Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

The influenza virus causes an acute, febrile, respiratory illness. Outbreaks follow a seasonal pattern, concentrated in winter, and vary in distribution and severity between years. Symptoms include fever, cough, nasal congestion, headache, sore throat, fatigue, and joint and muscle aches. In otherwise healthy people, symptoms are usually self-limiting. However, in vulnerable people, such as the elderly, chronically ill or immunocompromised, the illness may be prolonged and the development of serious complications more common. In England and Wales, influenza is thought to be responsible for over 10,000 deaths from respiratory disease annually.

For periods in which influenza is reported to be 'circulating in the community', existing National Institute for Health and Clinical Excellence (NICE) guidance recommends the use of antiviral treatment (either oseltamivir or zanamivir) only in 'at-risk' populations as defined by the Department of Health in the *Green Book*. Since this guidance was issued, the marketing authorisation for zanamivir has been extended to include children aged 5 years and over. This review provides an updated assessment of the evidence for the clinical effectiveness and cost-effectiveness of antivirals (oseltamivir, zanamivir and amantadine) for the treatment of influenza.

Objectives

The objective of this review is to evaluate the clinical effectiveness (including adverse events) and cost-effectiveness of antivirals for the treatment of naturally acquired influenza. This evaluation considers these issues for at-risk and otherwise healthy populations.

It is important to note that this health technology assessment was carried out to address the use of antiviral treatments for influenza within the context of a seasonal outbreak, not a pandemic.

Methods

Systematic reviews of the evidence on the clinical effectiveness and cost-effectiveness of antivirals for the treatment of influenza were undertaken. In addition, an independent decision model was developed to evaluate the cost-effectiveness of antiviral treatment from the perspective of the UK NHS. Data for the review were sought systematically from 11 electronic databases [MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Pascal, Science Citation Index (SCI), BIOSIS, Latin American and Caribbean Health Sciences (LILACS), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database], including those specific to adverse event data (TOXLINE), and the grey literature [Inside Conferences, Dissertation Abstracts, ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, Clinical Trial Results, World Health Organization International Clinical Trials Registry Platform (ICTRP), GlaxoSmithKline Clinical Trials Register, and Roche Clinical Trial Protocol Registry and Results Database]. The searches covered the time since those conducted for the original guidance, October 2001 to November 2007. A supplementary search was undertaken in June 2008 for information relating to drug resistance during the 2007–8 influenza season. In addition, trial reports and extra data were provided by GlaxoSmithKline (zanamivir) and Roche (oseltamivir).

Randomised controlled trials (RCTs) comparing antivirals with each other, placebo, or best symptomatic care were included in the evaluation of clinical effectiveness in patients presenting with an influenza-like illness (ILI). Standard meta-analytic techniques were applied to data stratified by the following patient groups: otherwise healthy adults, 'at risk', the elderly, children, and the overall population. The primary outcomes considered were measures of symptom duration (median time to alleviation of

symptoms and median time to return to normal activity). Incidence of complications, mortality, hospitalisations, antibiotic use (as a surrogate for complications) and adverse events was also assessed. Pooled odds ratios or weighted median differences, with 95% confidence intervals, were estimated. Analyses were carried out for both the intention to treat (ITT) and the intention to treat, confirmed, influenza-infected (ITTI) populations whenever possible.

In the absence of head-to-head evidence on the relative effectiveness of the alternative antiviral treatments, an indirect comparison was also undertaken using Bayesian approaches to characterise the joint distribution of the efficacy of the antiviral treatments in terms of symptom duration. These estimates were subsequently used to inform the independent economic model, which provided an overall framework for combining data from the synthesis of symptom outcomes with the wider data on complications and other relevant parameters required for cost-effectiveness considerations.

The economic model evaluated the cost-effectiveness of oseltamivir and zanamivir for the treatment of influenza compared with standard care without antiviral treatment. The evaluation was undertaken for individuals presenting to a health-care provider who were also considered eligible for treatment according to the respective licences for each of the neuraminidase inhibitors (NIs). The model considered events within a single influenza season with a lifetime horizon employed to appropriately quantify lost quality-adjusted life-years (QALYs) associated with premature mortality due to complications. Costs were assessed from the perspective of the NHS and Personal Social Services (NHS and PSS), expressed in pounds sterling at a 2006–7 price base. The costs included both the acquisition costs of the NIs themselves and the costs of managing secondary complications. Outcomes were evaluated using QALYs (based on symptom duration), complications and premature mortality due to secondary complications. Results from a 'base-case' analysis were presented alongside a broad range of scenarios considering alternative assumptions.

Cost-effectiveness estimates for influenza treatment were presented for five separate subgroups: (1) otherwise healthy children aged 1–14 years, (2) at-risk children aged 1–14 years, (3) otherwise healthy adults aged 15–64 years, (4) at-risk adults aged 15–64 years and (5) the elderly (aged 65 years or over). No separate analyses were presented for an at-risk elderly population, as age itself is considered a risk factor according to existing definitions for at-risk groups. Consequently, all subjects aged 65 years or over were considered together, regardless of whether or not other pre-existing comorbidities were present.

Results

Clinical effectiveness results

Literature searches yielded 1061 references, and 100 potentially relevant full papers were retrieved and screened. Amantadine was excluded at an early stage of the review owing to a lack of any new trials that met the inclusion criteria and the limitations of the existing evidence. The earlier review noted both the poor quality of amantadine trial data and its lack of comparability with other antiviral treatments; this was reflected in the previous NICE guidance which did not recommend amantadine for the treatment of influenza. This review therefore focused on the NIs, oseltamivir and zanamivir.

