

Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Influenza is an acute, febrile illness caused by infection of the respiratory system by the influenza virus. The illness is usually self-limiting in otherwise healthy people. In individuals considered to be at high risk, such as those aged over 65 years or having concomitant disease, it carries the risk of increased morbidity, potentially serious complications and mortality. A Health Technology Assessment of amantadine, oseltamivir and zanamivir for the prophylaxis of influenza was reported earlier by Turner and colleagues. Since that review, the marketing authorisation for zanamivir has been extended to include intervention in the prophylaxis of influenza as well as in its treatment. This report presents an updated assessment of new and existing evidence for the clinical effectiveness and cost-effectiveness of amantadine, oseltamivir and zanamivir in the prevention of influenza.

Objectives

To evaluate the clinical effectiveness of amantadine, oseltamivir and zanamivir in seasonal and post-exposure prophylaxis against influenza and to estimate the incremental cost-effectiveness of the above interventions in comparison with each other and no prophylaxis.

Methods

A systematic review was undertaken and an independent health economic model developed, based on a detailed review of existing cost-effectiveness models together with ongoing clinical advice. The model draws together a broad spectrum of evidence relating to the costs and consequences associated with influenza and its prevention. Importantly, where direct evidence concerning the effectiveness of prophylaxis within specific model subgroups is lacking, the model uses effectiveness estimates from mixed subgroups (e.g. effectiveness of oseltamivir and zanamivir as post-exposure prophylaxis taken from studies of households of mixed composition) or extrapolates from other mutually exclusive subgroups (e.g.

effectiveness of seasonal prophylaxis using amantadine in adults assumed to be the same in children and elderly individuals). Cost-effectiveness estimates are presented according to subgroups distinguished by age, risk status and vaccination status. For the purposes of the model, 'at-risk' is defined as the presence of an underlying medical condition; this definition may not necessarily coincide with Department of Health definitions of target groups for vaccination (for example, an otherwise healthy adult working in a hospital setting may be eligible for influenza vaccination).

Results

Clinical effectiveness

Twenty-six published references relating to 22 randomised controlled trials (RCTs) were included in the clinical effectiveness review. An additional unpublished report was included in the assessment, giving a total of 23 RCTs. Eight, six and nine RCTs were included for amantadine, oseltamivir and zanamivir respectively. The quality of the studies identified was highly variable and gaps in the evidence base limited the assessment of the clinical effectiveness of the interventions across population subgroups and settings.

Seasonal prophylaxis

Evidence for the use of amantadine in prophylaxis was very limited and drawn from older research of relatively poor quality. Evidence was presented for its efficacy in preventing symptomatic, laboratory-confirmed influenza (SLCI) in seasonal prophylaxis in healthy adults [relative risk (RR) = 0.40, 95% confidence interval (95% CI) 0.08–2.03]. Oseltamivir was effective in preventing SLCI, particularly when used in seasonal prophylaxis in at-risk elderly subjects (RR = 0.08, 95% CI 0.01–0.63). The preventative efficacy of zanamivir in seasonal prophylaxis was most notable in at-risk adults and adolescents (RR = 0.17, 95% CI 0.07–0.44) and healthy and at-risk elderly subjects (RR = 0.20 (95% CI 0.02–1.72)

Post-exposure prophylaxis

Again, very few data were available for the use of amantadine in post-exposure prophylaxis

and were taken from older research of lower quality. A relative risk of 0.10 (95% CI 0.03–0.34) for the prevention of SLCI in adolescents by post-exposure prophylaxis with amantadine was reported. Oseltamivir was effective in post-exposure prophylaxis within households of mixed composition (RR = 0.19 (95% CI 0.08–0.45), and the efficacy of zanamivir in post-exposure prophylaxis within households was also reported (RR = 0.21 (95% CI 0.13–0.33)). Interventions appeared to be well tolerated, with a relatively low occurrence of subjects experiencing drug-related adverse events and withdrawals. Very limited evidence was available for their effectiveness in preventing complications and hospitalisations and in minimising length of illness and time to return to normal activities. No data were identified for health-related quality of life or mortality outcomes.

Cost-effectiveness

Seasonal prophylaxis

In healthy children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £44,000 per quality-adjusted life-year (QALY) gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be around 0.97.

In at-risk children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £17,000 per QALY gained for unvaccinated at-risk children, and in previously vaccinated at-risk children greater than £50,000 per QALY gained. Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that oseltamivir is optimal in unvaccinated at-risk children is expected to be approximately 0.70, and assuming a threshold of £30,000 per QALY gained, the equivalent probability is around 0.94. For previously vaccinated at-risk children, the probability that no prophylaxis is optimal at £30,000 per QALY gained is 0.97 or higher.

In healthy adults

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected

to be greater than £148,000 per QALY gained, irrespective of vaccination status. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is close to 1.0.

In at-risk adults

Based on the current list price for zanamivir, both amantadine and zanamivir are ruled out of the analysis. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £64,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is close to 1.0. When the proposed price reduction for zanamivir is incorporated, the incremental cost-effectiveness of zanamivir versus no prophylaxis is expected to be around £53,000 per QALY gained in unvaccinated at-risk adults and £157,000 in previously vaccinated at-risk adults. The incremental cost-effectiveness of oseltamivir is likely to be around £108,000 per QALY gained in unvaccinated at-risk adults and around £314,000 in previously vaccinated at-risk adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be 0.99 or higher.

In healthy elderly

Amantadine and zanamivir are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in healthy elderly individuals is expected to be greater than £50,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be close to 1.0.

In at-risk elderly

Amantadine and zanamivir are expected to be extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in at-risk elderly individuals is expected to be greater than £38,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be around 0.77 or higher.

