Review

TRIVAC decision-support model for evaluating the cost-effectiveness of *Haemophilus influenzae* type b, pneumococcal and rotavirus vaccination

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**A B S T R A C T**

The TRIVAC decision support model has been used widely in Latin America and other regions to help national teams evaluate the cost-effectiveness of *Haemophilus influenzae* type b (Hib) vaccine, pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV). We describe the structure and functioning of this model, and identify the parameters with the greatest influence on the results.

The TRIVAC model is a spreadsheet software program that calculates incremental cost-effectiveness ratios (ICERS) and other indicators for three childhood vaccines (Hib, PCV and RV) utilising parameters such as demography, disease burden, vaccine costs, vaccine coverage, vaccine efficacy, health service utilisation and costs. There is a good deal of uncertainty about the local values of many of the parameters that have most influence on the cost-effectiveness of these new vaccines. Cost-effectiveness models can be used to explore the implications of different values of these parameters. However, for such models to be seen as relevant and helpful by decision-makers, they need to be transparent, flexible, easy to use, and embedded in a process which is owned and led by national teams.

In this paper the key drivers of cost-effectiveness in the model are identified by one-way sensitivity analyses, run for each vaccine in 147 countries. The data used are mainly from standard international sources and the published literature. The primary indicator was the discounted cost per Disability Adjusted Life-Year (DALY) averted, from a government perspective, over a 20-year period (2013–2032). For all three vaccines, the ICER was most sensitive to changes in relative coverage (the coverage of the children who would have become diseased or, more importantly, died if the population had not been vaccinated, as a % of overall national coverage) and the herd effect multiplier. Other influential parameters for all three vaccines were: the incidence and case fatality of disease, the baseline trend in disease mortality in the absence of vaccination, vaccine efficacy, vaccine price and the % decline in vaccine price per year. Important vaccine-specific parameters included the cost of Hib meningitis sequelae, PCV serotype coverage and the rotavirus gastro-enteritis (RVGE) admission rate. While vaccine efficacy, herd effects, disease mortality and vaccine price are commonly cited as important drivers of cost-effectiveness, this analysis highlights the potentially important influence of relative coverage, a parameter rarely considered in models of vaccine impact and cost-effectiveness.

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1. Introduction

The Expanded Programme on Immunization (EPI) has already had a major impact on the numbers of deaths and episodes of disease caused by diphtheria, pertussis, tetanus, polio and measles [1]. In more recent years a new generation of vaccines has become available. Two of these (Haemophilus influenzae type b [Hib] vaccine and pneumococcal conjugate vaccine [PCV]) protect against pneumonia, meningitis and other invasive bacterial diseases, and one (rotavirus vaccine [RV]) protects against severe diarrhoea. In the year 2008, diarrhoea and pneumonia were estimated to have caused 28% of all deaths in children aged less than 5 years. With the inclusion of meningitis and other invasive bacterial diseases, this fraction increases to around one-third [2]. Hib vaccine, PCV and RV have the potential to prevent a significant proportion of these deaths and have already been introduced in many countries.

Historically, vaccines have been among the 'best buys' for public health programmes, costing a matter of cents per dose [3]. The newer vaccines are more expensive. If the aim is universal coverage, even a relatively modest cost for each child can add up to a large amount for a population, so budgetary constraints and prioritisation emerge as critical issues.

Inevitably, government decisions about the introduction of new vaccines will be subject to advocacy and lobbying by interested parties. However, if the maximum public health benefit is to be had from health care spending, prioritisation should be based on how much improvement in health an intervention produces in relation to its cost. Cost-effectiveness depends on factors such as the incidence and severity of the diseases in question, the effectiveness and cost of the vaccine, and to some extent the health care costs avoided by preventing disease. Most of these factors vary considerably between countries, so cost-effectiveness will also vary by country. Ideally then, each country should determine its own priorities using evidence relevant to its own circumstances. There is growing recognition of and support for this principle, both in general and for vaccines in particular [4].

The evidence is not straightforward however. There is a good deal of uncertainty about the scale of the burden of disease and how much of it could be prevented by these new vaccines. There is also uncertainty about the future prices of new vaccines and the extent and duration of funding support from the GAVI Alliance and other donors. Uncertainties of this kind can lead to a view that evidence-based decision-making is ‘too hard’, leading in turn either to decision paralysis or to decisions based on less worthy considerations. This is where decision support models (DSMs) can be helpful, not so much to provide the answer as to provide a framework within which data and assumptions are made explicit, and the implications of choosing different options under different scenarios can be explored. In particular, they allow the implications of the evidence, and the uncertainties about the evidence, to be presented in a transparent and coherent way.

