Influenza treatment with neuraminidase inhibitors: cost-effectiveness and cost-utility in healthy adults in the United Kingdom


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 options for influenza treatment were studied. These were usual care (UC), oseltamivir (OSE) and zanamivir (ZAN). UC comprised over-the-counter medications. Both OSE and ZAN were administered twice daily for 5 days. OSE was taken orally, while ZAN was inhaled using a special device. The two treatments needed to be initiated within 48 hours of symptom onset.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of otherwise healthy adults (age 13 to 64 years).

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
Most of the effectiveness data were derived from studies published between 1997 and 2003. Resource use was estimated from a source published in 1997. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A decision tree model was constructed to assess the clinical and economic implications of the three influenza treatments in a hypothetical cohort of 10,000 individuals. The model structure reflected the morbidity and mortality associated with influenza, as well as its complications. The model started at the general practitioner's (GP) office since both OSE and ZAN were available only with a GP's prescription. The model distinguished between two periods for the start of treatment (within 48 hours of onset of symptoms and after 48 hours) and also between influenza-positive and influenza-negative cases (diagnostic certainty), since treatment with neuraminidase inhibitors was confirmed to be effective against the influenza virus only if taken within 48 hours of onset of symptoms. Three disease states were described:

- outpatient (symptomatic infection resulting in outpatient treatment in the primary sector),
inpatient (symptomatic infection resulting in hospitalisation, including outpatient treatment pre- and post-hospitalisation), and

dead (symptomatic infection resulting in death).

Only deaths related to influenza-like illness (ILI) or to its complications were included in the model. Bronchitis and pneumonia were the only complications included in the model. The structure of the model was depicted in a graph. The time horizon appears to have been the lifetime of the individual.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the probability of ILI inpatient,
- the probability of ILI death,
- the probability of bronchitis,
- the probability of pneumonia,
- the probability of pneumonia inpatient,
- the probability of pneumonia death,
- days to return to normal activity,
- the quality weight associated with ILI, and
- the quality weights associated with bronchitis and pneumonia.

**Study designs and other criteria for inclusion in the review**
The authors stated that a review of the literature was undertaken to identify the primary estimates. The inclusion and exclusion criteria referred to the quality of the study, outcome parameters measured, and comparability across studies.

**Sources searched to identify primary studies**
MEDLINE was searched from 1997 to 2003.

**Criteria used to ensure the validity of primary studies**
The use of specific inclusion criteria should have ensured the validity of the primary studies.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Approximately 10 primary studies provided clinical data.

**Methods of combining primary studies**
Not stated.
Investigation of differences between primary studies
Not stated.

Results of the review
The probability of ILI inpatient was 0.00323 with UC and 0.00116 with OSE.

The probability of ILI death was 0.00002 with UC.

The probability of bronchitis was 0.01234 with UC, 0.00802 with OSE, and 0.00759 with ZAN.

The probability of pneumonia was 0.00278 with UC, 0.00067 with OSE, and 0.00132 with ZAN.

The probability of pneumonia inpatient with all treatments was 0.07293.

The probability of pneumonia death with all treatments was 0.01883.

The days to return to normal activity were 8.83 (range: 6.63 - 11.04) with UC, 7.43 (range: 5.57 - 9.29) with OSE, and 7.27 (range: 5.85 - 9.74) with ZAN.

The quality weight associated with ILI was 0.94 for OSE.

The quality weights associated with bronchitis and pneumonia (regardless of the treatment) were 0.99 and 0.90, respectively.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive clinical estimates that were not retrieved from the literature.

Estimates of effectiveness and key assumptions
The probability of ILI inpatient with ZAN was 0.00116 (assumed to be the same as for OSE).

The probability of ILI death was 0.00002 with OSE and 0.00002 with ZAN.

The probability of bronchitis inpatient with all treatments was 0.00323.

The probability of bronchitis death with all treatments was 0.00005.

