An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States

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 two-dose measles-mumps-rubella (MMR) vaccination programme was compared with no vaccination and with a one-dose MMR vaccination scheme.

Type of intervention
Primary prevention.

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

Study population
The study population consisted of a hypothetical US birth cohort of 3,803,295 infants born in 2001. No further inclusion or exclusion criteria were reported.

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

Dates to which data relate
The effectiveness evidence was derived from literature published from 1962 to 2000. The resources used referred to the years 1985 to 2001 (both published and unpublished data). Prices relating to 2001 were used.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of published studies. Some estimates of effectiveness were based on opinion.

Modelling
A decision analytic model was developed to evaluate the cost-effectiveness of the 2-dose MMR vaccination scheme. The model incorporated vaccination coverage and disease incidence data with associated costs. A hypothetical US birth cohort of 3,803,295 infants born in 2001 was vaccinated according to US vaccination coverage rates, and was subsequently followed up until the age of 40. Following vaccination, the model included potential subsequent states such as adverse events, immunisation or remaining susceptibility, and infection. For the part of the population that was not vaccinated, the health states described were infection or no infection. In the case of infection, the probabilities of subsequent complications were included in the model, depending on the cause of infection (measles, mumps or rubella), and the age and gender of the patient infected.
Outcomes assessed in the review
The outcomes assessed were:

- the coverage with the first and second dose of the MMR vaccine in the population;
- the age-specific annual incidence of measles, mumps and rubella in the USA, with and without vaccination;
- the probabilities of complications associated with infection from these viruses (including case fatality ratios);
- the frequency of adverse effects due to vaccination; and
- the efficiency rates of the two-dose MMR vaccination programme for hospitalised measles, non-hospitalised measles, mumps, rubella and congenital rubella syndrome (CRS).

Study designs and other criteria for inclusion in the review
The authors deliberately focused on studies that provided population-based disease surveillance and vaccination coverage data, rather than vaccine efficacy rates.

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
Not relevant.

Methods of combining primary studies
The primary studies referred only to adverse events due to vaccination. It was not stated whether and how their results were combined.

Investigation of differences between primary studies
Differences between the primary studies included in the review were not discussed.

Results of the review
The coverage with the first dose of the MMR vaccine was 3.98% in children aged less than 1 year, and between 90.20% and 95.00% in children aged between 1 and 6 years.

The coverage with the second dose of the MMR vaccine ranged from 0.99% in 1-year-old children to 79.19% in 6-year-old children.

The original paper provided a very detailed list of all the annual incidences of measles, mumps and rubella for each age group examined and the vaccine efficiency rates.
Methods used to derive estimates of effectiveness
Some estimates of effectiveness were based on authors’ assumptions.

Estimates of effectiveness and key assumptions
A key assumption of the model was that, compared with the one-dose programme, the second dose of MMR vaccine was responsible for 100% of the reduction in measles and mumps cases among schoolchildren, and for 50% of the reduction in measles and mumps cases in all other age groups, although it had a minimal impact on rubella cases. The incidence of complications due to mumps or rubella virus infection was assumed to be the same, independent of vaccination status. The incidences of vaccine-associated adverse events for the second dose were assumed to be 10% of the respective incidences for the first dose. Finally, it was assumed that women infected with rubella during a childbearing year had an overall 18% risk of having a foetus with CRS.

Measure of benefits used in the economic analysis
The measures of benefits used were the number of cases averted because of vaccination, and the number of life-years (LYs) saved. The number of LYs saved was discounted at an annual rate of 3% and was given a monetary value, based on the human capital approach, in order to conduct a cost-benefit analysis.

Direct costs
The direct health care costs consisted of:

- inpatient and outpatient costs associated with the treatment of measles, mumps, rubella and CRS, and their complications;
- the costs of MMR vaccines purchased and administered by either public or private providers (the relative proportions of type of provider were estimated), including the costs of distribution, federal excise tax and administrative costs, after taking the rate of wastage into consideration; and
- the costs of treating adverse events due to vaccination.

Other direct costs in the analysis were those relating to institutional care for mental disability, special schooling for deafness, blindness and mental disability, costs borne by audiological evaluation of hearing and hearing aids, and travel costs (for children and caregivers) to the clinic providing the MMR vaccine. There was no mention of direct costs to the patient.

