Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness

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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 study examined Bacillus Calmette-Guerin (BCG) vaccination against childhood tuberculous meningitis and miliary tuberculosis (TB).

Type of intervention
Primary prevention.

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

Study population
The study population comprised a cohort of newborns in 2002.

Setting
The setting was primary care. The economic study referred to nine world regions, namely Africa (high human immunodeficiency virus, HIV), Africa (low HIV), central Europe, established market economies, Eastern Mediterranean, the former Soviet Union, Latin America, Southeast Asia and Western Pacific.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1965 and 2005. The price year was not reported.

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

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

the number of children born in 2002;

the yearly risk of infection (calculated from estimates of the prevalence rate of smear-positive pulmonary TB multiplied by the per capita contact rate for each smear-positive case);

the proportion of infections that leads to tuberculous meningitis in unvaccinated children aged 0 to 4 years (calculated from the ratio of tuberculous meningitis incidence to annual risk of infection);
vaccine coverage;
vaccine efficacy; and

the disability-adjusted life-years (DALYs) lost for a child who dies aged 2.6 years.

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

It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The primary studies may therefore have been identified selectively. Vaccine efficacy was derived from case-control studies. Data on births and yearly risk of infection were derived from international sources and national surveys. DALYs lost were obtained from a World Health Organization (WHO) standard life table.

**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**

Forty-four primary studies provided the clinical data.

**Methods of combining primary studies**

Estimates of vaccine efficacy were aggregated using a meta-analysis. Other estimates appear to have been combined using a narrative approach.

**Investigation of differences between primary studies**

The heterogeneity of studies that were used to derive vaccine efficacy was tested.

**Results of the review**

The number of children born in 2002 was 132.8 million.

The annual risk of infection was:

0.57 to 2.16% in Africa (high HIV);
0.13 to 1.95% in Africa (low HIV);
0.07 to 0.20% in central Europe;
0.01 to 0.12% in established market economies;
0.01 to 1.07% in Eastern Mediterranean;
0.19 to 0.66% in the former Soviet Union;
0.02 to 0.74% in Latin America;
0.13 to 1.87% in Southeast Asia; and
0.08 to 1.21% in Western Pacific.

The proportion of infections in children younger than 5 years of age that leads to tuberculous meningitis was 0.96% (range: 0.7 to 1.0).

The risk of miliary TB, which has been quantified in relation to tuberculous meningitis, was between 0.25 and 0.5.

BCG coverage worldwide was 76% (100.5 million).

The estimates of vaccine efficacy were 73% for tuberculous meningitis and 77% for miliary TB.

The DALYs lost for a child who died aged 2.6 years were 30.2.

The case-fatality rate (before anti-TB drugs became available) was 100%.

Methods used to derive estimates of effectiveness
The authors made some conservative assumptions to estimate effectiveness data not easily available from the literature.

Estimates of effectiveness and key assumptions
The annual risk of infection remained constant during the period 2002 to 2007.

There was no coverage in countries where BCG vaccination was not used at all (e.g. the Netherlands and the USA). There was also no coverage where BCG was given only to school age or older children (five countries including Norway), and where BCG was administered to risk groups only (five countries including the UK, Sweden and Switzerland).

Average estimates of efficacy applied for the 5 years after vaccination in 2002.

BCG vaccination provided the same protection everywhere against childhood TB.

Measure of benefits used in the economic analysis
The summary benefit measures used were the cases prevented, deaths prevented and DALYs gained. The number of cases prevented corresponded to the number of deaths prevented since the case-fatality rate was 100%. The analysis distinguished between cases of tuberculous meningitis and cases of miliary TB. An annual discount rate of 3% was applied to future DALYs gained.

Direct costs
The authors did not explicitly state the perspective chosen for the study. The analysis of the costs included only the cost of vaccination. The unit cost of vaccination was reported separately from the number of vaccines administered. The cost of vaccination was based on authors’ assumptions arrived at in consultation with the WHO department of vaccines, immunisation and biologicals. The quantities of resources used (number of vaccines administered) were based on published data. Discounting was not relevant as the costs were incurred during a short timeframe. The price year was not reported.