In this paper we describe the structure, methods and assumptions of the TRIVAC decision support model. The model has been designed for use at country level by teams led by the Ministry of Health [5,6]. The development of the model was funded by the Pan American Health Organization (PAHO) ProVac Initiative (www.paho.org/provac) and GAVI Hib Initiative (www.hibaction.org). To date, it has been used to perform national and/or sub-national cost-effectiveness evaluations in Albania, Argentina, Belarus, Bolivia, Costa Rica, Ecuador, El Salvador, Guatemala, India, Nicaragua, Pakistan, Panama, Paraguay, Peru and Uzbekistan.

In 2011, the PAHO ProVac Initiative received requests from other regions (e.g. Africa, Eastern Mediterranean, Eastern Europe) to use both the TRIVAC model and the ProVac methodology of which the model is just one part. This methodology involves providing practical training at facilitated regional workshops, forming national teams, providing technical assistance, and supporting presentation of results to National Immunization Technical Advisory Groups (NITAGs) and high-level Ministry of Health authorities [5]. In response to these requests, a ProVac International Working Group (IWG) has been established with funding from the Bill and Melinda Gates Foundation [see Toscano C, same Supplement].

One of the challenges of using a standardised model in a diverse set of countries is that the influence of each parameter may vary across settings. A better understanding of this from the outset should allow national teams with limited time and resources to prioritise their data collection efforts and scenario analyses.

This paper aims to: (i) provide a methodological reference document for national teams and partners working with the TRIVAC model; and (ii) identify the TRIVAC parameters likely to have the greatest influence on the cost-effectiveness of Hib vaccine, PCV and RV, in different epidemiological and economic contexts.

2. Methods

The TRIVAC model is a spreadsheet software program that calculates incremental cost-effectiveness ratios (ICERs) and other indicators for three childhood vaccines (Hib, PCV and RV) utilising parameters such as demography, disease burden, vaccine costs, vaccine coverage, vaccine efficacy, health service utilisation and costs. Where more than one vaccine is evaluated, the common model framework provides a consistent basis for comparison.

The model is designed for use in low- and middle-income countries (LMICs) and a small number of countries that have recently graduated to high-income [7]. The 147 countries included in the model can be grouped according to geographical region, and WHO mortality strata B, C, D and E [8]. The model excludes all countries in WHO mortality strata A (very low mortality) and a number of countries with very small populations.
2.1. Rationale for a user-friendly model

Many LMICs are constrained by poor data quality and a shortage of technical capacity in economic evaluation. The TRIVAC model can be used at different levels, from the basic or introductory (simple structure, fewer inputs) to the more complex and demanding of data. To increase transparency and accessibility of the model to national teams, it has been developed in Microsoft Excel [9] with a number of additional features in Visual Basic for Applications (VBA). It includes a user-friendly interface with different language options, ‘pop-up’ parameter definitions, and built-in features for scenario and uncertainty analysis. It is populated with baseline parameter values taken mainly from international databases, and where values are not available at country level (e.g. vaccine efficacy, health care access), estimates for the WHO sub-regional mortality strata are typically used. National teams are encouraged to scrutinise these estimates and suggest improvements if they have better information, or propose alternative scenarios if they are uncertain.

2.2. Outcome indicators

The model calculates a variety of indicators, including numbers of prevented cases, outpatient visits, admissions and deaths, % of under-five mortality prevented, life-years gained, costs of vaccination and prevented health-care costs. However, the primary task for cost-effectiveness analysis is to estimate the incremental cost-effectiveness ratio (ICER). For each scenario, or combination of parameter values, the model calculates the costs and benefits arising over a given period with and without the vaccine in question. TRIVAC generates ICERs for each type of health outcome (cost per death averted, cost per life-year gained, etc.) but the ratio most commonly reported to national authorities, is the cost per DALY averted. This is calculated as:

\[
\text{Costs with the new vaccine} - \text{Costs without it} \\
\text{DALYS without the new vaccine} - \text{DALYS with it}
\]

Costs include both vaccination programme costs and health care costs associated with treating vaccine-preventable diseases. DALYs are healthy years lost due to disease mortality and morbidity. Morbidity is included by applying an international standard set of ‘weights’ to years of ill health, thus providing a more comprehensive basis for comparing different interventions than impact on mortality alone [10].

The model includes the option of discounting future costs and health benefits to the year of vaccine introduction at a rate chosen by the user. Another option allows greater weight to be given to life-years gained during productive working age (DALY age weighting).

2.3. Time horizon and stacked cohorts

Estimates of costs, health benefits and cost-effectiveness are calculated by tracking the experience of annual birth cohorts from 1 to 59 months of age. Vaccination programme costs are assumed to occur in the first year of each cohort, while disease cases, deaths and treatment costs are estimated for the first five years of age. Years of life lost, DALYs and costs of sequelae are estimated over the lifetime of the population in each cohort using current and projected life expectancies.