The costs and the quantities were analysed separately for treatment of complications and adverse effects due to vaccination. Where applicable, the number of days of hospitalisation, outpatient visits and days of home care were provided together with the unit costs. The unit costs of vaccination and the coverage rates were also analysed separately. The total direct costs were derived using modelling. The costs were obtained from a database containing national statistics on hospital stays (accessed in 2001), a national insurance payment database (5-year average costs between 1993 - 1997 were adopted), published literature (1985 - 2000) and unpublished data (2000). The national insurance payment database provided inpatient and outpatient health care services, drug claims, physician costs, and the costs of supplies. Prices relating to 2001 were used. Discounting was carried out at an annual rate of 3%, which was appropriate since the costs were incurred over 40 years.

Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

Indirect Costs
The indirect costs were estimated in the analysis that adopted a societal perspective. These costs included productivity losses due to permanent disability (e.g. deafness and mental disability) and productivity losses of parents who stayed at
home to care for sick children, or took the children for vaccination. The economic value of a life lost prematurely was only included in the dollar per discounted LY saved ratio. The economic value of life was estimated on the basis of the human capital approach. Productivity losses were calculated using the average wages for males and females. The costs and the quantities were not reported separately. The total indirect costs were derived using modelling. All the data were taken from the Bureau of Labor Statistics and the Bureau of the Census, and referred to 2000. Prices relating to 2001 were used. Discounting was carried out at an annual rate of 3%, which was appropriate since the costs were incurred over 40 years.

**Currency**
US dollars ($).

**Sensitivity analysis**
A one-way sensitivity analysis was carried out to estimate the impact of potential changes to the vaccination programme on the results. The parameters investigated included the percentage of disease reductions due to the second-dose programme for both pre-schoolers and adults, the adverse events rate, and the post-vaccination incidence of measles, mumps and rubella. Other parameters were the proportion of vaccines purchased and administered in the public versus the private sector, the administration cost of vaccination, indirect caregiver cost and travel cost for vaccination, the wastage rate and the discount rate. The ranges of values used in the sensitivity analysis were not justified.

**Estimated benefits used in the economic analysis**
In a cohort of 3,803,295 children, without MMR vaccination, 3,433,722 measles cases, 2,100,718 mumps cases, 1,786,334 rubella cases, 616 CRS cases and 2,888 deaths occurred over 40 years.

In the presence of a national two-dose MMR vaccination programme, there were 686 measles cases, 4,801 mumps cases, 2,304 rubella cases, 14 CRS cases and 3 deaths over 40 years. Compared with no vaccination, the two-dose MMR vaccination programme prevented 3,433,036 measles cases, 2,095,917 mumps cases, 1,784,030 rubella cases, 602 CRS cases and 2,885 deaths. The programme resulted in 202,093 LYS saved (undiscounted) or 72,246 LYS saved (discount rate of 3%).

The second dose of the MMR vaccine, compared with the one-dose MMR vaccine, prevented 66,712 measles or mumps cases and 16 deaths. It resulted in an additional 1,070 LYS saved (undiscounted) or 500 LYS saved (discount rate of 3%).

All the benefits referred to a 40-year period. The adverse effects of vaccination were considered when estimating the benefits.

**Cost results**
Without vaccination, the total direct cost was $3,784,890,878 and the total societal cost (including indirect costs) was $7,887,224,473.

The two-dose vaccination programme resulted in a total direct cost equal to $5,531,412 (cost of disease) plus $266,136,613 (vaccination programme cost). The total societal cost was equal to $8,846,091 (cost of disease) plus $303,078,877 (vaccination programme cost).

The total net direct saving resulting from the two-dose vaccination programme was $3,513,222,853 and the total net societal saving was $7,575,299,505.

Compared with the one-dose vaccination programme, the additional total direct costs of the second dose of vaccination were $114,000,000 and the societal costs were $128,000,000.

The total costs referred to a population of 3,803,295 children followed-up over 40 years and were discounted at an annual rate of 3%. The costs of adverse effects of the vaccination programme were included in the analysis.
Synthesis of costs and benefits

The costs and benefits were combined in two principal ways.

