or more diagnostic methods.

Whatever the "true" influenza-positive rate fixed in base case analysis, a more specific clinical case definition of influenza did not really improve positive predictive value during flu epidemics. Cough and fever during the first 48 hours following disease onset were the best predictors of influenza infections in pooled results from randomized clinical trials of zanamivir,[58] but their positive predictive value of 79% should be compared to the influenza-positive rate of 66% in those trials, i.e. an absolute increase of positive predictive value of 13%. Interestingly, bedside Rapid Flu Tests , which should increase positive predictive values for diagnosing influenza, were consistently shown to not be cost-effective when compared to systematic treatment with NA-inhibitors during flu epidemics.

This emphasizes the fact that bedside Rapid Flu Test should not take the place of the necessary collection of clinical specimens of viral culture needed by influenza surveillance information systems. Systematic treatment by NA-inhibitors dominated a selective prescription based on tests during flu epidemics. The former strategy is possible only if influenza surveillance systems provide timely information on the beginning of flu epidemics, even if the end of the epidemics may be harder to make out. Although it is never done, the costs of surveillance systems should be taken into account in economic studies of NA-inhibitors.

Measure of effectiveness by QALYs or a willingness-to-pay approach

Major health outcomes assessed in populations at high risk of influenza-related complications,[29,40,46] are inapplicable to the otherwise healthy population, since influenza did not cause a significant excess of deaths among healthy people < 65 years (0.02 per 10,000 individual-months (95%CI: -0.01 to 0.05)),[59] nor a significant increase in the number of annual influenza-related hospitalizations of those at low risk (i.e., maximum of 11 hospitalizations per 10,000 individuals).[59] In the cost-effectiveness analyses reviewed, effectiveness was assessed by the number of flu days averted and often the recommended QALY approach.[56] These two measures are linked, since the health outcome depends on morbidity alone. In our opinion, the use of QALYs for short-term non-fatal diseases like ILI is problematic, since QALYs were constructed to assess the loss of quality of life in chronic diseases. The computation of QALYs gained by NA-inhibitors as a change in generic multi-attribute utility scores (i.e. EQ-5D, HUI3, QWB) with a secondary rescaling of QALYs gained over one year with previous instruments to one day for study purposes is not a validated method.[60] Moreover, small variations in QALYs at the denominator imply an implausibly huge variation of cost per QALY in sensitivity analysis. Finally, there is no consensus on the generic multi-attribute utility instrument to be used in economic evaluation of health interventions. The differences in instruments and sample surveyed explain the different utility weights shown in Table 2. Interested readers in that topic could refer to Hawthorne and Richardson's review.[61]

The failures of these recommended methods to measure effectiveness of NA-inhibitors in otherwise healthy adults and previous considerations of the relevance of cost-benefit analysis for the evaluation of NA-inhibitors favor willingness-to-pay for a day of flu symptoms averted as a

measure of health benefits.[62] Two economic studies in our review involved median willingness-to-pay estimates for one day of symptom relief, i.e. US\$ 15.49 in a conjoint analysis with 210 patients without ILI and seeking medical care,[34] and FF 198 (US\$ 30 ; 95%CI: 26 to 36) in a contingent valuation with 172 patients with ILI during the 1999-2000 flu epidemic.[51] The willingness-to-pay for flu vaccination was also recently tested.[63]

The opportunity cost of antibiotic use in patients with ILI

NA-inhibitors during flu epidemics prevented secondary infectious complications,[53] and thus reduced antibiotic use and follow-up visits in economic studies. However, this approach does not consider the unnecessary antibiotics prescribed to meet the expectations of patients with ILI, i.e. those given to about 50% of healthy patients visiting a physician in Europe,[14,64] and the US.[65] Transforming these prescriptions for antibiotics to prescriptions for NA-inhibitors (rather than an overoptimistic crude decrease in antibiotics) should contribute to an overall decrease in antibiotic use --an important public health goal if we are to reduce the emergence and spread of antibiotic-resistant bacteria.[66,67] As recently stated, antibiotic treatment of adults with nonspecific upper respiratory tract infection is not recommended.[68,69] Economic methods are currently lacking to account for the opportunity cost of unjustified antibiotic use with possible emergence of resistance and future decrease in antibiotic effectiveness in justified indications.[70,71] However, we believe that the benefits associated with NA-inhibitors instead of unjustified antibiotic prescriptions should be substantial.