Simple sensitivity analysis suggests that the cost-effectiveness of seasonal prophylaxis is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk

of hospitalisation in uncomplicated cases, and the discount rate.

Post-exposure prophylaxis

In healthy children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated healthy children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be £19,000–£23,000 per QALY gained, depending on the list price for zanamivir, and for vaccinated healthy children at least £59,000 per QALY gained. Based on the current list price for zanamivir, the probability that zanamivir is optimal in unvaccinated healthy children is expected to be 0.15 and 0.45 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is incorporated, the equivalent figures are expected to be 0.47 and 0.79 respectively. For the vaccinated subgroup, the probability that no prophylaxis is optimal at a threshold of £30,000 per QALY gained is expected to be close to 1.0.

For children under the age of 5 years, oseltamivir is the only licensed antiviral prophylaxis. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £24,000 and £74,000 per QALY gained in unvaccinated and vaccinated groups respectively.

In at-risk children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated at-risk children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8000 per QALY gained at the current list price, and around £6000 per QALY gained when the proposed price reduction for zanamivir is assumed. For vaccinated at-risk children, the equivalent figures are expected to be around £28,000 and £23,000 respectively. Based on its current list price, the probability that zanamivir is optimal in unvaccinated at-risk children is expected to be 0.67 and 0.73 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the probability that zanamivir is optimal is expected to be 0.85 at both thresholds. Based on the current list price for zanamivir, the probability that it is optimal in vaccinated at-risk children is expected to be 0.08 and 0.31 at willingness

to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the equivalent figures are expected to be 0.26 and 0.65 respectively.

For at-risk children under the age of 5 years, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £9000 and £29,000 per QALY gained for unvaccinated and vaccinated at-risk children respectively.

In healthy adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated healthy adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £34,000 per QALY gained, and for previously vaccinated healthy adults around £104,000 per QALY gained. The probability that oseltamivir is optimal in unvaccinated otherwise healthy adults is expected to be around 0 and 0.19 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively, and for healthy adults who have previously been vaccinated close to zero at a threshold of £30,000 per QALY gained.

In at-risk adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is around £13,000 per QALY gained, and for previously vaccinated at-risk adults around £44,000 per QALY gained. Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated at-risk adults is expected to be 0.89 and 0.84 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. The probability that oseltamivir is optimal in previously vaccinated at-risk adults is below 0.05.

In healthy elderly

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £11,000 per QALY gained, and for previously vaccinated healthy elderly individuals around £28,000 per QALY gained. Based on the current list price

for zanamivir, the probability that oseltamivir is optimal in unvaccinated healthy elderly individuals is expected to be 0.87 and 0.82 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. For previously vaccinated healthy elderly individuals, the equivalent figures are expected to be 0.09 and 0.50 respectively.

In at-risk elderly

Amantadine and zanamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8000 per QALY gained, and for vaccinated at-risk elderly individuals around £22,000 per QALY gained. Based on its current list price, the probability that oseltamivir is optimal in unvaccinated at-risk elderly individuals is expected to be around 0.83 and 0.77 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. For vaccinated at-risk elderly individuals, the equivalent figures are 0.35 and 0.78 respectively.

The simple sensitivity analysis suggests that the cost-effectiveness of post-exposure prophylaxis is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, and the comparative efficacy of oseltamivir and zanamivir, the efficacy of influenza vaccination, multiple prescribing of prophylaxis to contact cases, the risk of hospitalisation in uncomplicated cases, and the discount rate.

Discussion and conclusions

The clinical effectiveness data used in the cost-effectiveness modelling was limited for a number of population subgroups. This must be borne in mind in the interpretation of the findings. Additional consideration should be given to the occurrence of adverse events attributable to amantadine and the issue of resistance to antivirals among influenza isolates, which, although not directly reflected within the trials identified for inclusion, are factors that may have an important influence on the effectiveness of antiviral prophylaxis in clinical practice. Variation in the levels of resistance to antivirals among influenza isolates was taken into account in the cost-effectiveness analysis. Although the base case assumes oseltamivir resistance to be zero, multiple sensitivity analyses were undertaken in order to assess the impact of variation in levels

of resistance amongst influenza strains to the interventions under study. It should be noted that in the 2 weeks preceding completion of this report, the Health Protection Agency issued a press release stating that approximately 5% (8/162) of H1N1 influenza tested isolates were resistant to oseltamivir. Further research is required to assess the impact of this resistance. Sensitivity analysis suggests that low levels of resistance are likely to have a minor impact upon the cost-effectiveness of oseltamivir. However, increasing levels of resistance could dramatically influence the conclusions of the economic analysis. It is centrally important that the results of the economic analysis are interpreted in the light of current levels of influenza activity and resistance.

A number of uncertainties are apparent within the evidence base, including variation in the quality of trials in terms of internal and external validity, study design and clarity of reporting. The absence of head-to-head RCTs meant that a direct comparison of the effectiveness of the interventions was not possible. These weaknesses are directly relevant to the interpretation of the health economic model results and rendered the use of more advanced statistical analyses inappropriate. A central area of uncertainty is the paucity of robust preference-based valuations of the impact of influenza and influenza prophylaxis on health-related quality of life.

Several areas warrant further research:

- additional RCTs of influenza prophylaxis in subgroups for which data are currently lacking
- RCTs in which the follow-up period extends beyond the duration of prophylaxis
- head-to-head RCTs in which the clinical effectiveness of the interventions in different subgroups is directly compared
- quality of life studies to inform future economic decision modelling
- further research concerning the incidence and management of complications of influenza.

Publication

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NIHR Health Technology Assessment Programme

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