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

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Three strategies for influenza A outbreaks in long-term care facilities (LTCFs) with high staff vaccination were compared:

- no prophylaxis;
- post-exposure prophylaxis with amantadine; and
- post-exposure prophylaxis with oseltamivir.

Prophylaxis lasted for 12 days. In addition, a strategy of rimantadine was evaluated in case it was available in Canada in the future.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The target population comprised a hypothetical elderly cohort living in Canadian LTCFs who received influenza vaccination. The cohort was followed from the start of the influenza A season.

Setting
The setting was an institution. The economic study was conducted in Canada.

Dates to which data relate

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A decision tree was used to evaluate the health outcomes and costs during a 30-day time horizon. The analysis began at the start of an influenza season, and only influenza A outbreaks were considered. Post-exposure prophylaxis was
initiated after an influenza outbreak, which was defined as three or more laboratory-confirmed influenza-like illness cases over a 48- to 72-hour period.

**Outcomes assessed in the review**

Input parameters for the model included:

- the probability of an outbreak,
- the risk of developing an influenza-like illness (ILI) if exposed to the influenza A virus,
- the development of resistance with amantadine,
- drug discontinuation due to adverse events,
- the development of severe complications or death, and
- the relative risk reduction of the active comparators.

**Study designs and other criteria for inclusion in the review**

No inclusion criteria for the studies were stated. The designs of the studies used ranged from randomised controlled trials (RCTs) to case series.

**Sources searched to identify primary studies**

Not reported.

**Criteria used to ensure the validity of primary studies**

Not stated.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

Fifteen studies were included as sources of effectiveness evidence.

**Methods of combining primary studies**

A narrative method was used to combine the primary studies.

**Investigation of differences between primary studies**

No differences between the primary studies were investigated.

**Results of the review**

The parameters used for the base-case analysis included:

- a 40% probability of an outbreak in the LTCF,
- a 17% risk of developing an ILI if exposed to the influenza A virus,
a 24% probability of resistance with amantadine,
9.8% drug discontinuation due to adverse events with amantadine and 2% with oseltamivir,
20% development of severe complications if ILI,
11% death if ILI, and
a 60% relative risk reduction of ILI with amantadine and a 63% relative risk reduction with oseltamivir.

Methods used to derive estimates of effectiveness
Authors’ assumptions were also used as estimates of effectiveness.

Estimates of effectiveness and key assumptions
As there were no RCTs of post-exposure prophylaxis of oseltamivir, it was assumed that the efficacy would be the same as that of seasonal prophylaxis. Also, as there were no RCTs of amantadine in LTCFs, its efficacy was assumed to be similar to that of rimantadine. The study assumed that no antiviral treatment was given to new emergent ILI cases while on prophylaxis, and that those who discontinued drugs due to adverse events would develop ILI at the rate of those not treated. The probabilities of events given ILI were assumed to be halved by any prophylactic regime. Authors’ assumptions were also used to estimate the days on prophylaxis before discontinuing because of adverse events or developing ILI.

Measure of benefits used in the economic analysis
The primary outcome was the occurrence of ILI per 100 patients. Hospitalisations and deaths were also reported.

Direct costs
The cost categories included prophylaxis drugs, acute care and others. Acute care covered transfer to acute care facilities for influenza complications, and hospitalisation due to adverse events. “Other” costs included routine assessment of renal function for amantadine dose calculation, and antibiotic treatment for ILI or influenza complications. Pharmacist or nursing time required to review the patients’ charts was not considered in the base-case analysis. The quantity/cost boundary adopted was that of the health service. The cost estimation was derived using modelling. In order to bias results against prophylaxis, dying patients were assumed to cost the same as those who survive. Discounting was not performed, which was appropriate given the short-term horizon of the study. Sources of the cost data comprised medical literature and public sources from Ontario. The price year was 2001.

Statistical analysis of costs
The costs were treated deterministically and no statistical tests were carried out.

Indirect Costs
No indirect costs were included.

Currency
Canadian dollars (CAD).

Sensitivity analysis
Clinically relevant ranges of the input parameters were tested in one-way sensitivity analyses to reflect best- and worst-case scenarios of the active strategies. The ranges were mainly derived from the literature but were also based on
authors’ assumptions. A scenario including the pharmacist or nursing time required to review the patients’ charts for amantadine dose adjustment was also reported.

**Estimated benefits used in the economic analysis**

With no prophylaxis there were 6.8 ILI cases, 0.82 hospitalisations, and 0.75 deaths per 100 patients. Compared with no prophylaxis, amantadine prevented 2.80 ILI cases, 0.54 hospitalisations and 0.49 deaths per 100 patients, while oseltamivir prevented 4.20 ILI cases, 0.66 hospitalisations and 0.60 deaths per 100 patients.