The model also estimates health benefits and costs arising in each calendar year by ‘stacking’ the results from each cohort. For the second modelled year, the results from the second year of the first cohort are added to those for the first year of the second cohort, and so on. This has proved to be helpful for policy makers, many of whom find it more natural to think in terms of year-on-year trends than lifetime events in a specific cohort. Also cost-effectiveness can be evaluated over a sustained period of routine vaccination, during which key parameters may be changing. For example: (i) a vaccine can be phased into the programme gradually by steadily increasing coverage; (ii) the proportion of circulating serotypes that are ‘vaccine type’ can be reduced in future years to simulate serotype replacement; (iii) the vaccine price or co-financing contribution can be varied over time; and (iv) baseline disease mortality can follow long-standing declining trends in the absence of vaccination due to generalised improvement of health conditions. In order to capture the effect of such changes, the model can evaluate up to 20 successive (or ‘stacked’) annual birth cohorts.

2.4. Model structure

TRIVAC is a static cohort model. This means that effects in unvaccinated children (indirect effects, whether positive through e.g. herd effects, or negative through e.g. type replacement) can only be crudely taken into account, using simple and highly speculative adjustments to the impact of the direct effects.

The structure of the disease burden part of the model is shown in Fig. 1. Life-years lived between 1 and 59 months of age are derived for each successive birth cohort using annual projections of births, neonatal mortality, infant mortality and under-five mortality. To estimate the number of disease cases attributed to each cohort, the projected number of life-years lived between 1 and 59 months is multiplied by the estimated incidence of disease in the same age group.

For Hib, disease categories B, C and D correspond respectively to pneumonia, meningitis and all other forms of invasive non-pneumonia and non-menigitis (NPNM), namely epiglottitis, cellulitis, septic arthritis, septicaemia, osteomyelitis and pericarditis [11]. Disease category A (less severe disease, causing no deaths or admissions) is not used. For pneumococcal disease, disease categories A, B, C and D correspond respectively to cases of acute otitis media, pneumonia, meningitis and other invasive NPNM disease e.g. sepsis and bacteremia. For rotavirus, disease categories A and B represent non-severe and severe rotavirus gastroenteritis (RVGE) respectively, as defined by the Vesikari 20-point scale for RV1 [12] and the Clark 24-point scale for RV5 [13]. However, disease categories can be redefined by the user if: (a) there is better local evidence on the incidence and health care costs for a different definition of disease and/or severity and (b) international efficacy estimates are available for this disease category. For example, information about RVGE admissions can be used instead of RVGE severe cases and all cause radiological pneumonia admissions instead of pneumococcal pneumonia cases. When this option is used, case fatality ratios are assumed to be the ratio between e.g. RVGE admissions and RVGE deaths, thus capturing the correct number of deaths in the community.

Total numbers of cases in each disease category are multiplied by their respective case fatality ratios (CFRs) to give total disease-specific deaths up to age 59 m, and total cases and deaths are then distributed across the following age bands: <3 m, 3–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m. Estimates of vaccination coverage for each age band are used to account for delayed vaccination.

A risk of permanent disability is applied to all children who survive an episode of Hib meningitis or pneumococcal meningitis. Sequelae can be divided into two user-defined categories depending on the availability and quality of local data e.g. major and minor, single-syndrome and multiple-syndrome, auditory and neurologic, etc.

2.5. Health care use and costs

The numbers of outpatient visits and inpatient admissions are estimated by assuming an average number of visits/admissions per
case for each disease. Each outpatient visit and admission can be assigned to the public, social security or private sector by selecting one of up to ten user-defined categories of healthcare provider. Costs per visit and costs per admission can be specified for each type of provider.

The total health care costs avoided in a given cohort are equal to:

\[
D \times [ (O \times C_O) + (H \times C_H) ]
\]

where

- \(D\), the number of cases of disease avoided among children in the cohort
- \(O\), average number of outpatient visits per case
- \(C_O\), weighted cost per outpatient visit
- \(H\), average number of inpatient admissions (hospitalisations) per case
- \(C_H\), weighted cost per inpatient admission

The weighted costs are calculated from the proportions of visits or stays in different types of user-defined provider and their respective costs. Costs borne by governments (e.g. bed day costs, drugs and diagnostics) and costs borne by households (e.g. productivity losses, travel costs and user fees) are treated separately. This allows for analysis from different cost perspectives e.g. one perspective might include all costs, while another may exclude household costs and assume the government bears a % of the Social Security costs. For life-long sequelae an average cost per year is applied from year of onset of meningitis until death.

2.6. Vaccination programme costs

The starting point is the vaccine cost per dose which is calculated as follows:

\[
P = \frac{(1 + F + H)}{(1 - W)}
\]

where

- \(P\), price per dose
- \(F\), freight cost (expressed as a % of price per dose)
- \(H\), handling cost (expressed as a % of price per dose)
- \(W\), % wastage

Costs can also be included for safety boxes and syringes, using the same formula.

