WHO guide for standardization of economic evaluations of immunization programmes

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Contents

1.1 Preface ................................................................................................................................. xi
1.2 Acknowledgements ............................................................................................................ xii
1.3 Abbreviations and acronyms ............................................................................................ xiii
1.4 Glossary of terms ............................................................................................................... xv

Chapter 1: Introduction ....................................................................................................... 1
1.1 Evidence-based decision-making ..................................................................................... 1
1.2 Existing guidance and recent changes in economic evaluation .................................... 2
1.3 Overall aim and target audience ..................................................................................... 2
1.4 Structure of the guide ....................................................................................................... 3

Chapter 2: Economic evaluation of health care .............................................................. 4
2.1 Different types of economic evaluation ........................................................................... 4
2.2 The role of economic evaluation .................................................................................... 5
2.3 Budget impact analysis/financing of programme implementation .......................... 6

Chapter 3: Framing the analysis ....................................................................................... 8
3.1 Target audience ............................................................................................................... 8
3.2 Study question ............................................................................................................... 8
3.3 Type of evaluation ......................................................................................................... 9
3.4 Target population ......................................................................................................... 12
3.5 Comparator .................................................................................................................... 12
3.6 Perspective ..................................................................................................................... 15
3.7 Time frame and analytic horizon .................................................................................. 15
3.8 Scope of benefits .......................................................................................................... 16
3.9 Recommendations ....................................................................................................... 17

Chapter 4: Estimating costs .............................................................................................. 18
4.1 Approaches to costing ................................................................................................... 18
   4.1.1 Bottom-up and top-down costing ........................................................................ 18
   4.1.2 Full and incremental costing .............................................................................. 18
   4.1.3 Choosing the price level and currency ............................................................ 19
Chapter 7: Discounting

7.1 Why vaccination programmes are sensitive to the choice of discount rates

7.2 Equal or differential discounting

7.3 Other discounting schemes

7.4 Recommendations

Chapter 8: Estimating, presenting and interpreting cost-effectiveness data under uncertainty

8.1 Why accounting for uncertainty?

8.2 How should costs and effects be linked?

8.3 Which uncertainties to account for?

8.3.1 Types and sources of uncertainty

8.3.2 Which uncertainties (not) to account for?

8.3.3 How (large) should the uncertainties be specified?

8.3.4 How to be transparent on the uncertainties (not) included?

8.4 Propagating the uncertainties into the results of the economic evaluation

8.4.1 Propagating uncertainty in a deterministic way

8.4.2 Propagating uncertainty in a probabilistic way

8.4.3 Deterministic and probabilistic sensitivity analysis combined

8.5 Determining the most optimal strategy

8.5.1 Deterministic cost-effectiveness analysis (DETCEA)

8.5.2 Probabilistic cost-effectiveness analysis (PROBCEA)

8.5.3 Deterministic and probabilistic cost-effectiveness analysis combined

8.6 Identifying what causes (decision) uncertainty

8.6.1 How does the outcome of interest change when using different input parameter value(s), and/or different model(s) and/or methodological choice(s)?

8.6.2 How much do the model choices impact the results?

8.6.3 Which uncertain aspects of the disease and interventions under study induce most uncertainty in incremental costs, incremental effects, cost-effectiveness ratios and/or net benefits?

8.6.4 Which uncertain aspects of the disease and interventions under study induce most decision uncertainty?

8.7 General approach and presenting results to decision makers

8.8 Recommendations
Chapter 9: Economic evaluation and the decision-making process ........................................ 93
  9.1 The use of economic evaluation in policy and practice ........................................... 93
  9.2 Decision-making bodies ....................................................................................... 94
  9.3 Equity-related criteria ............................................................................................ 95
  9.4 Potential “broader” benefits of vaccines ............................................................... 96
  9.5 Budget-impact and multi-product analyses .......................................................... 99
  9.6 Assessing models made by third parties .............................................................. 100
  9.7 Recommendations ............................................................................................... 100

Chapter 10: Conclusions and summary of recommendations ........................................... 101
  References .................................................................................................................. 111
  Appendix 1: Sources of data ....................................................................................... 132
  Appendix 2: List of useful websites ............................................................................ 134
List of tables

