Cost-effectiveness of newer treatment strategies for influenza

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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
Rapid testing and antiviral agents for influenza were studied. In total, seven strategies were considered in the analysis:

strategy 1 was no testing or treatment;
strategy 2 was oseltamivir or zanamivir treatment without testing;
strategy 3 was amantadine treatment without testing;
strategy 4 was rimantadine treatment without testing;
strategy 5 was testing then the treatment of positive tests with oseltamivir or zanamivir;
strategy 6 was testing then amantadine treatment; and
strategy 7 was testing then rimantadine treatment.

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 32-year-old patients with typical influenza symptoms and a temperature (37.8 degrees C during an influenza season). Patients had influenza A or B based on their relative likelihoods. They were at risk of influenza complications, which may lead to pneumonia and death.

Setting
The setting was unclear, but it was likely to have been primary care. The economic analysis was carried out in Pittsburgh (PA), USA.

Dates to which data relate
The effectiveness data were gathered from studies published between 1978 and 2000. The resource data were gathered from studies published between 1999 and 2000. The price year was 2000.

Source of effectiveness data
The effectiveness data were gathered from published studies.
**Modelling**
A decision analytic model was created, using Decision Maker 7.07 and DATA 3.5 software, to simulate the costs and the health outcomes assigned to each strategy. The time horizon was not clear. An illustrative representation of the model structure was provided in the paper.

**Outcomes assessed in the review**
The outcomes assessed in the review and used as model inputs were:
- the probability of influenza and the length of untreated illness, the decrease in illness length with antiviral agent, and the relative likelihood of influenza A;
- the duration of non-influenza illness;
- the probability of pneumonia and the length of illness, and the associated risk of death;
- the probability of influenza-related sinusitis or bronchitis and the associated length of illness;
- the sensitivity and specificity of the influenza test; and
- the proportion of medication discontinued due to side effects.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not specified.

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

**Number of primary studies included**
Approximately 20 studies were included in the review.

**Methods of combining primary studies**
The results of the individual primary studies were combined using a narrative method.

**Investigation of differences between primary studies**
The authors did not investigate differences between the primary studies.

The authors chose parameter values in the baseline analysis to ensure a slight bias against antiviral treatment and towards testing strategies. For example, the highest reported values for test sensitivity and specificity were used, thus biasing the analysis toward rapid testing.

**Results of the review**
The probability of influenza was 59.6%.

The length of untreated influenza illness was 7 days.

The decrease in illness length with an antiviral agent was 1.27 days.

The relative likelihood of influenza A was 81.5%.

The duration of non-influenza illness was 5 days.

The probability of pneumonia was 1%.

The length of pneumonia was 10 days.

The associated risk of death was 10%.

The probability of influenza-related sinusitis or bronchitis was 15%.

The associated length of illness was 7 days.

The sensitivity of the influenza test was 81% and the specificity was 99%.

The proportion of medication discontinued due to side effects was 15% with amantadine, 6% with rimantadine, 3% with zanamivir and 3% with oseltamivir.

**Methods used to derive estimates of effectiveness**
The authors made several assumptions to estimate outcomes. It would appear that the estimates were based on the authors' opinion.

**Estimates of effectiveness and key assumptions**
The main assumptions were as follows.

The complication rates and mortality were identical in the intervention and no-intervention arms of the model, thus biasing the analysis against antiviral therapy.

Illnesses due to influenza A and B had equal duration, severity and complication rates.

All antiviral agents had similar benefits on the symptoms and duration of illness for which they were effective (influenza A and B for oseltamivir and zanamivir, influenza A for amantadine and rimantadine).

Decreases in symptoms resulted in proportional decreases in illness disutility.

All antiviral medications were assigned identical side-effect disutility, which might have led to bias toward amantadine and rimantadine treatment, given their more severe side effects.

