Exposure to tuberculosis among newborns in a nursery: decision analysis for initiation of prophylaxis

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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
The authors evaluated the administration of isoniazid prophylaxis (approximately 10 mg/kg per day) against tuberculosis (TB). Two prophylaxis strategies were investigated. Strategy 1 was prophylaxis administration (5 days per week for 3 months) under direct observation (DO strategy). Strategy 2 was prophylaxis given daily for 7 days per week by the parent (non-DO strategy). These two strategies were compared with no prophylaxis.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 28 newborns exposed to a mother whose sputum was direct-smear negative for acid-fast bacilli, but culture positive for Mycobacterium tuberculosis.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1939 and 2000. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies. If unavailable, data were derived using assumptions made by the authors.

Modelling
A decision tree model was used to determine whether the administration of prophylaxis to Mycobacterium tuberculosis in a nursery would be preferable to no administration of prophylaxis. The model examined the costs and outcomes of a 3-month course of prophylaxis. After 3 months, the decision about whether to continue prophylaxis would be based on the tuberculin skin test (TST) result. The model assumed that if an infant had a positive TST result at 3 months of age, a complete 9-month course of prophylaxis would be given. The time horizon was 4 years.

Outcomes assessed in the review
The outcomes assessed were:
the probability of onset of TB infection;
the probability of onset of TB disease given TB infection if prophylaxis was not administered;
the efficacy of prophylaxis in the DO strategy and the non-DO strategy;
the probability of onset of TB disease given TB infection if prophylaxis was administered;
the probability of surviving TB;
the probability of onset of hepatotoxicity; and
the probability of surviving hepatotoxicity.

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 reported.

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

Number of primary studies included
Approximately 21 primary studies were included in the review.

Methods of combining primary studies
The authors did not report the method used to combine outcome values from the primary studies. The probability of TB disease when prophylaxis is administered was calculated by multiplying the probability of TB disease associated with the no-prophylaxis strategy for patients who have TB infection by (1 minus efficacy).

Investigation of differences between primary studies
Not reported.

Results of the review
The probability of onset of TB infection was 0.001.

The probability of onset of TB disease given TB infection if prophylaxis was not administered was 0.5.

The efficacy of prophylaxis was 0.8 in the DO strategy and 0.6 in the non-DO strategy.

The probability of surviving TB was 0.90.

The probability of onset of hepatotoxicity was 0.001.
The probability of surviving hepatotoxicity was 0.99.

**Methods used to derive estimates of effectiveness**
If no data were available from the literature, the authors’ own assumptions were used.

**Estimates of effectiveness and key assumptions**
The authors assumed that the efficacy of non-DO prophylaxis would be lower than that of DO prophylaxis (0.6 versus 0.8), because non-DO prophylaxis was not supervised by a health care worker.

**Measure of benefits used in the economic analysis**
The measure of benefits used was survival.

**Direct costs**
The direct costs to the health care system were included in the analysis. These covered the costs of medication, time travelling to visit patients, outpatient costs, and hospitalisation costs at the regular ward and the intensive care unit (for diagnosis and treatment). Direct medical costs were obtained from managing agencies such as hospital clinics and health departments. If such data were unavailable, the authors used their own assumptions. Since the costs could be incurred during a 4-year period, future costs were appropriately discounted at an annual rate of 5%. The study reported the average costs. The price year was not reported.

**Statistical analysis of costs**
The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
A series of one-way sensitivity analyses was undertaken. The parameters varied were the probability of developing infection, the probability of developing disease in the absence of prophylaxis, the probability of dying, the probability of hepatotoxicity and the probability of dying from hepatotoxicity. A series of two-way sensitivity analyses was also performed, in which the probability of infection and the probabilities of developing TB disease, surviving TB, developing hepatotoxicity and surviving hepatotoxicity were varied simultaneously.

**Estimated benefits used in the economic analysis**
The expected value of survival was 0.999980 in the DO prophylaxis strategy and 0.999950 in the no-prophylaxis strategy. This means that 3 more infants per 100,000 patients would die if no prophylaxis were administered.