In one approach, the net present value (NPV) of the programme was calculated by subtracting the total costs from the total benefits of the two-dose MMR vaccination programme. The benefits (LYs saved) were given a monetary value on the basis of the human capital approach. In this case a cost-benefit analysis was performed. The NPV of the program was $7,575,299,505 for a population of 3,803,295 children, equal to the net societal saving due to the programme, since the valuation of life according to the human capital approach was performed in the estimation of societal costs. The direct NPV of the two-dose MMR programme was also provided (excluding societal costs), but this represented only an incremental cost since it did not include a monetary valuation of the LYs saved.

In the other approach, the costs and benefits were combined in the form of incremental cost-effectiveness ratios, expressed as the cost (saving) per case averted and per LY saved. In this case, the productivity losses due to death were excluded from the calculation of the total costs, to avoid double counting of the benefits. For measles or mumps, the incremental cost per case prevented was $1,204 from the direct perspective and $998 from the societal perspective. For deaths, the incremental cost per case prevented was $4,895,313 from the direct perspective and $4,059,933 from the societal perspective. The incremental cost per LY saved was $75,075 from the direct perspective and $75,508 from the societal perspective. The incremental cost per discounted LY saved was $160,721 from the direct perspective and $161,647 from the societal perspective.

These results were shown to be robust in the sensitivity analysis. The most influential parameter was the discount rate. The benefit-cost ratio of the two-dose MMR programme remained greater than 1 in all scenarios examined.

Authors' conclusions

From both "total direct" and societal perspectives, under even the most conservative assumptions, the two-dose measles, mumps and rubella (MMR) vaccination programme was highly cost beneficial and resulted in substantial cost-savings. From an economic point of view, the second dose of MMR vaccine was not cost-saving. However, the second dose had achieved the elimination of endemic measles, a goal not achieved with the one-dose strategy. In addition, its relative cost-effectiveness was comparable to that of other life-saving interventions in the USA.

CRD COMMENTARY - Selection of comparators

The selection of no vaccination as a comparator to the two-dose MMR programme allowed the net value of the programme to be assessed. The selection of the one-dose vaccination programme was implicitly justified, as one-dose measles elimination programmes had been implemented in the USA before. These programmes reduced the incidence of measles substantially but did not eliminate endemic measles, in contrast to the two-dose MMR programme, which achieved the elimination of endemic measles in the USA. You should decide which of the technologies examined reflects routine practice in your own setting.

Validity of estimate of measure of effectiveness

It was not stated that a systematic review of the literature had been undertaken for any of the parameters. The primary studies included in the review provided only effectiveness data on adverse events due to vaccination. It was not stated whether and how their results were combined. All other estimates of effectiveness were derived from published reviews, national statistics and authors' assumptions. The latter were supported by references to the medical literature. The estimates were investigated in a sensitivity analysis, but the ranges used were not justified.

Validity of estimate of measure of benefit

The estimation of benefits was modelled. The decision analytic model used was appropriate for this purpose since it included all possible events associated with measles, mumps or rubella virus infection, and/or MMR vaccination.
Validity of estimate of costs
It was stated that the study adopted both a "direct cost" and a societal perspective. Most of the categories of cost relevant to these perspectives were included in the analysis. The direct costs to the patient were not considered. The costs and the quantities were reported separately for treatment of complications and adverse events due to vaccination, which improves the generalisability of the results. A sensitivity analysis of some costs was undertaken, but the ranges used were not justified. Discounting was appropriately conducted since the costs were incurred during 40 years. In some cases, charges were used to proxy costs when no other data were available. The date to which the prices related was reported, which enables the results to be reproduced.

Other issues
The authors made appropriate comparisons of their findings with those from other studies and found them to be consistent. Where a difference from other findings was reported, a justification was provided. The issue of generalisability to other settings was implicitly considered (there was reference to different health care delivery situations). The results of the analysis were reported in full. It should be noted that the magnitude of the NPV and benefit-cost ratio, which were used as means of presenting the results, is specific to the size of the patient cohort examined and cannot be generalised. The authors’ conclusions reflected the scope of the analysis.

Implications of the study
The authors suggested that their study might serve as a useful tool for other countries that are examining the possibility of replacing the single-antigen measles vaccine by the MR (measles-rubella) or MMR vaccine, for one or two doses. The economic model could be used to investigate the costs and benefits of using MR and MMR vaccines in different health care delivery situations.

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