**Measure of benefits used in the economic analysis**
The benefit measures used were the number of illness days avoided and the quality-adjusted days gained. Quality of life was measured by health-state utility weights on a scale from 0 to 1, and were derived from the literature. Discounting was not performed. Age-adjusted utilities for the well state were derived from the National Health Interview Survey, while those for influenza and non-influenza illness were derived from population-based values for short-term disability for an "unnamed infectious disease" (Sackett and Torrance, see Other Publications of Related Interest).

**Direct costs**
The societal perspective was adopted in the baseline analysis, while the third-party payer perspective was considered in a second analysis. The direct costs included the costs of rapid testing, symptomatic therapy (pseudoephedrine and ibuprofen), therapy for complications, pneumonia therapy (including hospitalisation) and physician visits. The cost of rapid testing was derived from the literature. The treatment costs were derived from the Red Book average wholesale price listings. The cost of pneumonia was derived from Medicare diagnosis-related group plus physician reimbursement for pneumonia. The unit costs and the quantities of resources used were reported separately. All of the costs were adjusted to 2000 US dollars. The total costs were derived using the decision analytic model. The costs were not discounted, which was appropriate since they were incurred during a single episode of illness (less than 2 years).

**Statistical analysis of costs**

No statistical analysis of the costs was performed.

**Indirect Costs**

The indirect costs for time spent seeking or receiving care were included in the cost analysis. The average hourly wage for US non-farm workers in July 2000 was used. The quantities of resources used were reported. The indirect costs were not discounted.

**Currency**

US dollars ($).

**Sensitivity analysis**

One- and multi-way sensitivity analyses were performed on all parameter values using ranges derived from the literature. A probabilistic (Monte Carlo) sensitivity analysis, in which several parameters were varied simultaneously, was performed using 1,000 iterations.

**Estimated benefits used in the economic analysis**

For each strategy, the number of illness days (quality-adjusted days lost) was:

- 6.20 (2.11) for no testing or treatment;
- 5.66 (1.69) for amantadine treatment without testing;
- 5.76 (1.75) for testing then amantadine treatment;
- 5.61 (1.62) for rimantadine treatment without testing;
- 5.72 (1.71) for testing then rimantadine treatment 5.60 (1.59);
- for testing then treatment with oseltamivir or zanamivir; and
- 5.46 (1.47) for oseltamivir or zanamivir treatment without testing.

Zanamivir treatment was the most effective strategy, minimising both days of illness (5.46) and quality-adjusted days lost (1.47).

Rimantadine and amantadine treatments were less effective since their effects were limited to influenza A.

Testing strategies were less effective than treatment alone because of the relatively low test sensitivity.

"No testing or treatment” was the least effective strategy.
Cost results
For each strategy, the total cost (incremental cost) was:

$92.70 for "no testing or treatment";

$97.50 ($4.90) for amantadine treatment without testing;

$115.00 ($17.50) for testing then amantadine treatment;

$119.10 ($21.50) for rimantadine treatment without testing;

$125.50 ($6.40) for testing then rimantadine treatment;

$134.30 ($15.20) for testing then treatment with oseltamivir or zanamivir; and

$137.10 ($39.50) for oseltamivir or zanamivir treatment without testing.

Synthesis of costs and benefits
The two strategies "test then treat with amantadine" and "test then treat with rimantadine" were dominated, that is, they were both more costly and less effective than the other strategies.

The two strategies "treat with rimantadine" and "test then treat with oseltamivir or zanamivir" were dominated because they were less cost-effective than treatment with zanamivir.

Compared with "no testing or treatment", the incremental cost-effectiveness ratio (ICER) of amantadine therapy was $9.06 per day of illness avoided and $11.60 per quality-adjusted day gained.

Compared with amantadine treatment, the ICER of zanamivir therapy was $198 per day of illness avoided and $185 per quality-adjusted day gained.

If oseltamivir was substituted for zanamivir, the ICER was $252 per day of illness avoided and $235 per quality-adjusted day gained.

When the third-party perspective was taken, the ICERs were unchanged.