To estimate the total numbers of vaccines administered, the model takes into account the differences in coverage for each dose, with surviving infants assumed to be the denominator for each coverage rate. To better represent the true cost, this denominator can also be adjusted to account for doses received by children who die from other causes between 1 and 11 months.

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It is assumed that Hib vaccine, PCV and RV are delivered at the same visit as other vaccines in the EPI programme (e.g. DTP, DTP-HepB, etc.). For Hib vaccine, costs are subtracted for any vaccines that would be replaced by the new vaccine, so that if DTP-HepB is replaced by DTP-HepB-Hib the incremental cost is the difference between the cost of the quadrivalent and pentavalent vaccines after accounting for differences in the freight, handling and wastage of the vaccines, syringes and safety boxes.

For all three vaccines, the model can accommodate estimates of the annual incremental costs to the ‘health system’, expressed per dose. This includes annualised start-up costs (e.g. social mobilisation, training, cold-chain expansion, buffer stock, printing vaccination cards) and any recurrent costs not included in the earlier estimate of vaccination costs per dose (e.g. maintenance of cold chain and surveillance for adverse events). To calculate this, national teams have developed their own costing templates tailored to the nuances of their specific programme.

TRIVAC also provides the option to display charts showing financial costs in each calendar year (i.e. year 1 buffer stock, year 1 capital costs, recurrent non-vaccine costs, and recurrent vaccine costs). This time-profile of financial costs does not inform the cost-effectiveness ratio, and is not intended as a replacement for a detailed budgeting exercise, but can start the process of communicating the financial implications of new vaccine introduction.

Changes in vaccine price can be modelled simply as an initial price with a fixed % change per year. Alternatively a specific price can be given for each year if prices are expected to change in an irregular fashion, or if for example a government is expected to pay only some fraction of a fixed price for a limited period, as in co-payments for the duration of GAVI support.

2.7. Vaccine impact

The key steps for estimating vaccine impact are described in Fig. 2. In summary, the model accounts for dose-specific efficacy, age- and dose-specific coverage, serotype coverage for PCV, age-specific waning protection and relative coverage. In many countries the children most at risk of disease and with poorest access to antibiotics and oral rehydration are also the children least likely to be reached by the vaccination programme; relative coverage is the coverage of the children who would have become diseased or, more importantly, died if the population had not been vaccinated, as a % of overall national coverage. Thus overall national coverage can be adjusted downwards by this ratio to better reflect the true impact of the programme. In the model the impact of the programme can be adjusted to account for this, and reasonable proxies can be used to inform its value such as coverage in severely underweight children divided by coverage in the cohort overall.

The user can also investigate some of the potential impact of herd effects by adding a % to the direct vaccination effect, and of serotype replacement, by reducing vaccine type coverage by a fixed % each year. These percentages can be informed by evidence about the possible scale of effects observed in post-licensure studies [14,15].

For a birth cohort, and age group, the number of cases prevented is equal to:

\[
\text{E} = \binom{(1 - N_{\text{MR}})}{(1 - P_{\text{NR}})}^* (1/12) \text{ life-years} 1-11 \text{ m for survivors to age 1 year} \\
B^* (1 - N_{\text{FR}})^* (P_{\text{NR}})^* (1/12) \text{ life-years for those dying between 1 and 12 m} \\
B^* (1 - U_{\text{MR}})^* (P_{\text{NR}})^* (1/12)^* 0.5 \text{ life-years for those dying between 1 and 12 m} \\
B^* (1 - U_{\text{FR}})^* (P_{\text{NR}})^* (1/12)^* 4 \text{ life-years for those dying between 1 and 12 m} \\
B^* (U_{\text{MR}} - U_{\text{FR}})^* (P_{\text{NR}})^* (1/12)^* 4 \text{ life-years for those dying between 1 and 12 m} \\
\]

\[
\text{I} \text{ % incidence of disease aged 1-59 m per year} \\
\text{A} \text{ % of disease in age group} \\
\text{B}, \text{ live births per year} \\
\text{N}_{\text{MR}}, \text{ neonatal mortality rate (% of live births dying before 1 month of age)} \\
\text{I}_{\text{MR}}, \text{ infant mortality rate (% of live births dying before 1 year of age)} \\
\text{P}_{\text{NR}}, \text{ post-neonatal mortality rate (% of children dying between 1 and 12 months of age)} \\
\text{U}_{\text{MR}}, \text{ under-five mortality rate (% of live births dying before 5 years of age)} \\
\text{I}, \text{ incidence of disease aged 1-59 months, per 100,000 per year} \\
\text{A}, \text{ % of disease in age group} \\
\text{E}, \text{ % efficacy with a booster dose} \\
\text{E}_{\text{P1}}, \text{ % efficacy with 3 doses} \\
\text{E}_{\text{P2}}, \text{ % efficacy with 2 doses} \\
\text{E}_{\text{P3}}, \text{ % efficacy with 1 dose} \\
\text{C}, \text{ % coverage of booster dose in age group} \\
\text{C}_{1}, \text{ % coverage of 3 doses in age group} \\
\text{C}_{2}, \text{ % coverage of 2 doses in age group} \\
\text{C}_{3}, \text{ % coverage of 1 dose in age group} \\
\text{T}_{1}, \text{ % vaccine serotype coverage in year of vaccine introduction} \\
\text{T}_{2}, \text{ % vaccine serotype replacement per year following vaccine introduction} \\
\text{T}_{3}, \text{ number in the sequence of future birth cohorts} \\
\text{R}, \text{ % of coverage reaching those who would have got the disease with no programme} \\
\text{W}, \text{ % decrease in protection due to waning} \\
\text{H}, \text{ % herd effect multiplier (note: maximum possible herd effect = disease elimination)}
\]