Table 1. Summary of the different types of economic evaluation ............................................. 6
Table 2. Examples of interventions and appropriate choice of analytic methodology for each according to the flow diagram in Fig. 2 ................................................................. 11
Table 3. Potential options against which to compare vaccines .................................................. 13
Table 4. Example calculation of vaccination programme costs in the presence of import tariffs in a hypothetical district ................................................................. 20
Table 5. Inputs to be assessed according to vaccine presentation ........................................... 23
Table 6. The strengths and weaknesses of different outcome measures .................................. 40
Table 7. Illustration of the relationship between important epidemiological parameters (for certain childhood infections) ................................................................. 47
Table 8. The acceptability of static versus dynamic models depending on pathogen (and epidemic situation), target group and vaccine effectiveness ........................................... 55
Table 9. Practical differences of static versus dynamic models for economic evaluation ....... 62
Table 10. Incremental costs and effects and the corresponding ICER, INMB and INHB, assuming an arbitrary willingness-to-pay value of €30,000 per unit health gain .................... 70
Table 11. Types of uncertainty in health economic evaluations and why they may arise (adapted from Bilcke et al. MDM 2011 (22)) ................................................................. 71
Table 12. An example of specifying plausible methodological choices, model structures and parameter values in a deterministic way ................................................................. 74
Table 13. Incremental costs, incremental effects and corresponding incremental net monetary benefit (INMB) and incremental net health benefit (INHB), assuming an arbitrary willingness-to-pay value of €30,000 per health gain .................................................................................................................... 79
Table 14. Average, marginal and incremental cost-effectiveness and intervention choices – comparison of three ways to deliver vaccination ................................................... 81
Table 15. For each intervention the % of frontiers they are part of .......................................... 83
Table 16. Results of a hypothetical cost-effectiveness analysis comparing two intervention options to the current situation, at a willingness-to-pay value of $200 per DALY averted. Uncertainty is accounted for in a probabilistic way, which is why there are n incremental net benefits (INBs) for each intervention option ................................................................. 85
Table 17. A Checklist for appraising the quality of economic evaluations of immunization programmes .......................................................................................................................... 102
Table 18. A critical appraisal of Antillon et al. (246) using the Checklist (answer either ‘yes’, ‘no’, ‘partially’, ‘not clear’ or ‘not applicable’) ............................................................. 107
List of figures

Figure 1: Key issues to consider when deciding on the introduction of a vaccine .................................................. 2
Figure 2: Appropriate type of economic analysis to use for a vaccine evaluation .................................................. 10
Figure 3: What happens when an individual is vaccinated? .................................................................................. 34
Figure 4: Flow chart to help determine when dynamic or static models are appropriate when one of the interventions being compared is vaccination against disease in humans ........................................................................................................... 53
Figure 5: Flow chart to help understand the limitations of potentially justifiable static models when epidemiologically influential subgroups are directly affected .................................................................................................................. 54
Figure 6: Basic static model structure options ..................................................................................................... 60
Figure 7: Distinguishing stochastic versus deterministic, and compartmental versus individual-based model structures ........................................................................................................................................ 61
Figure 8: Concepts of decision-making shown on a cost-effectiveness plane ..................................................... 78
Figure 9: Average, marginal and incremental cost-effectiveness and intervention choices – comparison of three ways to deliver vaccination .............................................................. 80
Figure 10: Cost-effectiveness plane using probabilistic cost-effectiveness analysis ........................................... 82
Figure 11: Example of a fragment cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) when only considering a single willingness-to-pay threshold (i.e. US$ 200 per DALY averted), as shown in Table 16 ........................................................................................................................................ 86
Figure 12: Example of cost-effectiveness acceptability curves: probability highest net benefit for the current strategy (no vaccination, black) and three different vaccination strategies (highlighted in blue, red and green), for a range of willingness-to-pay values ....................................................................................................................... 86
Figure 13: Example of cost-effectiveness acceptability frontier: probability highest net benefit for the strategies with the maximum expected net benefit, for a range of willingness-to-pay values ....................................................................................................................... 87
Figure 14: Example of expected values of partial perfect information (EVPPI) as a function of willingness to pay for a DALY averted for a range of uncertain input parameters .................................................................................. 92
Preface

This guide was developed to help meet the need of decision-makers for relevant, reliable and consistent economic information; it aims to provide clear and concise, practical, high-quality guidance to those who conduct economic evaluations.

The guide assumes the reader to be technically literate about the basic methods of economic evaluation, and so avoids long explanations: the emphasis is on what to do, rather than how to do it. However, a number of examples have been provided in order to illustrate some of the more challenging aspects of economic evaluations of immunization programmes.

