The prevention and treatment of influenza A and B

Systematic review and economic decision modelling for the prevention and treatment of influenza A and B

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Executive summary

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Executive summary

Objective

This study aimed to establish the clinical and cost-effectiveness of amantadine, oseltamivir and zanamivir for the treatment and prevention of influenza. The preventative strategies considered were amantadine, oseltamivir, zanamivir and vaccine, compared with no intervention. Vaccine was considered both on its own and in combination with amantadine, oseltamivir and zanamivir. The treatment strategies addressed were amantadine, oseltamivir and zanamivir compared with standard care. Four patient groups were considered: (i) children (aged ≤ 12 years); (ii) healthy adults (aged 12–65 years); (iii) 'high-risk' (aged ≥ 65 years and/or with concomitant disease); and (iv) elderly residential population.

Background

Influenza is a common condition affecting all age groups. For those individuals at 'high risk' (e.g. aged ≥ 65 years, or with concomitant disease such as chronic respiratory disease, diabetes or significant cardiovascular disease), influenza can cause serious complications and in some cases these complications lead to hospitalisation and even death. Current policy recommends that 'high-risk' individuals (as defined above) be vaccinated against influenza each year. For the 'otherwise healthy' individuals, influenza is usually considered to be a self-limiting illness with most symptoms alleviated within 1 week. Nevertheless, such individuals can still experience influenza complications and can inflict considerable costs on the economy through lost workdays.

Technologies

Amantadine (Lysovir or Symmetrel, Alliance Pharmaceuticals): licensed for prophylaxis use during an outbreak of influenza A, for persons aged ≥ 10 years and, more particularly, for certain groups (e.g. un-immunised, healthcare workers).

Oseltamivir (Tamiflu, Hoffman La Roche Pharmaceuticals): received US Food and Drug Administration approval in November 2000. Submitted to the Committee for Proprietary and Medicinal Products in February 2001 for the treatment of influenza A and B in adults and children and the prevention of influenza A and B in adolescents and adults.

Zanamivir (Relenza, GlaxoSmithKline Pharmaceuticals): licensed for the treatment of influenza A and B, for individuals aged ≥ 12 years, within 48 hours of onset.

Questions addressed by this review

1. To establish whether amantadine, oseltamivir and zanamivir are effective and cost-effective alternatives in the treatment of influenza types A and B (amantadine type A only) relative to the existing method of treatment (i.e. receiving either no treatment at all or antibiotics).
2. To establish whether chemoprophylactic use of oseltamivir and zanamivir are effective and cost-effective alternatives to the existing method of prevention (i.e. no intervention or vaccine).

Methods

A systematic review and meta-analysis of the randomised evidence was undertaken to investigate the effectiveness of oseltamivir and zanamivir for treatment and prophylaxis use for influenza A and B. Where necessary, pharmaceutical companies were contacted for additional information not available from the published literature. An additional systematic review of the effectiveness of amantadine for treatment and prophylaxis use for influenza A in children and the elderly was also undertaken.

Economic decision models were constructed to examine the cost-effectiveness and cost–utility of the alternative strategies for treating and preventing influenza A and/or B. This was informed by the systematic reviews outlined above and additional sources of information where required.

Effectiveness results

Oseltamivir

Treatment

Oseltamivir 75 mg twice daily for 5 days was found to reduce the median duration of symptoms in the influenza positive group by:

- 1.38 days (95% CI 0.80 to 1.96) for the otherwise healthy adult population
- 0.50 days (95% CI –0.96 to 1.88) for the high-risk population
- 1.5 days (95% CI 0.8 to 2.2) for the children population.

Prevention

Oseltamivir 75 mg once daily for 6 weeks was found to provide a relative risk reduction of developing influenza by between approximately 75 and 90% depending on the strategy adopted and the population under consideration.

Zanamivir

Treatment

Inhaled zanamivir 10 mg twice daily for 5 days was found to reduce the median duration of symptoms in the influenza positive group by:

- 1.26 days (95% CI 0.59 to 1.93) for the otherwise healthy adult population
- 1.99 days (95% CI 0.90 to 3.08) for the high-risk population
- 1.3 days (95% CI 0.3 to 2.0) for the children population (high-risk and otherwise healthy combined).

Prevention

Inhaled zanamivir 10 mg once daily for 6 weeks was found to provide a relative risk reduction of developing influenza by between approximately 70 and 90% depending on the strategy adopted and the population under consideration.

Economic evaluation

UK-based estimates of cost-effectiveness were derived using all data available.