Standard methods and calculations are used to incorporate discounting, age weighting and DALYs [16]. For cases in disease categories B, C and D, which have the potential to progress to admission and death, vaccine efficacy is assumed to be the same for severe cases, outpatient visits, admissions and deaths. Thus all B, C and D cases are assumed to be relatively severe (e.g. chest X-ray confirmed pneumonia, severe RVGI). For the non-severe disease A cases the same (lower) efficacy is applied to both cases and outpatient visits.

2.8. Uncertainty analysis

The model has a number of built-in facilities for sensitivity and scenario analysis.

1. Simple (one-way) sensitivity analysis. On request, the model varies each input parameter in turn by a fixed percentage. Then all the parameters considered are ranked according to the size of the resulting % change in the cost per DALY averted. This can be very helpful in demonstrating what the model does, and that it is working as it should be.

2. Scenario analysis. This allows country teams to build up to 20 ‘what-if’ scenarios involving different combinations of parameter values. They may select different combinations of
### Step 1
**Vaccine efficacy %**: Vaccine efficacy is estimated for dose 1, dose 2, dose 3 (if relevant) and a booster dose (if relevant).

### Step 2
**Vaccine type coverage (%):** the % of circulating sero/genotypes that are vaccine type (used for PCV and less commonly for RV). This can vary according to the type of disease e.g. meningitis vs pneumonia.

*Note: this can be set (exogenously) to decline by a small fraction each year to represent PCV-related serotype replacement.*

### Step 3
**Vaccine coverage (%):** Vaccine coverage in the year of vaccine introduction is estimated for dose 1, dose 2, dose 3 (if relevant) and a booster dose (if relevant) using DTP1, 2, 3 and Measles 1st dose as a proxy.

*Note: improvements in vaccine coverage over time are modelled by specifying a long-term target value for coverage (such as 99% over 20 birth cohorts), and reducing the ‘distance from target’ by a fixed percentage each year. The model includes a final option to adjust manually (override) the trend in coverage if required.*

### Step 4
**Vaccine timeliness:** Vaccine coverages for dose 1, dose 2, dose 3 (if relevant) and the booster dose (if relevant) are converted into age-specific coverage at ages 3m, 6m, 9m, 12m, 24m, 36m, 48m and 59m. Methods for estimating age-specific coverage using survival analysis have been reported elsewhere [22]. This approach involves analysing the reported date of birth and a data of vaccination (DTP1,2,3 and Measles 1st dose) for children represented in household surveys.

*Note 1: Disease cases and deaths are also converted into corresponding age bands so the model can account for the expected impact of vaccination delays.*

*Note 2: the model includes the option to apply manufacturers recommended age restrictions (Actual, restricted) for RV (1st dose<15 weeks; last dose<32 weeks) [23]. Alternatively they can choose to evaluate an unrestricted programme with delays similar to DTP1, 2, 3 and Measles 1st dose (actual, unrestricted) or evaluate what would happen if all vaccines were administered according to the schedule (on-time, unrestricted).*

### Step 5
**Relative coverage (%):** the coverage of the children who would have become diseased or, more importantly, died if the population had not been vaccinated, as a % of overall national coverage.

*Note: a useful proxy for this can be coverage in children who are severely underweight (e.g. estimated from household surveys) divided by coverage in the cohort overall.*

### Step 6
**Waning effect of vaccine per year (%):** Multiply by a fixed % each year using a waning matrix. With age bands (<3m, 4-5m, 6-8m, 9-11m, 12-23m, 24-35m, 36-47m, 48-59m) repeated in the rows and columns of the matrix, the direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

### Step 7
**Herd effect in cohort evaluated (%):** Rather than endogenous modelling of transmission dynamics, this is specified by the modeller as a simple multiplier of the direct effect i.e. % direct protection * herd effect multiplier.