The quality weight associated with ILI was 0.94 for ZAN (assumed to be the same as for OSE).

The diagnostic certainty rate was 70%.

The compliance rate with ZAN was 100%.

Measure of benefits used in the economic analysis
The summary benefit measures were the days of normal activity gained (in the cost-effectiveness analysis) and quality-adjusted life-years (QALYs) (in the cost-utility analysis). Both measures were estimated using a modelling approach. The approach used to calculate the QALYs was clearly described. The utility weights were obtained from the literature using rating scales to elicit patient preferences. An annual discount rate of 1.5% was applied to expected survival.

Direct costs
The cost analysis was performed from the perspectives of the NHS and society. The direct costs included in the economic evaluation were OSE, ZAN, GP visit, diagnostic tests for bronchitis and pneumonia, antibiotics for ILI,
bronchitis and pneumonia, over-the-counter medications and hospitalisation. The unit costs were presented, but the quantities of resources used were not provided for all items. The resource use data were estimated from a US database, the National Ambulatory Medical Care Survey (NAMCS). The costs came from typical NHS sources, such as the British National Formulary or the Personal Social Services Research Unit. The price year was 2001. No discounting was applied since the costs were incurred in the short term.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs (i.e. productivity losses) were included in the analysis because a societal perspective was adopted. However, such costs were not considered in the base-case analysis. The indirect costs were estimated by applying the human capital approach, thus using the time to return to normal activities. The unit costs were presented separately from the quantities of resources used. Days to return to normal activities were estimated from the literature, as reported already. The costs were estimated from the average gross UK income. No discounting was applied. The price year was 2001.

**Currency**
UK pounds sterling ()

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were carried out to examine the robustness of the cost-effectiveness and cost-utility estimates to variations in two key model inputs that were based on authors’ assumptions. The two inputs studied were diagnostic certainty and time of treatment initiation after the onset of symptoms. Other scenarios were considered in the multivariate sensitivity analysis, such as the assumption that neuraminidase inhibitors have no effect on hospitalisations, complications, or mortality and a low diagnostic certainty rate. Productivity loss was also considered, assuming that only 25% of the time to return to normal activities is productivity loss for outpatients, and that for inpatients, weekends would usually (if not sick) be leisure time and therefore not work loss. Finally, second-order Monte Carlo simulations were performed by assigning probabilistic distributions to clinical inputs (beta distributions for probabilities and gamma distributions for resource use). Acceptability curves were presented for the comparison between OSE and UC.

**Estimated benefits used in the economic analysis**
The days to return to normal activity per patient were 8.96 (range: 8.93 - 8.99) with UC, 7.95 (range: 7.92 - 7.98) with OSE and 7.84 (range: 7.81 - 7.87) with ZAN.

The discounted QALYs per patient were 31.3797 (range: 31.3726 - 31.3818) with UC, 31.3823 (range: 31.3714 - 31.3836) with OSE and 31.3821 (range: 31.3745 - 31.3836) with ZAN.

**Cost results**
When using the NHS perspective, the estimated costs per patient were 50.66 (range: 47.73 - 54.53) with UC, 65.24 (range: 63.67 - 66.83) with OSE and 77.54 (range: 75.88 - 79.81) with ZAN.

When using the societal perspective, the estimated costs per patient were 808.23 (range: 803.97 - 813.30) with UC, 736.96 (range: 733.87 - 740.57) with OSE and 740.03 (range: 736.20 - 743.60) with ZAN.

**Synthesis of costs and benefits**
The incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the
alternative treatments.

Using the NHS perspective, the incremental cost per day of normal activity gained in comparison with UC was 14.36 (range: 10.69 - 17.67) with OSE and 112.84 (range: 93.88 - 149.67) with ZAN. The incremental cost per QALY was 5,600 with OSE in comparison with UC, while ZAN was dominated by OSE (range for the incremental cost/QALY for ZAN over OSE: 3,737 - OSE dominant).