The main target audience for this guide is economists and health service researchers in the public and private sectors who conduct and critically appraise economic evaluations of immunization programmes at the local, national, regional and global levels. The secondary target audience is programme staff who use cost-effectiveness information to assist the policy-makers at all levels who are responsible for funding decisions relating to immunization programmes: programme staff at national level will be able to use this guide to assess the transparency, completeness and comparability of economic evaluations that have been conducted for their own country or for other countries in their region. A third target audience is agencies such as the Gavi Alliance, The Bill & Melinda Gates Foundation, the World Health Organization, United Nations Children’s Fund (UNICEF) and international development agencies who sponsor and commission economic evaluations, who may wish to use this guide to help draw up terms of reference for future economic evaluations and may consider sharing this guide with their grantees.
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## Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACER</td>
<td>average cost-effectiveness ratio</td>
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<td>CBA</td>
<td>cost-benefit analysis</td>
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<td>CEA</td>
<td>cost-effectiveness analysis</td>
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<tr>
<td>CEAC</td>
<td>cost-effectiveness acceptability curve</td>
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<tr>
<td>CEAF</td>
<td>cost-effectiveness acceptability frontier</td>
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<tr>
<td>CHEERS</td>
<td>Consolidated Health Economic Evaluation Reporting Standards</td>
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<td>CHOICE</td>
<td>CHOosing Interventions that are Cost-Effective</td>
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<td>CMA</td>
<td>cost-minimization analysis</td>
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<td>CMH</td>
<td>Commission on Macroeconomics and Health</td>
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<tr>
<td>cMYP</td>
<td>comprehensive multi-year plan</td>
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<tr>
<td>CUA</td>
<td>cost-utility analysis</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life-year</td>
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<td>DETCEA</td>
<td>deterministic cost-effectiveness analysis</td>
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<tr>
<td>DCPP</td>
<td>Disease Control Priorities Project</td>
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<td>DCP3</td>
<td>Disease Control Priorities in Developing Countries, Third Edition</td>
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<tr>
<td>DSA</td>
<td>deterministic sensitivity analysis</td>
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<td>DTP</td>
<td>diphtheria-tetanus-pertussis (vaccine)</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<tr>
<td>EVPI</td>
<td>expected value of perfect information</td>
</tr>
<tr>
<td>EVPPI</td>
<td>expected value of partially perfect information</td>
</tr>
<tr>
<td>EVSI</td>
<td>expected value of sample information</td>
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<td>FSP</td>
<td>financial sustainability plan</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<td>GDP</td>
<td>gross domestic product</td>
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<td>GIVS</td>
<td>Global Immunization Vision and Strategy</td>
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<td>GNI</td>
<td>gross national income</td>
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<td>GVAP</td>
<td>Global Vaccine Action Plan</td>
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<tr>
<td>HAV</td>
<td>hepatitis a virus</td>
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<tr>
<td>HBV</td>
<td>hepatitis b virus</td>
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<tr>
<td>HCV</td>
<td>hepatitis c virus</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>HIC</td>
<td>high-income country</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HPV</td>
<td>human papilloma virus</td>
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<td>IS</td>
<td>international dollar</td>
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<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
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<td>INHB</td>
<td>incremental net health benefit</td>
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<td>INMB</td>
<td>incremental net monetary benefit</td>
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<td>IPV</td>
<td>inactivated polio vaccine</td>
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<tr>
<td>IVB</td>
<td>Immunization, Vaccines and Biologicals</td>
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<td>IVR</td>
<td>Initiative for Vaccine Research</td>
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<tr>
<td>LCU</td>
<td>local currency unit</td>
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<tr>
<td>LIC</td>
<td>low-income country</td>
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<tr>
<td>LMIC</td>
<td>lower- or middle-income country</td>
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<tr>
<td>MCER</td>
<td>marginal cost-effectiveness ratio</td>
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<td>MYP</td>
<td>multi-year plan</td>
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<tr>
<td>OPD</td>
<td>outpatient department</td>
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<tr>
<td>OPV</td>
<td>oral polio vaccine</td>
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<td>PROBCEA</td>
<td>probabilistic cost-effectiveness analysis</td>
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<td>7PPP</td>
<td>purchasing power parity</td>
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<td>PSA</td>
<td>probabilistic sensitivity analysis</td>
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<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RSV</td>
<td>respiratory syncytial virus</td>
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<td>SA</td>
<td>statistical analysis</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
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<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
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<td>VE</td>
<td>vaccine efficacy</td>
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<td>VHW</td>
<td>village health worker</td>
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<tr>
<td>VPD</td>
<td>vaccine-preventable disease</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WTP</td>
<td>willingness-to-pay value</td>
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Glossary of terms

Affordability
Relates to whether a new vaccine can be introduced and absorbed into an immunization budget over the medium to long term without significantly affecting available resources for other public health priorities.

Allocative efficiency
Choosing the mix of interventions that maximizes health gain for a given level of expenditure.

Analytic horizon
The period of time over which the costs and health outcomes that occur as result of the vaccine(s) are considered.

Average cost-effectiveness ratio
The total cost divided by total effectiveness of an intervention.

Basic reproduction number (R₀)
The number of secondary cases an average infectious individual causes in a completely susceptible population. See effective reproduction number.

Budget impact analysis
Estimates the financial impact on annual health care use and costs for the first, second and subsequent years after the introduction of a new vaccine.

Cohort Analysis
An analysis done for a specific group of people (cohort) defined at a particular period in time and followed as they pass through different ages during part or all of their life span (see Cross-Sectional Analysis).

Comparator
An alternative against which a new intervention is compared.

Constant returns to scale
Is considered in economics literature to represent long-run efficient returns to scale of production, i.e. production at the minimum of a ‘U-shaped’ cost curve. A vaccination site or programme is said to exhibit constant returns to scale if a one-unit increase in the proportion of inputs will result in a one-unit increase in the proportion of outputs.

Cost-benefit analysis
Converts programme benefits in all forms into a monetary value. In principle, it has many potential applications as it can address both technical and allocative efficiency concerns within the health sector and between health and non-health uses. However, expressing health outcomes in monetary terms is problematic and controversial. Consequently, this technique remains little used in the health field.

Cost-effectiveness acceptability curve
A method of displaying graphically the uncertainty around the results of a probabilistic cost-effectiveness analysis.

Cost-effectiveness acceptability frontier
A method of displaying graphically the main results of a probabilistic cost-effectiveness analysis.
Cost-effectiveness analysis
In cost-effectiveness analysis, programme outcomes are measured in physical or natural units of health status, such as the number of lives saved, life-years gained or reduction in disease incidence. In practice, there has been a blurring of the distinctions between CEA and cost-utility analysis, with the latter seen as an extension of the former; as a result, literature on cost-effectiveness often encompasses both these approaches.

