Comparison of effectiveness of BCG vaccination and preventive therapy in Japanese settings, with special emphasis on the sensitivity and specificity of tuberculin testing

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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 use of BCG vaccination for tuberculosis (TB) was studied.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of the Japanese population who are born in a year which has a 0.1% annual risk of TB infection.

Setting
The setting was unclear, but it appears to have been the community. The economic study was conducted at the Epidemiology Division, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo.

Dates to which data relate
The effectiveness data were derived from studies published between 1940 and 2000. The year relating to the cost data was not stated. The price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a review of earlier studies.

Modelling
Decision trees were used to compare the health status of BCG vaccinated groups and non-vaccinated groups. The period of analysis was the lifetime of the cohort born in the reference year. A clear graphical representation of the decision trees was provided. The software package used for the analysis was Microsoft Excel.

Outcomes assessed in the review
The outcomes assessed and used as input parameters for the model were:

- the effectiveness, fatality and side effects of BCG;
- the proportion of contact tracing;
the effectiveness and risk associated with PT;
the prevalence, fatality and risk associated with TB;
the sensitivity and specificity of the tuberculin test with and without BCG; and
the number of secondary cases.

**Study designs and other criteria for inclusion in the review**
The inclusion and exclusion criteria were not stated.

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

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

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

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

**Methods of combining primary studies**
A narrative method was used to combined the studies.

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

**Results of the review**
The author provided a detailed breakdown of the data in their paper (table 1). The data considered to form the principal drivers of the model are reported in this abstract.

The effectiveness of BCG vaccination was 0.80, fatality was 0.0000001 and the prevalence of side effects was 0.01.

The average proportion of infected persons among contacts was 0.2, while the proportion of contact-tracing target among the newly infected was 0.1.

The effectiveness of PT was 0.85 (effectiveness among non-compliant individuals was 0.15).

The prevalence of TB infection was 0.02 at 20 years old, 0.03 at 40 years old and 0.04 at 60 years old.

The risk of clinical breakdown without PT was 0.07 for those infected within 2 years and 0.0008 for those who had been infected more than 2 years previously.

The sensitivity of the tuberculin test with BCG was 0.3 to 0.7 and the specificity was 0.85.

The sensitivity of the tuberculin test without BCG was 0.94 (0.75 to 0.9 among those older than 40 years old) and the
specificity was 0.986.

The number of secondary cases was 1.2 for adults and 0.1 for children.

The above figures were either the actual figures from the earlier papers, or the author’s approximations from the published studies.

**Measure of benefits used in the economic analysis**
The measure of benefit was the avoided loss of disability-adjusted life-years (DALYs). The weights for the DALYs were 0.4 for hepatitis due to PT (duration 3 months), 0.2 for TB diseases (duration 6 months), 0.4 for sequelae (lifetime) and 0.1 for BCG side effects (for 3 months). The weights were derived from estimates provided in the literature. A discount rate of 3% was used for the benefits.

**Direct costs**
The direct costs reported were for BCG vaccination, the tuberculin test for contact, PT, and the medical costs for liver dysfunction and TB diseases. A discount rate of 3% was used for the cost analysis. The costs and the quantities were not reported separately. The source for the resource use and cost data was not reported. The price year was not stated.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were included.

**Currency**
Japanese yen (Y).

**Sensitivity analysis**
One-way sensitivity analyses were carried out to examine the changes in cumulative TB prevalence rate, TB death rate and loss of DALYs. The extensiveness of contact tracing (coverage of contact tracing among newly infected persons) was varied up to 0.4.

**Estimated benefits used in the economic analysis**
In the baseline analysis, the cumulative loss of DALYs was lower among the BCG groups in comparison with the PT and no intervention groups.

The cumulative loss of DALYs was 0.000633 for BCG alone, 0.000628 for BCG with PT, 0.000742 for PT targeted at those under 30 years old, 0.000713 for PT targeted at all age groups, and 0.000745 for no intervention.