Using the societal perspective, the incremental cost per day of normal activity gained was 28.19 (range: 8.00 - 56.75) with ZAN in comparison with UC, while OSE dominated both UC and ZAN. OSE was also the dominant treatment in the cost-utility analysis.

The cost-effectiveness acceptability curve showed that the probability of OSE being cost-effective in comparison with UC at an assumed cost per QALY threshold of 30,000 was 0.85.

The sensitivity analysis (which was presented only for the comparison between OSE and UC, as ZAN was dominated by OSE) showed that the results were sensitive to variations in the level of diagnostic accuracy. However, OSE had a cost per QALY below the ceiling of 30,000 even when assuming only 34% diagnostic certainty.

With respect to the impact of time to treatment initiation on the cost-effectiveness results, the analysis showed that OSE remained cost-effective from the NHS perspective, even with 47.5% of patients receiving no benefits (30% influenza negative plus 25% late presenters among the influenza-positive patients). OSE remained dominant from the societal perspective.

**Authors' conclusions**
In comparison with both usual care (UC) and zanamivir (ZAN), oseltamivir (OSE) was a cost-effective treatment for influenza among otherwise healthy adult individuals aged 13 to 64 years.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators. Only two other competing treatments (amantadine and rimantadine) existed in some markets. However, amantadine was not recommended by the National Institute for Clinical Excellence for influenza treatment, while rimantadine was not available in the UK. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a synthesis of published studies. Limited information on the design and characteristics of the primary studies was reported. The inclusion of clinical trials ensures a high internal validity for the primary studies. Some inclusion criteria and details of the search strategy were reported. The authors selected only studies that were comparable in dosage and other treatment patterns. This enhances the robustness of the analysis. Some assumptions were also made, and their impact on the results of the study was investigated in the sensitivity analysis.

**Validity of estimate of measure of benefit**
Two benefit measures were used in the analysis. Time to return to normal activity is a disease-specific measure, commonly used for studies of influenza treatment. The authors stated that return to normal activity was the measure that best captured the "cure" of the disease and the total duration of illness. However, it was noted that the interpretation of the cost per day of normal activity gained was not straightforward. The use of QALYs, which capture the impact of the interventions on both survival and quality of life, allows comparisons with the benefits of other health care interventions. Discounting was applied, as UK guidelines for cost-effectiveness recommend, but it had a limited impact because of the reduced mortality associated with influenza treatment. The source of the utility values was described, and limitations of the method used (rating scale) were illustrated.
Validity of estimate of costs
The cost analysis was carried out from the perspectives of the NHS and society. A detailed breakdown of the cost items included for each perspective was not provided. Further, the indirect costs, which should represent the key feature of the societal perspective, were considered only in the sensitivity analysis. The unit costs were presented for almost all categories of costs, whereas the information on resource use was less clear. No statistical analyses of the costs were performed. Moreover, the cost estimates were not varied in the sensitivity analysis. The source of the costs, which represented typical NHS sources, was reported. However, resource use was estimated using US data, owing to the lack of detailed resource consumption information for the UK. The price year was reported, which aids refiation exercises in other settings.

Other issues
The authors reported the cost-utility ratios for ZAN and OSE estimated in a published study and stated that comparable results were observed. The issue of the generalisability of the study results to other settings was not explicitly stated and few sensitivity analyses were performed. Thus, the external validity of the study was limited. The authors noted that the lack of reliable information about influenza complications, mortality and hospitalisation rates in the UK represented a limitation of the analysis. Also, some other complications, such as cardiac events or asthmatic exacerbations, were not included in the analysis. It was also noted that the baseline probabilities were based on ILI and not on confirmed influenza cases. Finally, the analysis used data that referred to specific influenza seasons.

Implications of the study
The study results suggested that OSE is a cost-effective treatment for influenza in the otherwise healthy adult population.

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Bibliographic details

Other publications of related interest


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