Twenty-nine RCTs were included in the final assessment of clinical effectiveness. Fourteen of these were additional to those considered in the previous review: six of zanamivir (three in healthy adults, one in the elderly, one in at-risk adults and one in children, which included a minority of at-risk participants) and eight of oseltamivir (four in healthy adults, one in an at-risk population of undefined age, one in at-risk children and two in adult populations, which included both healthy and at-risk individuals). The RCTs included were of variable quality and the completeness of follow-up was an issue in many; despite the trials' short duration (up to 28 days), only half of the studies achieved follow-up of at least 95% of the participants.

Both zanamivir and oseltamivir were found to be effective in reducing symptom duration, as measured by time to alleviation of symptoms and/or time to return to normal activity; however, the effect sizes were often small and unlikely to be clinically significant in many cases, particularly in healthy adults.

In healthy adults, zanamivir reduced the median duration of symptoms by between approximately 0.5 and 1 day and oseltamivir by between 0.5 and 1.5 days; the median reduction in the time taken to return to normal activity was about 0.5 days with

zanamivir and approximately 1.5–2.5 days with oseltamivir.

For the at-risk subgroups, effect sizes for differences in symptom duration were generally larger, and potentially more clinically significant, than those seen in healthy adults. However, there was greater uncertainty around these results, with estimates often failing to reach statistical significance. For the overall at-risk population, treatment reduced the median duration of symptoms by approximately 1–2 days with zanamivir, and by 0.50–0.75 days with oseltamivir. A similar pattern was seen in the time taken to return to normal activity, with the median reduction being between 1 and 2 days with zanamivir and 0.75 and 2.50 (data for at-risk adults only) days with oseltamivir.

As might be expected, estimates derived from ITTI populations generally produced greater reductions than those from ITT populations. Similarly, the time to return to normal activities was generally longer than the time to the resolution of symptoms.

Estimates of clinical effectiveness in reducing symptoms derived from the standard meta-analysis were broadly consistent with the results derived from the Bayesian synthesis. However, the 'borrowing of strength' and consideration of the number still ill at the end of follow-up increased the precision of the subsequent estimates of effect sizes derived from the multiparameter synthesis model in specific populations (particularly at-risk populations). Across both symptom measures and populations, the probability that NI treatment was more effective than placebo was 100%. In otherwise healthy adults, oseltamivir consistently had a higher probability of success; however, in at-risk populations, zanamivir was consistently more successful. The results for the otherwise healthy children were more varied across the separate analyses due to more limited data being available. However, the strength of these findings needs to be considered in relation to the indirect nature of these comparisons and the clinical (and biological) plausibility of these results.

When data were available for adverse events and complication rates, there was little overall difference associated with the use of either zanamivir or oseltamivir when compared individually with placebo. However, data were reported for few trials, studies were not designed to detect changes in these outcomes, and the numbers of events were generally very small. The most consistent data and strongest evidence related to antibiotic use, with both zanamivir and oseltamivir resulting in statistically significant reductions in antibiotic use.

Cost-effectiveness results

The results from the cost-effectiveness model demonstrated important variation across the separate populations in terms of the cost-effectiveness estimates. In general, the estimates were more favourable in at-risk populations (including adults and children with comorbid conditions and the elderly) compared with otherwise healthy populations. Within each of the separate at-risk populations considered, zanamivir appeared to be the optimal NI treatment based on cost-effectiveness considerations. In contrast, oseltamivir was considered the optimal NI treatment for healthy populations (both adults and children). However, the overall differences between the NIs, in terms of the absolute estimates of both costs and outcomes, were minor across all populations.

The overall conclusions and cost-effectiveness estimates in the at-risk populations appeared remarkably robust to a wider range of alternative assumptions. The cost-effectiveness results for the otherwise healthy populations were less robust to these alternative assumptions with many scenarios reporting incremental cost-effectiveness estimates of over £20,000 per QALY.

Discussion

The clinical effectiveness data for population subgroups, used to inform the multiparameter evidence synthesis and cost-effectiveness modelling were, in places, limited and this should be borne in mind when interpreting the findings of this review. Trials were often not designed to determine clinical effectiveness in population subgroups and hence, although the direction of effect was clear, estimates of differences in symptom duration tended to be subject to greater uncertainty in subgroups. This limitation was more apparent for data on the rates of complications: studies with sample size and duration not designed to detect these outcomes resulted in low event rates and relatively weak evidence, even when available data were combined in meta-analyses. However, despite these concerns, the use of NIs in at-risk populations appeared to be a cost-effective approach to the treatment of influenza.

The main areas of outstanding uncertainty are:

- the impact of NI treatments on the rates of complications, hospitalisation and mortality associated with influenza
- the uncertainty surrounding the effect size of antiviral drugs in at-risk populations
- the relative effectiveness of the separate NIs
- the probability that a patient presenting to a health-care provider has true influenza as opposed to another ILI and the impact of this upon clinical and cost-effectiveness of NIs
- the impact on quality of life of influenza symptoms and the relative effect of NI treatments on this aspect.

A well-designed, adequately powered head-to-head trial (with a placebo arm), in a representative at-risk population (with sufficient follow-up time to also evaluate complications) would reduce the uncertainty around the estimates of clinical effectiveness of antiviral drugs in this population. However, the conduct of such a trial would need to be carefully assessed in terms of the cost-effectiveness of the research itself, as well as the potential feasibility and ethical issues (i.e. the inclusion of a placebo arm) which may arise. Well-designed observational studies might also be considered to evaluate the clinical course of influenza in terms of complications, hospitalisation, mortality and quality of life, as well as the impact of NIs.

Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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