In elderly patients who required reduced dosage, rimantadine cost $128 per quality-adjusted day gained compared with amantadine.

In younger patients, amantadine was preferred if the likelihood of influenza A was greater than 67%, otherwise, neuraminidase inhibitors were preferred.

Testing strategies were more costly and less effective when the influenza probability was greater than 30%.

"No testing or treatment" was preferred if the influenza probability was less than 32% and the influenza utility was greater than 0.77.

In elderly patients, amantadine was favoured over rimantadine if the utility of medication side effects was greater than 0.94.

If society or third-party payers were willing to pay ($100 per quality-adjusted day gained, then amantadine or no treatment was preferred in all scenarios.

If the willingness-to-pay was $200 to $300, neuraminidase inhibitors were preferred in younger patients and rimantadine was preferred in elderly patients.

If the willingness-to-pay was $500 or more per quality-adjusted day gained, neuraminidase therapy was preferred.
Authors' conclusions
Antiviral treatment of influenza without rapid testing is cost-effective in febrile patients with typical symptoms during an influenza season. The choice of antiviral agent depends on age, the likelihood of influenza A, and the willingness-to-pay per quality-adjusted day gained.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator (no testing or treatment) was clear. You should decide whether it represents the currently used approach in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. The sources searched and the methods used to select the data were not reported. It appears that the effectiveness estimates have been combined using narrative methods. The impact of differences between the primary studies was not investigated. The authors chose parameter values in the baseline analysis to bias slightly against antiviral treatment and towards testing strategies. These facts make it difficult to ascertain whether the best available evidence was used as inputs to the model. In addition, crucial assumptions were made in the model. For example, all antiviral agents were assumed to have similar benefits on the symptoms and duration of illness. However, sensitivity analyses were performed with ranges of variation derived from the literature. The authors showed that the model was sensitive to changes in the age, the probability of influenza and the level of the willingness-to-pay, but the model was insensitive to change in the parameter values with possible bias in the baseline analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The utility weights were derived from the literature, but the authors did not report whether the studies reported utility values from patients’ preferences or from experts’ opinion. This fact limits the relevance of the quality of life measurements. The time horizon seems to have been that of a season of influenza, which appears appropriate for the study question. Therefore, discounting was not relevant and, appropriately, was not performed.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted appear to have been included in the analysis. Details on the unit costs, quantities of resources and sources of resources were reported, which may ease the transferability of the economic analysis to other settings. The price year was reported and this allows reflation exercises. It should be noted that Medicare reimbursements were used as proxies for the cost of pneumonia, and these do not reflect true opportunity costs. Discounting was not relevant since the follow-up considered in the analysis appears to have been no longer than one influenza season. A sensitivity analysis was performed on the costs in order to take variability in the cost estimates into consideration.

Other issues
The authors did not compare their results with those from other published studies. They also did not address the issue of the generalisability of the study results to other settings. The results were well reported and the conclusions drawn reflected the scope of the study. The authors highlighted one limitation of their study in that the measure of influenza utility was derived from the literature. Sensitivity analyses were performed to take variability in the cost or effectiveness data into consideration. Consequently, the external validity of the study should be high.

Implications of the study
The authors did not explicitly state any areas for future research.
Source of funding
None stated.

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetamides /administration & dosage /economics /therapeutic use; Adult; Age Distribution; Aged; Aged, 80 and over; Amantadine /administration & dosage /economics /therapeutic use; Antiviral Agents /administration & dosage /economics /therapeutic use; Cost-Benefit Analysis; Decision Trees; Diagnostic Tests, Routine /economics; Drug Costs /statistics & numerical data; Female; Guanidines; Humans; Influenza, Human /diagnosis /drug therapy; Male; Middle Aged; Monte Carlo Method; Neuraminidase /antagonists & inhibitors; Oseltamivir; Pennsylvania; Pyrans; Quality-Adjusted Life Years; Sialic Acids /administration & dosage /economics /therapeutic use; Zanamivir

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