Amantadine

Treatment

The incremental costs per quality-adjusted life-year (QALY) gained in the base-case treatment analysis of amantadine were:

- £6190 per QALY for the otherwise healthy adults population
- £4535 per QALY for the high-risk population
- £5057 per QALY for the residential population
- £6117 per QALY for the children's population.

Uncertainty analysis suggests a probability of approximately 60% of a cost per QALY below £30,000 for any of four populations considered.

Prevention

In the base-case prophylaxis analysis, amantadine prophylaxis was dominated by vaccination. For both amantadine and vaccination the incremental cost per QALY gained for the residential population was £28,920 compared with vaccine. For all of the remaining populations the incremental costs per QALY gained were much higher, ranging from £124,854 to £909,210. These values do not include a value for adverse events from taking amantadine; including adverse events would worsen the cost per QALY ratios. Probabilistic analysis suggests a probability of 45% for a cost per QALY below £30,000 for the residential population if the effect of adverse events is excluded. None of the other models had a probability >1% of a cost per QALY below £30,000.

Oseltamivir

Treatment

The incremental costs per QALY gained in the base-case treatment analysis of oseltamivir were:

- £19,015 per QALY for the otherwise healthy adults population
- £22,502 per QALY for the high-risk population
- £21,781 per QALY for the residential population
- £19,461 per QALY for the children population.

Uncertainty analysis suggests a probability between approximately 55% and 60% of a cost per QALY below £30,000 for any of four populations considered.

Prevention

In the base-case prophylaxis analysis, oseltamivir was dominated by vaccine. For both oseltamivir and vaccine the incremental cost per QALY gained for the residential population was £64,841 compared with vaccine. For all of the remaining populations the incremental costs per QALY gained were much higher, ranging from £251,004 to £1,693,168 per QALY. Uncertainty analysis suggests a probability of 3% of an incremental cost per QALY below £30,000 in the residential population. None of the other populations have a probability of >1% of an incremental cost per QALY below £30,000. ▶

Zanamivir

Treatment

The incremental costs per QALY gained in the base-case treatment analysis of zanamivir were:

- £31,529 per QALY for the otherwise healthy adults population
- £17,289 per QALY for the high-risk population
- £16,819 per QALY for the residential population
- £30,825 per QALY for the children population.

Uncertainty analysis suggests a probability between approximately 50% and 68% of a cost per QALY below £30,000 for any of four populations considered.

Prevention

In the base-case prophylaxis analysis, zanamivir was dominated by vaccine. For zanamivir in addition to vaccine the incremental cost per QALY gained for the residential population was £84,682 compared with vaccine. For all of the remaining populations the incremental costs per QALY gained were much higher, ranging from £324,414 to £2,188,039 per QALY. Uncertainty analysis suggests a probability <1% of a cost per QALY below £30,000 for all populations.

Vaccine

Prevention

The incremental cost per QALY gained in the base-case prophylaxis analysis of vaccine were:

- £10,184 per QALY for the otherwise healthy adults population
- £2333 per QALY for the high-risk population
- –£769 (cost saving) per QALY for residential population
- £5024 per QALY for the children population.

Sensitivity analysis

Sensitivity analyses showed the results to be highly sensitive to a number of model parameters.

Treatment model

- Mortality, hospitalisations, QALY values, the probability that influenza-like illness is influenza and the probability that patients receive treatments if presenting after 48 hours.

Prophylaxis model

- Attack rate, deaths, QALY value of a death.

Generally conclusions were not changed by varying model parameters

Analysis of cost-effectiveness

In all cases the cost-effectiveness ratios for vaccination were either low or cost-saving. In the base case the cost-effectiveness of antivirals was relatively unfavourable, there were scenarios relating to the elderly residential care model where antivirals as an additional strategy could be cost-effective.

Conclusions

The cost-effectiveness varies markedly between the intervention strategies and target populations. The effectiveness literature that was used to inform the economic decision model spans many decades and hence great caution should be exercised when interpreting the results of indirect intervention comparisons from the model. Further randomised trials making direct comparisons would be valuable to verify the findings from the model.

This study identified a number of areas where further research would be useful.

- Randomised trials making direct comparisons between the two NI drugs and with amantadine would aid the identification of the most appropriate drug treatment.
- More evidence is needed on the effectiveness of NIs for treatment in 'high-risk' individuals.
- More evidence is needed on the effectiveness of NIs in preventing influenza in elderly residential care settings.
- There is insufficient evidence on the effectiveness of antiviral drugs in decreasing hospitalisations and deaths. Because of the rarity of these events this information is most likely to be obtained from well-designed observational studies.
- There is a need for high quality-of-life data for estimating utilities in cost per QALY studies.
- Further appraisal and development of rapid diagnostic testing to evaluate the use of this technique alongside antiviral drugs.

Publication

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