**Cost results**

The total costs per 100 patients during the 30-day horizon were CAD 6,611 with no prophylaxis, CAD 4,503 with amantadine and CAD 3,254 with oseltamivir. Compared with no prophylaxis, amantadine would save CAD 2,108 and oseltamivir would save CAD 3,357.

**Synthesis of costs and benefits**

Prophylaxis strategies were less expensive and provided better outcomes than no prophylaxis. They resulted in savings of between CAD 2,108 and CAD 3,357 per 100 patients in medical care costs and prevented between 2.8 and 4.2 ILI cases per 100 patients over a 30-day period.

Oseltamivir post-exposure prophylaxis was less expensive than amantadine post-exposure prophylaxis (saved $1,249 per 100 patients), with marginally better clinical outcomes (1.40 ILI prevented per 100 patients treated).

The analysis was sensitive to the cost of amantadine dose calculation, but to be cost-neutral with oseltamivir an unlikely scenario should be met: 19 of 20 patients would have to already have a recent serum creatinine value in their chart and not require any additional laboratory tests, and the pharmacists would require less than 2 minutes per patient to calculate creatinine clearance.

The robustness of the conclusions was supported by the analysis of good and bad scenarios for both strategies.

In addition, a hypothetical strategy of rimantadine showed that, if rimantadine was available in Canada and priced at 32% of the cost of oseltamivir, rimantadine 100 mg/day would be the least costly post-exposure prophylaxis strategy. Rimantadine 200 mg/day prophylaxis was more expensive than oseltamivir prophylaxis but less expensive than no prophylaxis.

**Authors’ conclusions**

Although amantadine has a lower acquisition cost than oseltamivir, it has more adverse events, lower efficacy, and individualised dosing requirements. This leads to higher overall costs and more influenza-like illness (ILI) cases than oseltamivir, which is more cost-effective than the current standard of care with amantadine prophylaxis or no prophylaxis.

**CRD COMMENTARY - Selection of comparators**

The authors clearly stated their reason for selecting the comparators (i.e. amantadine and no prophylaxis). Other relevant comparators, such as rimantadine, were included in an additional analysis. Zanamivir, however, was excluded as it was impractical in the elderly. You should check if these are the relevant comparators in your setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used and it cannot ensure that all relevant literature was identified. The estimates of effectiveness were derived credibly from the studies identified. Though there were no head-to-head comparisons between the active strategies, the authors derived effectiveness from RCTs against
placebo. Some assumptions were made and tested in sensitivity analyses (i.e. that oseltamivir efficacy would be the same as that of seasonal prophylaxis and that amantadine efficacy in LTCFs would be similar to that of rimantadine). The authors used data from published sources, experts’ opinions and their own assumptions. The authors usually justified their assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses, using ranges from the literature and assumptions.

Validity of estimate of measure of benefit
The benefit measure chosen (the occurrence of ILI per 100 patients) can be helpful in the specific context of comparing influenza prophylactic strategies, but it cannot be used to compare these against other strategies in other health fields.

Validity of estimate of costs
All the categories of cost relevant to the study perspective seem to have been considered. Although sometimes there was little detail within each category of cost (e.g. hospitalisation for an ILI), this would not have affected the study conclusions. The costs and the quantities were reported separately, thus providing greater generalisability of the analysis. Resource use and costs came mostly from published sources and some assumptions. The price year was reported, thus enabling future reflation exercises. Sensitivity analyses of the costs were conducted and reported. Discounting was not applied, which was appropriate given the short-term study horizon.

Other issues
The authors did not compare their findings with those from other studies. Generalisability to other settings, such as those with lower staff vaccination, was addressed. The authors’ conclusions reflected the scope of the analysis. The authors reported some limitations of their study. These included the inherent nature of modelling studies, the lack of RCT data on post-exposure prophylaxis of oseltamivir or amantadine, and the number of assumptions that had to be made.

Implications of the study
Long-term care resident and staff vaccination to prevent ILI outbreaks is still the most important first step in protection against influenza. Despite these measures, outbreaks continue to emerge in LTCFs. Post-exposure prophylaxis with oseltamivir after an influenza outbreak saves medical costs and provides better clinical outcomes than amantadine post-exposure prophylaxis or no prophylaxis. Thus, although oseltamivir appears promising, data in this environment are limited, warranting further research. The authors also stated that if rimantadine becomes available at the expected cost, it could become the least costly strategy. If influenza B is similarly severe as influenza A, this analysis could be extrapolated to cover influenza B as well.

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