Cost-effectiveness threshold
The level of cost per unit of outcome below which an intervention is considered cost-effective by a policy maker representing a given perspective.

Cost-minimization analysis
compares programme costs in situations where clinical evidence demonstrates alternative health programmes to have the same outcomes. It requires no explicit measurement of benefits.

Cost-utility analysis
Applies a generic measure of health status in order to compare programme outcomes. Such outcome measures combine the effect of mortality (length of life) and morbidity (quality of life). The past decade or so has seen the development of a variety of composite outcome measures that incorporate fatal and non-fatal conditions into the measurement of health status, e.g. the quality-adjusted life year (QALY) and disability-adjusted life year (DALY). This has expanded the scope for comparing dissimilar health programmes.

Cross-Sectional Analysis
An analysis done for a defined population at a particular point in time (see Cohort Analysis).

Deterministic cost-effectiveness analysis
A cost-effectiveness analysis in which only point estimates are used as input (none of the uncertainty around the aspects of the disease and intervention under consideration is specified as probability distributions).

Deterministic sensitivity analysis
A method to investigate how sensitive results from a model-based analysis are to variations in a specific input parameter, set of parameters and/or model structures. One or more parameters and/or model structures are manually changed (usually across a pre-specified range/set of options).

Deterministic model
Mathematical model in which there is no inclusion of chance or random variation in the modelled infectious disease process. Deterministic models can be solved by numerical analysis or computer simulation and give a fixed and exactly reproducible result.

Disability-adjusted life year (DALY)
A measure to adjust life years lived for disease related disability, age and time preference.

Discount rate
The rate at which costs and outcomes are discounted to account for time preference.

Dominance
When one intervention is both less costly and more effective than the comparators.

Dynamic model
Mathematical model in which the force of infection is a function of the proportion of infectious people in the population at each time point. The force of infection can thus change over time in this type of model.
Economic evaluation
Compares the costs and outcomes of at least two alternative programmes. There are four different types of economic evaluation: cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis.

Effectiveness
A measure of the extent to which an immunization intervention, when used according to the correct schedule and dosing regimen, does what it is intended to do for a specified population.

Effective reproduction number (Rt)
The number of secondary cases an infectious individual causes on average in a population (see also basic reproduction number).

Efficacy
A measure of the extent to which an immunization intervention produces a beneficial result under ideal conditions. Usually measured based on the results of a randomized controlled trial.

Elimination
When primary indigenous disease incidence is reduced to zero for a prolonged period of time in a particular part of the world, the disease is said to be eliminated in that part of the world (on a country, or a continental scale; e.g., indigenous polio infection is currently eliminated from the Americas). This implies that sporadic outbreaks may still occur but only as a consequence of imported primary cases. See eradication.

Eradication
Elimination on a worldwide scale. In addition to reducing the number of indigenous cases to zero, infection could no longer occur at a sub-clinical level. If this is achieved around the world for a safe period of time, without risk of the infection reappearing, the disease is said to be eradicated.

Expected value of information
The value (in monetary terms) of eliminating all uncertainty about an intervention being cost-effective yes or no.

Expected value of partial information
The expected value of information for a single or a group of uncertain aspects of the disease and/or intervention under study.

Expected value of sample information
The value (in monetary terms) of a decision to collect additional sample information.

Extended dominance (also referred to as weak dominance):
When one intervention is both less costly and more effective than a linear combination of two other interventions with which it is mutually exclusive.

Externalities
Costs (negative externalities) or benefits (positive externalities) arising from an individual’s production or consumption decision that indirectly affects the well-being of others.

Force of infection
The probability per unit of time that a susceptible person becomes infected. In other words, it is the per-susceptible rate of infection or the incidence of infection in susceptible people.

Herd immunity
The reduction in exposure of susceptible people to a pathogen through vaccination of other people; herd immunity can also be induced by non-vaccine interventions, such as administration of antivirals, isolation/quarantine.

Incremental cost-effectiveness ratio
The ratio of the difference in cost between two alternatives to the difference in effectiveness between the same two alternatives.
Incremental net health benefit
The difference in effectiveness between two alternatives minus the difference in cost between the same two alternatives, with the difference in cost expressed in health terms by assuming a willingness-to-pay threshold.

Incremental net monetary benefit
The difference in effectiveness between two alternatives minus the difference in cost between the same two alternatives, with the difference in effectiveness expressed in monetary terms by assuming a willingness-to-pay threshold.

International dollar
The international dollar has the same purchasing power as the United States dollar has in the United States. Costs in local currency units are converted to international dollars using purchasing power parity (PPP) exchange rates. The international dollar is therefore a hypothetical currency that is used as a means of translating and comparing costs from one country to the other using the common reference point of the US dollar.

Marginal cost
The change in total cost if an additional unit of output is produced.

Marginal cost-effectiveness ratio
Assesses the specific changes in cost and effect when a programme is expanded or contracted.

Multivariate sensitivity analysis
Another name for multi-way sensitivity analysis.

Multi-way sensitivity analysis (also referred to as multivariate sensitivity analysis)
An exploration of the impact on the results of changing the value of two or more parameters at the same time.