*Note 1: the total impact cannot exceed 100%.*

*Note 2: this value can usually be informed by post-licensure studies.*

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Fig. 2. Steps used to estimate vaccine impact in the TRIVAC model.
default distribution is triangular, which forms a simple basis for training and understanding of the method. Where data permits, or where better assumptions are required, more advanced users can import other distributions (e.g. gamma, beta, log-normal) from a companion Excel tool developed for TRIVAC. The sampling process is repeated many times, generating a distribution of possible values for health benefit and net cost. These are presented in a scattergram, in which relatively little uncertainty would appear as a small dense cloud of points around the central ICER value, and substantial uncertainty would appear as a larger, more dispersed cloud. This provides a systematic way of eliciting and representing uncertainty about the data and showing the implications for the ICER. Starting seeds can be used for each random number stream to provide reproducible results. The same seeds are used for specific groups of correlated parameters such as case fatality ratios.

2.9. Important drivers of cost-effectiveness for Hib vaccine, PCV and RV

To identify the most influential parameters in the TRIVAC model, we carried out simple one-way sensitivity analyses for each vaccine in each country. For each parameter, we reduced the base case value by 10% and observed the associated change in the discounted cost per DALY averted over a 20 year period (2013–2032), from both a government and a societal perspective.

This desk-based exercise is not designed to provide credible national estimates of cost-effectiveness, and the national ICERS are not presented here. Indeed this would contradict part of the purpose of the model, which is to help promote local data collection and national ownership of the analysis. However, there can be up to around 300 parameters in the TRIVAC model, and a preliminary one-way sensitivity analysis can help to make a start on the question of which parameters are likely to have the greatest influence on the results in each country. National teams can then focus on reviewing the quality of local data on these parameters, seeking better data if possible (e.g. ranges for PSA), and setting the agenda for scenario analysis.

For this exercise we used the standard data used to pre-populate the model. These estimates come from various international sources: (i) demographic projections from the United Nations Population Division (UNPOP) 2010 Revision; (ii) neonatal mortality, timeliness of vaccination and access to health care from Demographic and Health Surveys [DHS]; (iii) vaccination coverage from WHO/UNICEF; (iv) incidence, DALY weights and case fatality ratios used to inform WHO estimates of the Global Burden of Disease [GBD]; (v) vaccine price and supplies data from UNICEF and the PAHO Revolving Fund; (vi) health care costs from WHO-CHOICE [choosing interventions that are cost-effective] and National Health Accounts [NHA]; and (vi) GNI per capita from the World Bank. We used evidence from the global scientific literature to estimate hospitalisation rates, duration of illness and non-severe RVGE incidence. A fuller account of the methods used to support the country-specific assumptions is given in the Appendix.

An initial univariate analysis involved reducing each parameter by –10% and then ranking them in terms of the resulting % change in cost-effectiveness. Subsequent analyses were restricted to parameters with the largest effects, in practice parameters with an effect greater than –1% across all countries (11 parameters for Hib vaccine, 13 for PCV and 10 for RV). To standardise the presentation of ‘key drivers’ for each vaccine across a large number of countries, the percentage effect for each parameter was divided by the total of all the effects for the set of influential parameters, so that the total of all these effects for each vaccine in each country was 100%. Scaling factors were generated to allow this relative influence to be converted into absolute influence. For example, a relative influence of 14% could be scaled by a factor of 1.5 to give the absolute influence (21%) observed for a –10% change.

3. Results

Fig. 3 shows the relative and absolute influence of each key parameter on the cost-effectiveness of Hib vaccine, PCV and RV respectively, from a government perspective, in each WHO sub-region. The full country breakdown is available in the Appendix. For all three vaccines, relative coverage and the herd effect multiplier were the most influential parameters. Both factors are important because they have a direct impact on the amount of health and economic benefit without affecting the programme cost. Other influential parameters for all three vaccines were: (i) the baseline disease mortality trend in the absence of vaccination; (ii) vaccine price; and (iii) the % decline in vaccine price per year.

For Hib vaccine, other important parameters were: (i) the incidence and case fatality of Hib pneumonia and Hib meningitis; and, (ii) efficacy of 3 doses against Hib pneumonia and Hib meningitis.

For PCV, other important parameters were: (i) the incidence and case fatality of pneumococcal pneumonia and pneumococcal meningitis; (ii) efficacy of 3 doses against pneumococcal pneumonia and pneumococcal meningitis; and (iii) vaccine serotype coverage for pneumococcal pneumonia and meningitis.

For RV, other important parameters were: (i) the incidence and case fatality of severe RVGE; (ii) full-course efficacy against severe RVGE; and (iii) the rate of waning of vaccine protection.

When results were run from a societal perspective, the household costs of meningitis sequelae were influential for both Hib vaccine and PCV i.e. at least as influential as the other meningitis parameters shown in Fig. 3.

For Hib vaccine, the relative influence of most of the 11 parameters did not vary much across the WHO mortality strata. However, in the lower mortality strata, meningitis parameters had a greater influence on ICERS than pneumonia parameters. For PCV, the same effect can be seen but it is less marked. For RV, the inpatient admission rate had a greater influence in lower mortality (and higher income) strata. In higher mortality strata, RVGE mortality and RV waning rates were more influential.