Acceptance of annual flu shots in the otherwise healthy population

Head-to-head comparisons of NA-inhibitors and annual vaccination showed that vaccination was a dominant option in both the at-risk adult population[29] and the otherwise healthy population.[34,48] However, these two latter economic studies assumed that the annual vaccine acceptance rate would be 100% in the otherwise healthy population. Therefore, the costs of campaigns to promote and implement flu vaccination were reduced to those related to the administration of vaccine. However, the vaccination coverage rate in the at-risk population, already targeted by flu vaccination for a decade, has shown that adults < 65 years are less likely to be vaccinated than those over 65 (e.g. 30% and 66% in 2000 in the US, respectively).[18] In a recent review, the perceived effectiveness of the vaccine and having received the vaccine the previous year were consistent positive predictors of vaccine acceptance among healthy adults.[72] On the other hand, almost 60% of the 370 employees surveyed at a corporate workplace declined flu shots for the following reasons: perceived likelihood of getting the flu is low (30%) and perceived likelihood of reaction to the shot is high (38%).[72] In our opinion, flu vaccination campaigns are necessary to reach the level of coverage at which benefits from herd immunity could be achieved, e.g. the 60% goal in the US at-risk population in 2000.[18] Flu vaccination campaigns are surely associated with increasing marginal costs that should be added to the vaccination strategy. As patient financial incentives like reductions in patient payment or copayment are significantly associated with the use of influenza vaccination,[73] the question of who will pay for flu vaccination campaigns remains.

Additional economic studies are needed

As outlined in the previous chapter on the major uncertainty surrounding some of the model parameters, additional studies are needed to reduce the gap between knowledge and decision. Models should also be validated by observational economic studies designed to compare NA-inhibitors and vaccination strategies in the workplace and to account for year-to-year variations in ILI attack rates, ILI severity, and vaccine efficacy.

Whereas the costs incurred by patients with ILI are substantial, no economic study evaluated strategic options specifically dedicated to patients suffering from ILI, e.g. over-the-counter NA-inhibitors without physician visit,[74] Rapid Flu Test and physician visit if the test is positive (the test requires 15 to 20 minutes for completion and that is too long), and in-house prevention of influenza transmission.[27,28]

MARKET SIZE AND MARKET SHARE OF NA-INHIBITORS

Wall Street has essentially written off NA-inhibitors and anti-influenza drugs in general, due to poor sales of oseltamivir (Tamiflu®) and zanamivir (Relenza®) since their 1999 launch. With sales unable to top the US\$100 million mark, NA-inhibitors are viewed as disappointments to Roche and GlaxoSmithKline. Oseltamivir (Tamiflu®) has led the world market of NA-inhibitors since 1999, although its approval was delayed in Japan and Europe. Sales of Tamiflu® increased by 50% from 1999 (\$ 38 million) to 2001 (\$ 58 million). \$ 36 million sales have already been reported for the first semester of 2002.

FIVE-YEAR VIEW

We believe that the NA-inhibitor market is still immature and that it should grow continuously over the next five years. First, all influenza seasons have been mild to moderate in the United States, Japan and European countries since the 1999 launch of NA-inhibitors. A severe flu season, or a season marked by the introduction of a new strain not anticipated by vaccine developers, could significantly and rapidly increase the market potential of NA-inhibitors. Second, Tamiflu®, the world leader of NA-inhibitors, has only recently been marketed on the Japanese and European markets (2001 and 2002, respectively). In Japan particularly, upper respiratory infections are perceived as more serious than in the West, and the vaccination coverage rate decreased abruptly in the last decade due to a side effect scare in children and economic studies suggesting low cost-effectiveness of vaccination.[22] Third, indications of NA-inhibitors may be extended to prophylaxis in adults and adolescents (approval for Tamiflu® in 2002), at-risk unvaccinated population (randomized controlled trials are on-going in the at-risk population or with patients with influenza-related hospitalization, and e.g., the National Institute For Clinical Excellence (NICE) in UK has reversed an earlier decision and now recommends the use of NA-inhibitors in the at-risk population following Burls et al.[40]). Moreover, NA-inhibitors represent one of the first-line antiviral drugs in case of an influenza pandemic. WHO has recommended national authorities and vaccine manufacturers to consider developing plans for ensuring the availability of antivirals (<http://www.who.int/emc/diseases/flu/whoguidelines.htm>). Finally, a third NA-inhibitor, peramivir, should be available in 2003. Peramivir is designed for once daily oral administration, making peramivir potentially more convenient for patients. A second generation NA-inhibitor is also in progress (developed by Biota & GlaxoSmithKline).