Mutually exclusive interventions
When implementation of a particular intervention excludes the possibility of implementing other interventions.

One-way sensitivity analysis (also referred to as univariate sensitivity analysis)
An exploration of the impact on the results of changing the value of one parameter while keeping the values of all other parameters unchanged.

Parameter uncertainty
The acknowledgment that a precise value of a parameter is not always known. This is also referred to as ‘second order’ uncertainty. It is represented in an analysis by specifying variables as distributions/ranges.

Perspective (also referred to as viewpoint)
Perspective of the bearers of the costs and benefits of an intervention, e.g., society, government, health-care providers, patients.

Probabilistic cost-effectiveness analysis
A cost-effectiveness analysis in which at least some of the uncertainty around the aspects of the disease and intervention under consideration is specified as probability distributions rather than point estimates.

Probabilistic sensitivity analysis (PSA)
A method of analysis that explicitly incorporates uncertainty. The defining point is that variables are specified as distributions rather than point estimates as in a deterministic analysis.

Purchasing power parity (PPP) exchange rate
A PPP exchange rate is the number of units of a country’s currency required to buy the same amounts of goods and services in the domestic market as a US dollar would buy in the United States (see also International dollar).
Quality-adjusted life year
A single health state measure combining quantity and quality of life. A generic measure which sums years spent in different health states using weights (on a scale of 0 (dead) to 1 (perfectly healthy) for each health state).

Reproduction number
This is a measure of the intrinsic capacity for an infection to spread in a naive population. See basic reproduction number and effective reproduction number. The terms reproduction number, reproductive number, reproduction rate and reproductive rate have all been used interchangeably in the literature.

Sensitivity analysis
A method of analysis that explores the impact of (a set of) methodological, model and/or parameter choices on the results of the economic evaluation (see also Probabilistic Sensitivity Analysis and Uncertainty analysis).

Static model
Mathematical model in which the force of infection is assumed to be independent of the proportion of infectious people at each time point. Essentially this type of model assumes that vaccination does not infer herd immunity.

Stochastic model
Mathematical model in which there is allowance for chance or random variation in the modelled infectious disease process. In a stochastic model different outcomes can result from the same initial conditions (as opposed to a deterministic model).

Technical efficiency
Providing maximal health care for a given cost, or delivering a certain service at minimal cost.

Threshold analysis
The value of a parameter is varied to find the level at which the results changed, e.g. the level at which the cost per DALY averted reaches the GNI per capita of the country where the intervention is being evaluated.

Time frame
The period over which the vaccine(s) is applied.

Two-way sensitivity analysis
Analysis in which the sensitivity of the results is tested in relation to simultaneous variation of two parameters.

Uncertainty analysis
A method of analysis that explicitly accounts for the uncertainty involved in a health economic evaluation, i.e. identifying and quantifying the uncertainty in the input of the economic model, propagating the uncertainty into the results of the economic evaluation, and presenting cost-effectiveness results with uncertainty (see also Probabilistic Sensitivity Analysis and sensitivity analysis).

Willingness-to-pay threshold
See cost-effectiveness threshold.

Threshold analysis
The value of a parameter is varied to find the level at which the results changed, e.g. the level at which the cost per DALY averted reaches the GNI per capita of the country where the intervention is being evaluated.
Chapter 1: Introduction

The Global Vaccine Action Plan 2011–2020 (GVAP), a framework approved by the World Health Assembly in May 2012, aims to achieve universal access to immunization (1). One of the Strategic Advisory Group of Experts on Immunization (SAGE)'s recommendations is to encourage high-level officials of all member states to understand the value of investing more in and sustaining immunization programmes as an integral part of government-supported Universal Health Coverage packages (2). Health economic evaluation, often generically referred to as “cost-effectiveness analysis” provides crucial evidence considered for decision making of the introduction of vaccination into National Immunization Program (3, 4).

The 2008 WHO guide for standardization of economic evaluations of immunization programmes was developed to provide guidance to those who conduct or critically appraise economic evaluations of immunization programmes at the local, national, and global levels (5). The guide was also used to help programme staff assess transparency, completeness, and comparability of economic evaluations that have been conducted for their own country, or for other countries in the region. This document presents an update of the 2008 WHO guide.

1.1 Evidence-based decision-making

In 2014 the World Health Organization (WHO) published a document entitled Principles and considerations for adding a vaccine to a national immunization programme: from decision to implementation and monitoring (4). The key issues to be considered before deciding to introduce a vaccine can be grouped into three areas (see Fig. 1). The first area concerns the disease that the vaccine in question targets – whether it is a public health priority, the magnitude of the disease burden in the country and the existence and effectiveness of other strategies for preventing and controlling the disease. The second area relates to the vaccine – its safety, performance and other characteristics; its economic and financial attributes (cost, affordability, and cost-effectiveness); and whether the country can expect a reliable supply of the vaccine. The third area concerns the capacity of the immunization programme and underlying health system to successfully introduce the vaccine and to be able to continue to deliver it over the long term.