The scaling factors (used to generate the absolute influence for a 10% change) were around 1.0 for all three vaccines. For RV, there was more variation, and in a few countries (e.g. Argentina, Uruguay) the scaling factors were much higher.

4. Discussion

4.1. Strengths and weakness of the model

To date, TRIVAC has been used widely for decision support relating to PCV and RV in Latin America, and mainly for Hib vaccine in a few countries elsewhere. The challenge has been to devise a model that produces results that decision makers can believe in and defend, under sometimes hostile scrutiny, and TRIVAC has a number of advantages in this respect:

1. Transparency. National teams led by the Ministry of Health, and ultimately the committees and decision makers they engage with, need to understand what the model does. They cannot be expected to take the validity of a ‘black box’ model on trust, or to devote much time to studying documentation or deciphering computer code. This suggests using a methodology than can be easily explained to decision makers, and software that allows national teams get ‘inside the box’ and look round. TRIVAC’s
Fig. 3. Relative and absolute influence on ICER for a 10% change in key parameters.

relatively simple structure and Excel platform are advantages in these respects. There is also a stripped down version of the model to get national teams started and additional features that they can engage with as they gain experience and confidence.

2. Flexibility. Different decision-makers may have different views about what factors are important, what values are plausible, and even what outcomes are most important. This means that any attempt at producing a single best estimate will be controversial at least, and exploring different scenarios becomes essential. Ideally a model will be able to accommodate all the scenarios that the decision-makers are likely to want to consider. TRIVAC has been under continual development for several years, and new features have been added to accommodate new questions. Now the demand for additional features is perceptibly slowing, but improvements to the facilities for probabilistic sensitivity analysis are in the pipeline.

3. Speed of response. Gathering the inputs for the model and getting the right people together to review them can be a challenging and lengthy process. Thus when experts meet to review inputs, there is a critical window of opportunity to review results, explore key drivers, run scenarios and stimulate
thinking about new scenarios. TRIVAC’s calculations are fast enough for it to be used interactively and in an exploratory way, allowing national teams to finalise results and present evidence to senior decision makers sooner than would otherwise be possible.

The model does have material shortcomings however (Fig. 4). The most important is its crude way of modelling indirect effects. As a static model it does not directly simulate the changes in disease incidence rates resulting from changes in the risk of infection, or the replacement of sero- or genotypes associated with introduction of a new vaccine. In mitigation, if vaccines are shown to be cost-effective with a static model, then a dynamic model would generally only make them appear more so. However, dynamic models may still be required in situations where: (i) material negative indirect effects (e.g. pneumococcal type replacement) have to be balanced against material positive indirect effects (e.g. herd immunity); or (ii) the issue is a head-to-head comparison of competing vaccines (e.g. PCV10 versus PCV13). To model indirect effects properly would require a dynamic model and enough local epidemiological data to calibrate it [17]. Calibration of dynamic models involves inferring values for generally unobservable parameters such as basic reproductive rates for Hib/pneumococcal colonisation and rotavirus infection, which can be a complex and lengthy process. Such models often seem rather opaque to decision-makers and may not be responsive enough for decision support purposes. The way forward must be to develop static and dynamic models side by side, and validate the former against the latter, and/or to provide enough flexibility for advanced users to change the basic model structure so as to incorporate transmission dynamics while retaining the familiar interface. Where data permits, models such as TRIVAC can help national teams understand the impact of including or excluding specific features, and ideally help stimulate national demand for more advanced modelling techniques.

Another limitation of TRIVAC is that it models each vaccine separately, comparing its impact against the situation with no new vaccines. It thus assumes that the level of benefits from one new vaccine is unaffected by whether the others have been adopted or not. In theory this should only be a problem in countries with very high mortality indeed. Of greater concern is the fact that TRIVAC does not account for the effect of other complimentary health interventions that might be introduced or scaled up at the same time as the new vaccine. For example improving access to oral rehydration will reduce the cost-effectiveness of a rotavirus vaccine in subsequent cohorts, by reducing the burden of mortality from diarrhea.

In terms of model validation, a lack of good quality pre- and post-introduction surveillance data has generally prevented assessment of the predictive power of the model. However, the default inputs for demography, burden of disease, efficacy, age and dose-specific coverage, waning, etc., were shown to produce results consistent with the real-world impact observed in a case control study of rotavirus vaccination in Nicaragua [18]. In addition, TRIVAC has been shown to produce pneumococcal outcomes consistent with results from other PCV models [19] although meaningful comparisons with transmission dynamic models in LMICs have not been possible to date. Finally, the general structure and methods of the model were presented to WHO’s committee for assessing Quantitative Immunization and Vaccine related Research (QUIVER). The experts felt that although further work incorporating temporal dynamics could enhance comparability to other non-vaccine interventions, on the whole TRIVAC was a useful public health tool to build capacity for evidence-based decision making in low and middle income countries [20].

