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
A paediatric tetravalent vaccine for dengue was examined in children at 15 months of age.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of children aged 15 months living in SE Asia.

Setting
The setting was primary care. The economic study was carried out in the USA, but was applied to SE Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam).

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 2002. Some cost and resource use data were obtained from two studies published in 1995 and 2000. The price year was 1999.

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

Modelling
A deterministic model of dengue transmission was constructed to assess the costs and benefits of dengue vaccination over no vaccination in a hypothetical cohort of children aged 15 months in SE Asian countries. A simplified structure of the model was reported. The hypothetical cohort of children could suffer from dengue infection that might be asymptomatic or develop into a clinical case. Clinical cases were divided into cases of dengue fever (DF) (non haemorrhagic), or dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). In the case of DHF or DSS, patients may survive or die. The time horizon of the model was lifetime.

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

the population size of the 10 countries considered in the study;
the number of cases of DF or DHF in SE Asia from 1997 to 2001;
the target population (children aged 15 months);
the life expectancy of the target population;
the lifetime number of infections per person;
the expected average annual dengue infection rate;
the annual infection rates in children younger than 15 months and in adults;
the rates of asymptomatic infection and clinical cases;
the proportion of infected individuals with DF, or DHF or DSS;
the mortality rate among patients with DHF or DSS;
the average duration of DF and DHF;
the quality of life associated with DF and DHF; and
the loss of disability-adjusted life-years (DALYs) per dengue death.

Study designs and other criteria for inclusion in the review
It appears that a systematic review of the literature has not been undertaken to identify the primary studies. No information on the characteristics of the primary studies was provided.

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
Ten studies provided the clinical data.

Methods of combining primary studies
The primary studies appear to have been combined using a narrative approach.

Investigation of differences between primary studies
Not stated.

Results of the review
The population size of the 10 countries considered in the study was 529 million in 1999.
The number of DF or DHF cases in SE Asia from 1997 to 2001 was 1.2 million.

The target population was 11.6 million children.

The life expectancy of the target population was 66 years.

The lifetime number of infections per person was 3.3.

The expected average annual dengue infection rate was 5%.

The annual infection rate was 12.5% in children under 15 months of age and 2.8% in adults.

The rate of asymptomatic infection was 76%, with 24% being the rate of clinical cases. Of these, 94% were cases of DF and 6% were cases of DHF or DSS.

Among patients with DHF or DSS, the mortality rate was 0.8%, with 99.5% of infected patients surviving.

The average duration of illness was 5.5 days for DF and 9 days for DHF.

The quality of life during these episodes was 0.19 for DF (i.e. non-DHF) and 0.15 for DHF.

The quality of life values based on losses per day (compared with perfect health) were 0.81 for DF and 0.85 for DHF.

The loss of DALYs per dengue death was 34.

It was also estimated from the literature that additional doses would be procured to compensate for an estimated 20% wastage rate.

**Methods used to derive estimates of effectiveness**

The authors made some assumptions to derive estimates of effectiveness.

**Estimates of effectiveness and key assumptions**

The efficacy of the vaccine was 95% and the recipient's annual risk of infection was reduced to 0.25%. Vaccine side effects were negligible. Children were vaccinated with two doses and vaccine coverage was 85%.

**Measure of benefits used in the economic analysis**

The summary benefit measure used was the expected number of DALYs. These were derived by combining disability weights and expected survival estimated from the literature. The QALYs were discounted at an annual rate of 3%.

**Direct costs**

A societal perspective was adopted in the study. Discounting was relevant, as the lifetime costs were estimated, and an annual rate of 3% was applied. The unit costs were not presented separately from the quantities of resources used. The economic evaluation considered the treatment of dengue and vaccine administration. The direct costs associated with treatment included ambulatory visits, hospitalisations, medications and travel expenses. The treatment costs and resource use data were estimated from published studies, and estimates were adjusted for differences in prices among countries. The author set the vaccine price. It was projected that the public sector would serve 90% of recipients, with the remaining 10% of recipients being served in the private sector. Both public and private prices ($0.50 and $10, respectively) covered the supplier's cost of production, amortised development, and profit. The vaccination costs included syringes, labour, overheads, vaccine distribution, and storage for administering the vaccine. The price year was 1999. Conservative assumptions were made to estimate the revenues to vaccine producers.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
Since a societal perspective was adopted, the indirect costs (i.e. parents' time seeking treatment) were included in the economic evaluation. The indirect costs came from the same source as that used in the analysis of the direct costs. The price year was 1999.

Currency
Official exchange rates were used to convert foreign currencies into US dollars ($) in 1999.