The expected value of survival was 0.999970 in the non-DO prophylaxis strategy and 0.999950 in the no-prophylaxis strategy was. This means that 2 more infants per 100,000 patients would die if no prophylaxis were administered.

**Cost results**
The expected cost of DO prophylaxis was $624.18 per patient, compared with $2.87 per infant for no prophylaxis.
The expected cost of non-DO prophylaxis was $21.46 per patient, compared with $2.87 per infant for no prophylaxis.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-effectiveness ratio (ICER; i.e. the additional cost per death prevented). The ICER of DO prophylaxis when compared with no prophylaxis was $21,710,000 per death prevented. The ICER of non-DO prophylaxis was $929,500 per death prevented.

The results of the one-way sensitivity analysis of the probability of survival showed that the DO prophylaxis strategy was dominant (i.e. both more effective and less costly than no prophylaxis) under the following scenarios:

- when the probability of developing infection was greater than 0.0002;
- when the probability of developing disease in the absence of prophylaxis was greater than 0.12;
- when the probability of dying of TB was greater than 0.025;
- when the probability of hepatotoxicity was less than 0.04; and
- when the probability of dying from hepatotoxicity was less than 0.04.

Authors’ conclusions
The administration of prophylaxis was preferable to no administration of prophylaxis, unless the probability of infection was extremely low.

CRD COMMENTARY - Selection of comparators
An explicit justification was given for using no prophylaxis as the comparator. It represented current practice in the authors’ settings. You should decide if the comparator used represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature had been undertaken to identify relevant research and minimise biases. However, a thorough literature review appears to have been undertaken as numerous studies, spanning a considerable range of publication dates, were included in the review. A large proportion of studies were published during the 1970s, with some even dating from before the 1950s. Consequently, it is likely that these studies may no longer be generalisable to current medical practice and patient populations. The authors provided very brief details of their review of the literature and the methods and assumptions they used to derive measures of effectiveness. It was also unclear which estimates were derived from the authors’ own assumptions.

Validity of estimate of measure of benefit
The estimate of measure of benefits (i.e. survival) was derived from a decision tree model, which was appropriate for the study question. However, it would have been more appropriate, as an outcome measure, if the authors had converted survival (or deaths avoided) into life-years gained. Life-years gained is a more widely used and generalisable measure of outcome, and would therefore have been more useful for decision-makers.

Validity of estimate of costs
All the categories relevant to the health care system perspective adopted were included in the analysis. No major relevant costs appear to have been omitted. The resource use quantities and the unit costs were not reported separately, which will limit the generalisability of the authors’ results. The costs were derived from hospital wards and clinics and, if unavailable, from the authors’ own assumptions. As with measures of effectiveness, the authors did not report the assumptions they used or which costs were derived from their own assumptions. The authors performed sensitivity analyses, but it would appear that these were only carried out on effectiveness estimates and not on cost parameters.
Since the costs were incurred during a 4-year period, future costs were appropriately discounted. However, the price year was not reported, which will hamper any future inflation exercises.

Other issues
The authors reported that other studies had found the probability of hepatotoxicity to be extremely rare. The issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. However, their use of cost per death averted will hamper decisions on whether the interventions being assessed were cost-effective or not, as there was no clear cost-effectiveness threshold.

The authors acknowledged several further limitations to their study. First, there were few data on the true values or ranges ascribed to the probabilities used in the model. Second, the probabilities of TB associated with Mycobacterium tuberculosis exposure were obtained from studies performed before the availability of anti-tuberculosis chemotherapy. Third, the outcome measure was very narrow (i.e. it only considered survival and death). Finally, the cost and probability of litigation because of an adverse outcome for either strategy was not taken into consideration.

Implications of the study
The authors reported that their findings would be useful as a framework for enabling decisions to be made about the use of empirical anti-tuberculosis chemoprophylaxis in different situations with different probabilities of exposure to, and infection with, Mycobacterium tuberculosis.

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