4.2. The most influential parameters

We have identified parameters which influence the cost-effectiveness of Hib vaccine, PCV and RV in each country. This is only part of the story, because the range of plausible values is much greater for some parameters than for others, but this is as far as we can go in a desk-based exercise without extensive consultation on the appropriate ranges of values for each country.

In determining priorities for data collection it does seem important to consider vaccine coverage in children who are most likely to get the disease rather than coverage overall. While vaccine efficacy, herd effects and vaccine price are commonly cited as important drivers of cost-effectiveness, relative coverage is rarely considered in models of vaccine impact and cost-effectiveness [21]. In addition, good quality local evidence is needed on the incidence and case fatality of severe RVGE and Hib/pneumococcal pneumonia and meningitis. Other parameters that should be prioritised for local data collection are pneumococcal vaccine type coverage, RVGE admission rates, and meningitis sequela costs borne by households. Vaccine price and vaccine efficacy are also highly influential and attention should be given to uncertainties in ancillary parameters such as the rates of decline in vaccine price decline and vaccine efficacy.

A one-way univariate analysis highlights the effect of each parameter when varied in isolation. This is a useful check on whether the model is behaving as expected, but as a basis for assessing the relative influence of each parameter it has its limitations. Firstly some parameters, such as costs of health care from specific providers, only affect a minority of cases, and considered in isolation their effects may be small. However, if costs for all the different providers are correlated, taken as a group they may be important. To avoid this problem we could have varied groups of correlated parameters together rather than each in turn, but this would have required data or assumptions about the correlation structure. A univariate analysis has the advantage of being easier to explain, and to some extent the overall influence of a set of finely disaggregated parameters would still be captured by dependencies on other upstream parameters. For example none of the RVGE health care costs for specific types of provider are major drivers, but collectively they can be important, as can be inferred from the influence of the RVGE admission rate.

Second, although parameters are each varied by a constant percentage, their influence may depend on their baseline value. For example, the rate of RV waning had a large influence in Africa and in the high mortality countries in Latin America, but this is driven entirely by the larger but uncertain baseline value assumed in these mortality strata.

More generally, the results are conditional on the whole baseline scenario. If significant changes are made to e.g. the discount rate, the policy regarding RV age restrictions, or the vaccination schedule, then the rankings of parameters may change.

Third, the results will depend on the comparison being made. For example, if the issue is not whether PCV should be introduced but whether it should be PCV10 or PCV13, most factors will be the same for both vaccines, and will balance out. Then the few variables that do discriminate, such as the costs of acute otitis media, will increase in influence.

To conclude, the model provides the motivation and logical framework for a whole process. The first part of this – identifying people and resources within the country concerned, forming institutional collaborations, and collecting and evaluating local data – has often proved at least as valuable as the part that is the concern of this paper – exploring scenarios and interpreting cost-effectiveness results [5]. Experience with TRIVAC to date suggests that cost-effectiveness models have a much better chance of being seen to be relevant to decisions and understood by local...
TRIVAC does:

- Provide estimates of direct vaccine protection among children aged 1-59 months
- Include a fixed estimate of the potential influence of herd effects, informed by real-world post-introduction studies.
- Include a fixed estimate of the potential influence of serotype replacement, informed by real-world post-introduction studies.
- Compare the costs and benefits of competing vaccination schedules or brands of a vaccine, by constructing a wide range of plausible scenarios.
- Allow comparison of cost, impact and cost-effectiveness of alternative vaccines (Hib, PCV, RV) considered separately but on a consistent basis.
- Allow for univariate sensitivity analysis, multivariate scenario analysis, and simple probabilistic sensitivity analysis (PSA).

TRIVAC does not:

- Include vaccination benefits for individuals aged over 5 years. This will lead to conservative estimates of vaccination impact, particularly for PCV.
- Keep track of the number of susceptible, infectious and immune individuals over time, or the likely patterns of transmission between those individuals.
- Explicitly model the likely indirect herd effect of a vaccine or the likely changes in the average age of infection.
- Keep track of the number of susceptible, infectious and immune individuals over time.
- Differentiate each of the circulating types of a pathogen in terms of their transmissibility, efficacy, and propensity to replace other types.
- Provide a basis for making decisions between different vaccination schedules or brands of a vaccine when the results from a wide range of plausible simplified ‘scenarios’ are not persuasive i.e. do not clearly favour one particular schedule or brand of vaccine.
- Evaluate all three vaccines simultaneously to account for competing risks and subtle demographic effects e.g. preventing early rotavirus deaths, increases the pool of individuals susceptible to PCV.
- Provide a correlation structure for parameters varied in sensitivity analysis.

Fig. 4. Summary of situations where the TRIVAC model should be used with caution.

policymakers if they are embedded in such a process, owned and led by national teams.

Conflict of interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.05.045.

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