Sensitivity analysis
Univariate sensitivity analyses were carried out to examine the robustness of the estimated cost-utility ratios to variations in model inputs. For example, the public sector procurement price per dose, the use of combination vaccines against dengue and other diseases, the rate of clinical disease, and the length of vaccine protection. Other model inputs varied were an alternative scenario with low infection rate, a low vaccine efficacy, the highest public sector vaccine price and reduced coverage; alternative mortality rates; and the lowest coverage. The alternative values were based on published evidence or authors' assumptions, the sources being reported.

Estimated benefits used in the economic analysis
Without vaccination, the disease burden of dengue in SE Asia was 0.42 DALYs per 1,000 population (52% due to premature mortality and 48% due to acute morbidity).

Vaccination reduced both the mortality and morbidity burden by 82%, saving 0.34 DALYs per 1,000 population per year. It would save 182,000 DALYs per year.

Cost results
Without vaccination, the baseline cost of treatment was $99 per 1,000 population per year.

The incremental cost of vaccinating one child against dengue would be $4.85 in the public sector, $39.10 in the private sector, and $8.28 overall. Since each child would receive two doses, the cost per dose would be $4.14.

The gross cost per 1,000 population of the vaccination programme would be $154.

The net cost per 1,000 population (i.e. $17) was 89% below the gross cost because of the savings in health care costs from fewer dengue cases.

Overall, when fully implemented in SE Asia, dengue vaccination would cost $81.7 million per year, save $72.7 million in treatment, and have a net cost of $9.0 million.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and benefits of vaccination over no vaccination. The incremental cost per DALY saved with vaccination was $50, thus $1 million invested in dengue vaccination would save 20,000 DALYs.

At full implementation, the vaccine sales for SE Asia for each annual cohort of infants would result in revenues of $36 million per year, of which the private sector would represent 10% of the doses and 69% of the revenues. The present value of revenues would be $66 million at the 15% nominal (or 12% real) commercial discount rate, but would rise to $228 million at the 6% nominal (3% real) discount rate used in public sector analyses.
The sensitivity analysis showed that even under the most unfavourable scenario, vaccination remained cost-effective, with a cost per DALY below the per capital Gross National Income (GNI) level in SE Asia. Clearly, in contexts of high-incidence of disease, vaccination was more cost-effective. For example, at an incidence of DHF of 108 per 100,000 (double the base-case), the dengue vaccine was cost-saving for each vaccine price used ($0.25 to $1.50 per dose). At an incidence rate of 36 per 100,000 (half the base-case), the cost per DALY gained ranged from $438 at a vaccine price of $0.25 to $683 at a vaccine price of $1.50. However, the cost-effectiveness ratios were, again, always lower than the per capita GNI.

Authors' conclusions
The study results favoured the development and subsequent use of a dengue vaccine. Overall, the dengue vaccine was cost-effective in comparison with no vaccination.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (no vaccination) was appropriate as no dengue vaccination exists. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis was based on published evidence. However, it was unclear whether a systematic review of the literature was undertaken and the primary studies appear to have been identified selectively. It was not possible to assess the validity of the studies because details on the design and characteristics of the studies were not reported. A narrative approach appears to have been used to combine the primary estimates. Some assumptions were also made in the model and uncertain estimates were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of DALYs as the summary benefit measure was appropriate as it captured the impact of the intervention on quality of life and survival. Further, DALYs are a robust measure of benefits, widely used for interventions implemented in developing countries. DALYs are also comparable with the benefits of other health care interventions.

Validity of estimate of costs
The perspective adopted in the study was appropriate and all the relevant categories of costs were included in the analysis. Limited details on the unit costs and quantities of resources used were provided, which limits the possibility of replicating the study in other settings. Only the assumptions used to assess vaccine costs and revenues to producers were reported explicitly. The source of the data was reported. However, a detailed breakdown of the cost items was not given. The costs were treated deterministically and were specific to the study setting, but some key cost inputs were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings.

Other issues
The authors stated that their estimation of the cost-utility ratio compared favourably with that reported in other studies. The issue of the generalisability of the study results to other settings was addressed explicitly, with the authors stating that extending vaccination to other regions, older children and adults in SE Asia, and travellers would increase vaccine sales and revenues substantially. Further, the sensitivity analysis investigated the cost-effectiveness of vaccination in other settings, which enhances the external validity of the study.

Implications of the study
The study results supported the development of a paediatric dengue vaccine, which would be highly cost-effective and broadly beneficial.
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Bibliographic details

PubMedID
15003657

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10.1016/j.vaccine.2003.09.019

Other publications of related interest
Mahoney RT, Maynard JE. The introduction of new vaccines into developing countries. Vaccine 1999;17:646-52.


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