Under the broader heading of ‘policy issues’, the Vaccine Introduction Guidelines identify ‘Economic and Financial Issues’, which include cost-effectiveness, fiscal impact and financial sustainability. The present Guide provides detailed guidance as to how to evaluate the cost-effectiveness of vaccines.
1.2 Existing guidance and recent changes in economic evaluation

As limited health care budgets have highlighted the need to use resources effectively and efficiently, the desire has arisen to implement evidence-based policy decisions. Consequently, economic evaluation has acquired greater prominence among decision-makers, who need to know which interventions represent ‘value for money’.

The field of economic evaluation has been rapidly evolving in the last decade. Recent developments include updated general economic evaluation guidelines such as the second panel on cost-effectiveness in health and medicine (6), the Gates Reference Case of the Bill and Melinda Gate Foundation (7, 8), a WHO vaccine-specific economic evaluation guideline for influenza vaccines (9) as well as an ISPOR guide (10). In the meantime, the use of economic evaluation at national decision making level has become more common with increasing numbers of country-specific economic guidelines being developed in various countries and used widely in the last decade (11–20). Another important development was the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to summarise and update previous health economic evaluation guidelines into one useful reporting guidance (21). Given a proliferation of guidelines and growing attention for a range of methodological issues such as uncertainty analysis (22–24) and the broader economic impact of vaccination (25), it is timely to develop an updated WHO guide for standardization of economic evaluations of immunization programmes.

1.3 Overall aim and target audience

This updated guide brings together the recommendations and guidance from many recent guidelines, tools and other documents on specific aspects of immunization and on specific vaccines. As its predecessor, the overall aim is to provide practical “what to do” (rather than “how to do”) guidance to those who conduct economic evaluations.

The primary target audience for this guide consists of researchers who conduct economic evaluations of immunization programmes at the local, national, regional and international level.
global levels. The secondary target audience is individuals who use cost-effectiveness information to assist policy-makers at all levels for funding decisions relating to immunization programmes. Programme staff at national level will be able to use this guide to assess the appropriateness, transparency and comparability of economic evaluations that have been conducted for their own country, or for other countries in their region. This group would include National Immunization Technical Advisory Committees (NITAGs) that serve as a technical resource to provide guidance to national policy-makers and programme managers, facilitating evidence-based immunization-related policy and programme decisions. The third target audience is funding agencies such as the GAVI Alliance, The Bill & Melinda Gates Foundation, WHO, The United Nations Children’s Fund (UNICEF), and international development agencies who sponsor and commission economic evaluations, who may wish to use this guide in order to help draw up terms of reference for future economic evaluations and may consider sharing this guide with their grantees.

This guide was developed in order to meet the need of decision-makers for relevant, reliable and consistent economic information and aims to provide clear and concise, practical and high quality guidance to those who conduct economic evaluations. As the concepts and techniques used in economic evaluations of immunization programmes are generic in nature, this guide is appropriate for use in low-, middle- or high-income economies. Nevertheless, it is important to recognize that economic evaluations in low- or middle-income countries (LMICs) will encounter different challenges from those in high-income countries (HICs). For example, economic evaluations in LMICs will often face data availability and data quality problems. Another example is that in some countries a preference may exist for the use of disability-adjusted life years (DALYs) over quality-adjusted life years (QALYs) as outcomes in cost-utility analyses, whereas in most countries the preference seems to evolve clearly for QALYs over DALYs (see also section 5.3). Such challenges and differences notwithstanding, this publication provides guidance that is relevant to conducting economic evaluations in all settings.

This guide assumes the reader to be technically literate about the basic methods of economic evaluation, and so avoids long explanations: the emphasis is on what to do rather than how to do it. However, a number of examples have been provided in order to illustrate some of the more challenging aspects of economic evaluation that are of particular relevance to vaccines and vaccine-preventable diseases, and we also provide a glossary at the end of the guide.

1.4 Structure of the guide

After this brief introductory chapter, the Guide begins by describing the different types of economic evaluation and explaining the difference between economic evaluation and budget impact analysis. Chapter 3 considers the various ways of framing an evaluation. Chapter 4 describes the various costs that could be included in an assessment. Chapter 5 and Chapter 6 focus respectively on assessing the effects of a vaccination programme and issues related to modelling. Discounting is discussed in Chapter 7. Chapter 8 looks at the estimation, presentation and interpretation of cost-effectiveness data under uncertainty. Chapter 9 takes a broader look at the decision-making process and examines some other considerations in addition to cost-effectiveness, and illustrates these referring to example papers. Lastly, Chapter 10 summarizes the recommendations made and looks to the future.
Chapter 2: Economic evaluation of health care

This chapter briefly explains what economic evaluation is, describes the different types of economic evaluation and summarizes the role it plays; it also highlights the distinction between economic evaluation and budget impact analysis/financing of programme implementation.

2.1 Different types of economic evaluation

The methods and tools of economic evaluation are rooted in the fundamental problem by which economists characterize decision-making: making choices between alternatives in the context of scarce resources. Within the scope of national and international public health, these choices are often framed by the debate as to which interventions should have priority. Economic evaluation compares the costs and outcomes of at least two alternatives, one of which may be ‘doing nothing’ (26). There are several types of economic evaluation: cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA).

These different evaluation techniques all estimate costs in a similar fashion, but measure outcomes or consequences differently. Costs refer to the value of opportunities or benefits foregone as a result of not employing resources elsewhere. Benefits are gauged by the consequences of a health programme on people’s well-being or health status. The different ways of measuring benefits result in a trade-off between the potential scope for use and the practicality of various evaluation techniques.