We believe that the point of view on NA-inhibitors will move from a vaccination challenger to a complementary option of vaccination. The current point of view may be related to the situation in the at-risk population, in which annual flu vaccination is a consensual strategy, and NA-inhibitors were not seen favorably during their 1999 launch. Current developments showing the efficacy of NA-inhibitors as a complementary option of vaccination in the at-risk population, and the economic dominance of flu vaccination plus NA-inhibitors over flu vaccination alone or NA-inhibitors alone in the otherwise healthy population, should help us take a calmer view of NA inhibitors in times to come.[30-34]

KEY ISSUES

- Ten economic evaluations of neuraminidase inhibitors to control influenza in adults are reviewed. NA-inhibitors result in 1) health benefits measured by days of flu symptoms averted, QALYs gained or intangible benefits measured by the willingness-to-pay for a day of symptoms averted; 2) reduction of medical costs by decreasing secondary infectious complications and related antibiotic use; 3) productivity gains.
- Flu vaccination dominated NA-inhibitors (3 studies), systematic treatment by NA-inhibitors of consulting patients with influenza-like illness dominated a selective drug prescribing strategy based on Rapid Flu Test results during flu epidemics (4 studies). With the health-care payer perspective that includes only medical costs, NA-inhibitors were not cost-effective in otherwise healthy adults, but the cost-effectiveness ratio decreased substantially when all adults, including the at-risk population, were included (3 studies).
- Choice of key parameter estimates were sensitive to the perspective of analysis with conservative estimates disfavoring NA-inhibitors from the health-care payer perspective, e.g., the proportion of influenza-like illness due to the influenza virus targeted by neuraminidase inhibitors varies from 34% to 70%.
- Cost-benefit analysis is advocated for the evaluation of NA-inhibitors in the otherwise healthy population due to difficulties in measuring QALYs gained, and because a willingness-to-pay approach, i.e. wtp for a day of symptoms averted, is more convenient.
- The opportunity cost of unjustified antibiotic use in influenza-like illness is not valued.
- A future reduction in neuraminidase inhibitor efficacy related to the development of neuraminidase inhibitor-resistant influenza viruses should be watched out for.

- We recommend a cautious analysis of published economic evaluations of NA-inhibitors compared to annual influenza vaccine in the otherwise healthy population, given the fact that increasing marginal costs of vaccination are not taken into account.
- Annual flu vaccination and NA-inhibitors should be seen as complementary options rather than competing ones.

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Table 1: Neuraminidase inhibitors

Name	Zanamivir	Oseltamivir	Peramivir
Drug name	GG167	GS4104	BCX-1812 (formerly RWJ270201)
Proprietary name	Relenza	Tamiflu	-
Manufacturers	Biota & GlaxoSmithKline	Gilead & Hoffman-La Roche	BioCryst (partnership dissolved with Johnson & Johnson in 2001)
First approval in USA	1999	1999	ND
First approval in Japan	2000	2001	ND
First approval in European Union	1999	2002	ND
Indications in 2002:			
- treatment of influenza A and B in adults	Yes	Yes	-
- treatment of influenza A and B in children	> 7 years	> 1 year	-
- prevention of influenza A and B in adults and adolescents	No	Yes	-
Key features differentiating NA inhibitors:			
Route of administration	Dry power self-administered via oral inhalation	Oral capsule or suspension form	Oral
Recommended daily dosage	10 mg twice daily	75 mg twice daily (once daily if prevention)	Once daily
Adverse effects compared to a placebo in randomized controlled trials	No increase (each adverse event <5%)	Nausea and vomiting more frequent in adults and children (1% discontinued)	No increase expected
Limitation of usage	Patients with underlying airway disease	No	No
Post-treatment isolates with decreased susceptibility	No (but the number of tests is limited)	1.3% after >13 years to 8.6% among 1-12 years	-
Price in USA	44.40 \$	55.13\$	-
Price in UK	24 pounds	-	-
Price in France	22.4 euros	30 euros	-