Statistical analysis of costs
Vaccination costs had a uniform distribution of probability between the lower and upper limits of the uncertainty analysis.
Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
A multivariate sensitivity analysis was used to compute the best estimates of the numbers of cases, deaths and DALYs gained, and to assess the magnitude of errors surrounding these estimates (1,500 iterations used).

Estimated benefits used in the economic analysis
The number of cases (5th centile and 95th centile in parenthesis) of tuberculous meningitis prevented in children born in 2002 up to age 5 years worldwide was 29,729 (24,063, 36,192).

The number of cases of miliary TB prevented in children born in 2002 up to age 5 years worldwide was 11,486 (7,304, 16,280).

Most of the cases would have been prevented in Southeast Asia (46%), Africa (27%; both African regions combined) and Western Pacific (15%). These are also the regions in which fewest inoculations were required to prevent one case.

The number of DALYs gained and deaths avoided were not reported.

Cost results
The expected total costs of vaccination were not reported.

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of vaccination versus no vaccination.

In the case of tuberculous meningitis, the incremental cost per case or death prevented (5th centile and 95th centile in parentheses) was $8,592 (6,320, 11,311). The incremental cost per DALY gained was $285 (209, 375).

In the case of miliary TB, the incremental cost per case or death prevented was $23,294 (14,518, 36,001). The incremental cost per DALY gained was $771 (481, 1,192).

The cost per tuberculous meningitis case prevented was lowest in Southeast Asia and highest in the established market economies.

Authors' conclusions
Bacillus Calmette-Geurin (BCG) vaccination is a cost-effective intervention against severe childhood tuberculosis (TB) worldwide. The cost per disability-adjusted life-year (DALY) gained in every region of the world was much less than the average annual income per head, which can be considered as a threshold for defining an intervention as cost-effective. BCG was most cost-effective in Southeast Asia, Africa and the western Pacific region, where TB infection rates and BCG coverage are highest. Vaccination was least favourable in the few developed countries where BCG vaccination is still routine, but where the risk of infection is now fairly low.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparator (no vaccination) was appropriate for assessing the net value of the vaccination strategy. However, in most countries, it was likely that BCG vaccination had already been implemented. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from published studies. However, it was not explicitly stated whether a systematic review of the literature was undertaken. Therefore, the primary studies might have been identified selectively. There was limited information on the design and other characteristics of the primary studies, which limits the possibility of assessing the validity of the primary sources. Vaccine efficacy was obtained using a meta-analysis and tests of homogeneity were performed. With the exception of the data used to assess vaccine efficacy, the methods used to combine the primary estimates were not described and the issue of heterogeneity across the primary studies was not addressed. The robustness of the study conclusions to variations in the clinical estimates was investigated in the sensitivity analysis.

**Validity of estimate of measure of benefit**
Both disease-specific and more generalisable benefit measures were used. DALYs were an appropriate benefit measure because they are usually employed to assess the impact of health care interventions on patient health in developing countries. Further, DALYs capture the impact of the intervention on both disability and survival. Discounting was applied, as recommended by guidelines for the economic evaluation of long-term interventions.

**Validity of estimate of costs**
The cost analysis included only the costs of vaccination, which were based on an author's hypothesis, supplemented by WHO information. The same unit cost of vaccination was used for all countries, even though it is likely to vary in different settings. However, the cost of vaccination was varied in the probabilistic sensitivity analysis, although the results of using different values were not highlighted. Resource use was based on the actual number of eligible children worldwide. The price year was not reported, which will make reflation exercises in other time periods difficult.

**Other issues**
The authors did not compare their findings with those from other studies. Sensitivity analyses were carried out to assess the impact of uncertainty in some data, and the results were reported as means and 5th or 95th percentiles in order to show the variability in cost-effectiveness estimates. The authors highlighted the reasons why the results of their analysis should be considered conservative. However, some key issues of the study were also pointed out. For example, the best estimate of BCG vaccine against meningitis was taken. Moreover, if the case-fatality rates of tuberculous meningitis and miliary TB were less than 100% (base-case assumption), the effectiveness of BCG might have been overestimated. The authors noted also that several sources of uncertainty were difficult to assess.

**Implications of the study**
The study results appear to support the widespread use of BCG vaccination against childhood tuberculous meningitis and miliary TB.

**Source of funding**
Supported by the WHO.

**Bibliographic details**

**PubMedID**
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
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