Cost-minimization analysis involves the assessment of two or more interventions that have identical outcomes in order to see which is the cheapest way of delivering the same outcome. For example, if two rotavirus vaccines had equivalent levels of effectiveness against severe gastroenteritis, cost minimization analysis would identify which of the two vaccines was the least costly. Cost-effectiveness analysis measures the outcomes of approaches in terms of ‘natural units’. For example, if the outcome of interest was a reduction in childhood pneumonia, cost-effectiveness analysis might compare vaccines against Hib and pneumococcal diseases in order to determine which averted a case of pneumonia most cheaply. Cost-effectiveness analysis also enables comparisons to be made between vaccines and other health care interventions that seek to address the same condition, such as rotavirus vaccination and management

1 The terms outcomes, consequences, effects and benefits are used interchangeably in this text.
of childhood diarrhoea using zinc. **Cost-utility analysis** values outcomes using measures of utility that reflect people’s preferences. The outcomes are then expressed in terms of measures such as quality- (QALYs) or disability-adjusted life years (DALYs). For example, it might be used to compare vaccines against rotavirus and Hib in terms of which averts a DALY most cheaply. However, it also enables comparisons between different health sector interventions, such as interventions to control HIV/AIDS, TB and malaria. In practice, there has been a blurring of the distinction between CEA and CUA, with the latter being seen as an extension of the former. Lastly, there is **cost-benefit analysis**, which expresses health outcomes in terms of monetary units. This type of analysis enables comparisons between vaccines or other interventions in the health sector or in other sectors, such as education, in order to identify which generates the greatest return on investment. The need to measure outcomes in monetary units limits the use of this type of analysis in determining health policy.²

In a situation where an infectious disease and interventions against it can have economy-wide impacts that exceed the impacts on infected individuals, their contacts, their employers and the health care sector, a **macroeconomic evaluation using a computable general equilibrium (CGE) model** would be more appropriate than the traditional microeconomic approach in health care (e.g. CUA), even when the latter is conducted under a societal perspective. A CGE model could typically estimate the impact of an emerging infectious disease of international concern (and interventions) through shocks in labour supply, consumption and investments in different sectors of the economy. That is, by creating disequilibrium in a model of an entire economy, and simulating how the economy would evolve after those shocks, the productivity impact on the economy as a whole (e.g. Gross Domestic Product) can be estimated for different infectious disease scenarios in specific countries, regions or the whole world. This is quite different from health economic analyses which are mostly confined to the health care sector and to societal actors affected directly by ill patients (e.g. their families, their social contacts and their employers). Background on such wider sector models can be found in the macroeconomic literature, and requires high level literacy in economics. The circumstances under which such a CGE model would be appropriate for vaccinations are highly exceptional (such as the prevention of influenza and SARS pandemics (e.g. (27, 28)), and therefore not relevant for the vast majority of vaccination programme evaluations, as further explained in Chapter 3. This approach is mentioned in this guide mainly for completeness.

### 2.2 The role of economic evaluation

Economic evaluation attempts to identify ways in which scarce resources can be employed efficiently. Efficiency has two principal meanings in this context.³ First, there is technical (or operational) efficiency, which concentrates on maximizing the achievement of a given objective within a given budget – the vaccination of children through fixed, outreach or mobile clinics, for example.

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² For a rare example of an inter-sectoral priority-setting exercise visit the Copenhagen Consensus webpage: [https://www.copenhagenconsensus.com](https://www.copenhagenconsensus.com).

³ Note that several other terms for and definitions of efficiency have been used by economists, including productive, cost-effective, social, X-, static and dynamic efficiency, that are not discerned here for the purpose of focus and readability.
Second, there is allocative efficiency, which is a broader concept as it focuses on choosing the optimal mix of interventions for a given level of expenditure – optimal in the sense that they maximize health gains. This definition of efficiency allows comparisons to be made among different health care interventions with different objectives and outcomes, e.g. malaria versus TB versus diarrhoeal disease control, in order to address how a ministry of health’s budget should best be distributed between programmes. It thus follows that, although interventions may have different objectives and outcomes of interest, these must all be converted into commensurable units. CUA, which uses more complex measures of outcomes, can therefore be used to assess allocative efficiency within the health sector. However, as economic evaluation using CUA can still only compare programmes within the health sector, strictly speaking it only deals with quasi-allocative assessments.