Table 2: Economic evaluations of systematic prescription of NA inhibitors (all costs are rounded to US\$)

Study	Country setting	Analysis viewpoint	Type of economic evaluation	Key base case parameters									NA inhibitors are recommended (and reason why?)
				NA inhibitors considered	Alternative strategy other than doing nothing	Population	Influenza infections, %	Health benefits per avoided day of flu symptoms	Median earnings for one day, US\$	Cost per day of symptoms averted, US\$	Cost per QALYs gained, US\$		
Mauskopf Pharmacoconomics 2000	Australia 1998	Health-care payer	CEA	zanamivir	-	At-risk	70	QWB: 0.0012 QALY experts	-	8	6500	Yes (CEA threshold of 44000\$/QALY)	
Burls HTA 2002 (report to NICE 2000)	UK 2000	Health-care payer	CEA	zanamivir	-	At-risk and all adults	34	EQ-5D: 0.0008 QALY experts	-	80 (all adults) or 66 (at-risk population)	102000 (all adults) or 85000 (at-risk population)	No in all-adults ; Possibly in at-risk population (poor value for money)	
Brady 2001 (report to CCOHTA)	Canada 2000	Health-care payer (and societal)	CEA	zanamivir	-	At-risk and all adults	35	HUI3: 0.0001 11 adults without ILI	50	93 (all adults) or 77 (at-risk population)	95000 (all adults) or 77500 (at-risk population)	No (poor value for money)	
Blitz Am J Manag Care 2002	USA	Health-care payer	CEA	zanamivir	RFT	Otherwise healthy adults	25- 50- 75- 100	-	-	200\$- 100\$ - 67\$- 50\$ tested	-	Up to the decision maker WTP (systematic zanamivir dominant strategy)	
Lee Ann Intern Med 2002	USA 2001	Societal	CBA	zanamivir, oseltamivir	Vaccination alone, vaccination and antiviral	Otherwise healthy adults	*	WTP: \$ 15.49	142	Net benefit with zanamivir (1.97\$), net costs with oseltamivir (-0.032\$)	-	No (vaccination and antiviral preferred in 80% Monte Carlo simulations; vaccination alone in 15%; NA-inhibitors alone in 2%)	
Muenning CID 2001	USA 2000	Societal	CEA	oseltamivir	Vaccination alone	Otherwise healthy adults	*	QWB:0.0011 QALY experts	Caregiving costs 54	-	27619\$	No (vaccination alone results in savings)	
Smith Am J Med 2002	USA 2000	Health-care payer and societal	CEA	zanamivir	RFT	All adults	59,6	0.0004 QALY Sackett D. J Chron Dis 1978	108	60 (M2 inhibitors not considered)	25000 (M2 inhibitors not considered)	Yes (dominant strategy)	
Schwarzinger Options for the Control of Influenza	USA 1999	Societal	CBA	zanamivir oseltamivir	RFT	Otherwise healthy adults	66	-	135	Net benefit with zanamivir (29.8\$)	-	Yes (dominant strategy)	

2000

Schwarzinger MD thesis 2001	France 1999	Societal	CBA	zanamivir	RFT	Otherwise healthy adults	56	WTP: \$ 30	105	Net benefit with zanamivir (26\$)	-	Yes (dominant strategy)
Scuffham Vaccine 2002	UK, France, Germany	Health-care payer	CEA	NA-inhibitors	vaccination alone, chemoprophylaxis	Elderly population	*	Days of morbidity avoided	-	568 Euros in UK, 41 Euros in France, 371 Euros in Germany	-	No (vaccination alone results in savings in UK, and is dominant in France and Germany)

* ILI attack rate is specified but not proportion of influenza infections. However, effectiveness of NA-inhibitors rely on intention-to-treat analysis from RCT.

CBA: Cost-benefit analysis; CEA: Cost-effectiveness analysis; RFT: Rapid Flu Test; QWB: Quality of Well-Being; EQ-5D: EuroQol; HUI3: Health Utility Index

WTP: Willingness-to-pay for 1 day of symptom relief