When secondary cases were considered, the figures were 0.001350 for BCG alone, 0.001322 for BCG with PT, 0.001477 for PT targeted at those under 30 years old, 0.001407 for PT targeted at all age groups, and 0.001483 for no intervention.

**Cost results**
The direct costs for the BCG groups were higher than those for the PT and no intervention groups.

The costs were Y6,693 for BCG alone, Y6,728 for BCG with PT, Y3,506 for PT targeted at those under 30 years old,
Y3,425 for PT targeted at all age groups, and Y3,515 for no intervention.

When secondary cases were considered, the costs were Y9,460 for BCG alone, Y9,414 for BCG with PT, Y6,267 for PT targeted at those under 30 years old, Y6,034 for PT targeted at all age groups, and Y6,288 for no intervention.

**Synthesis of costs and benefits**
The costs and benefits were not combined. The results of the sensitivity analysis showed that when the extensiveness of contact tracing was over 5%, among the non-BCG groups, those with PT had lower TB prevalence rate, death rate and loss of DALYs. On the other hand, among the BCG groups, when the contact tracing was under 10%, those with PT had a higher cumulative loss of DALYs than those without PT. When the contact tracing rate was 5% and the secondary cases were considered, the cumulative TB prevalence rate, death rate and loss of DALYs were lower among the PT-only groups than the BCG groups. When the secondary cases were not considered, the BCG groups showed advantages in terms of the prevalence rate, death rate and DALYs.

**Authors’ conclusions**
"Under the current programme conditions, the merit of BCG vaccination is greater than the merit from preventive therapy without BCG", although possible extensive screening without BCG might reduce the loss of tuberculosis (TB)-related disability-adjusted life-years (DALYs) in comparison with the present BCG vaccination programme. It would still be necessary to examine the feasibility of expanding the screening.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators, namely no intervention, BCG vaccination (further divided into two sub-categories) and PT (further divided into two sub-categories) was clear. These covered all the likely permutations. The reader should consider which, if any, are applicable to their own context.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from a review of the literature, although there was no evidence to indicate whether the review was conducted systematically. For example, the sources searched, inclusion criteria, and methods used to extract the data and combine the studies were not reported. However, the author did outline the rationale for choosing particular values for the model in a narrative manner. Sensitivity analyses were performed within the modelling to account for variability in the effectiveness data and explanations were provided for some of the ranges used.

**Validity of estimate of measure of benefit**
The benefit measure used in the cost-utility analysis was the DALYs. This was an appropriate choice for the programme being considered. Utility weights were provided for each health state considered and were derived from other literature. Discounting was appropriately applied and was consistent with the long time horizon adopted in the modelling.

**Validity of estimate of costs**
The perspective adopted in the economic analysis was unclear, but it was likely to have been that of the Japanese health care system. TB and related health states are associated with long periods of absence from work and, therefore, if a societal perspective were to be of interest, productivity losses and other intangible costs would need to be considered. However, for the narrower perspective, all the direct costs appear to have been provided. The costing suffered from a number of limitations in terms of assessing the transferability and generalisability of the results. More specifically, the costs and the quantities were not reported separately, the source of the cost data was not provided, and the price year was not given. However, discounting was applied and was consistent with the long timeframe of the analysis.
Other issues
The author made informative comparisons in relation to BCG vaccination programmes in other countries and why some of them terminated these programmes. A comprehensive description of the situation in Japan was also provided. In this respect, the author did consider the generalisability of the results, but the emphasis was on how to respond within the setting of Japan. The author also noted one particular shortcoming of their study, in that the sensitivity and specificity data for the tuberculin test for the non-BCG group were derived from American data.

Implications of the study
The findings of the study suggested that the benefits of BCG vaccination are greater than PT without BCG. However, a caveat to this finding is that possible extensive screening without BCG may be able to reduce the loss of TB-related DALYs in comparison with the present BCG vaccination programme. The feasibility of extending screening, however, needs to be considered as there is some doubt if this can be achieved in reality.

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