In theory, CBA has the widest scope of the four types of analysis because the monetization of outcomes enables inter-sectoral comparisons, i.e. it can address how a government budget should be distributed between different ministries. In practice however, the difficulty of valuing health benefits has meant that since the late 1970s initially CEA – and later also especially CUA – have emerged over other types of analysis as the method of choice for evaluating health care programmes in both developed and developing countries (29–31). While only CBA (and CUA within the health sector) can be used to assess allocative efficiency, technical efficiency can be assessed using any of the different types of economic evaluation (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Outcomes</th>
<th>Technical efficiency?</th>
<th>Allocative efficiency?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMA</td>
<td>Not applicable</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CEA</td>
<td>Natural Units</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CUA</td>
<td>QALYs, DALYs</td>
<td>Yes</td>
<td>Yes, within health care</td>
</tr>
<tr>
<td>CBA</td>
<td>$</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### 2.3 Budget impact analysis/financing of programme implementation

Whilst CEA estimates the incremental costs and effects of a new vaccine compared with current practice (which often means no vaccination) and provides an estimate of the efficiency or ‘value’ of the new vaccine, a budget impact analysis estimates the financial impact on annual health care use and costs for the first, second and subsequent years following the introduction of the vaccine (32–34). A budget impact analysis provides an estimate of the impact of a new vaccine based on its rate of uptake as well as of the magnitude and timing of its impact on health care use and costs. It should be noted that the notion of treatment cost savings assumes that resources from the substituted alternative, i.e. existing practice, can be used to finance the new alternative, i.e. the vaccine. In practice, however, not all resources will become available for introduction of the vaccine. Not only are budgets often fixed and earmarked for specific pur-

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4 Note that CEA can be used to assess allocative efficiency within and potentially beyond the health sector for life-saving interventions where outcomes are measured in terms of lives saved (or deaths averted), life-years gained, etc.
poses, but the resources within those budgets are often fixed or semi-fixed (35). Thus, much depends on the perspective, i.e. long- or short-term. Decision-makers need such estimates of the impact of a new vaccine on annual immunization and health system spending for the purposes of financial planning. Based on ISPOR’s best practice recommendations for conducting BIAs (32), a vaccine-specific checklist has been developed to assess the potential extensibility of CEAs for providing sufficient evidence about budget impact to enable decision-making (36). With relatively straightforward changes to the presentation of CEA results analysts could facilitate the adaptation of most CEA studies into BIAs, potentially increasing their utility and application.

The WHO-UNICEF Guidelines for Developing a Comprehensive Multi-Year Plan (cMYP) (35) set out a series of steps for developing a comprehensive plan. Step 6 relates to analysis of the costs, financing and financial gaps of a cMYP. An accompanying cMYP Costing and Financing Tool and User Guide have been prepared which build on the costing tools and methodologies developed for the immunization Financial Sustainability Plans (FSP). Once programme or strategy costs including the new vaccines have been estimated, these can be put into perspective using a variety of indicators, such as:

- programme costs with and without the new vaccine as a proportion of total national immunization programme budget or spending;
- programme costs with and without the new vaccine as a proportion of total government health budget or government health spending;
- programme costs with and without the new vaccine as a proportion of total health spending;
- programme costs with and without the new vaccine as a proportion of gross domestic product (GDP);
- per capita estimates of programme costs with and without the new vaccine;
- programme costs with and without the new vaccine per child that has received the third dose of diphtheria–tetanus–pertussis vaccine (DTP3).

Interpretation of these indicators is relatively subjective, and ideally these indicators should be compared with those for other public health interventions and programmes in order to have a better sense of relative impacts. However, if the programme-specific costs associated with a new vaccine represent a substantial share of total government health budget or expenditures in a particular year, the programme may be pushing the limits of affordability, and would require significant efforts to mobilize resources to expand the fiscal space for immunization and sustain the new vaccine in the following years.

5 See https://www.who.int/immunization/programmes_systems/financing/.

6 The concept of affordability relates to whether a new vaccine can be introduced and absorbed into an immunization budget over the medium- to long-term without significantly affecting available resources for other public health priorities (2).

7 There are three main ways of expanding the fiscal space for immunization: reallocating the Ministry of Health budget; obtaining new funds from the Ministries of Finance or Social Security; and external funding. The results of economic evaluations may help to build the case for expanding the fiscal space for immunization.
Chapter 3:
Framing the analysis

The first step to conducting an economic evaluation is to frame the study. Decisions made at this stage will directly determine which costs and outcomes are considered relevant and should therefore be included in the analysis. This means that choices made in the framing of the evaluation will have an impact on the final results of an analysis. In this chapter, we look at the variety of ways in which an evaluation should be framed.

3.1 Target audience

The target audience includes all persons or institutions that will use the results of the study to make decisions. While not restricted in size or composition, the nature of the primary target audience will determine some of the methodological choices for an analysis. Potential users could include some or all of the following:

- International financing agencies, aid agencies, international development agencies and non-governmental organizations funding or supporting vaccination in different countries.
- Ministries of Health and Finance, National Immunisation Technical Advisory Groups (NITAGs), health technology agencies, national health insurance agencies and other stakeholders within a country who make decisions about funding an immunisation programme within a particular country.
- Private health care purchasers who make decisions to fund vaccines to individuals who are enrolled in their programmes.
- Health care providers like clinicians, hospital managers and EPI staff who offer vaccination to individuals.
- Individual users who make decisions about whether to seek and accept vaccines for themselves and for people under their care.

3.2 Study question

The study question should be well-defined, stated in an answerable form and relevant to the decision the target audience is facing. The study question will determine the choice of intervention and comparators in the evaluation.

Examples of the kinds of questions that could be informed by economic evaluation include:

- Should an under-utilized or new vaccine be introduced, e.g. Hib or rotavirus?
- For which new vaccine(s) should Gavi, the Vaccine Alliance, open a window of funding?
• What is the maximum price that should be paid for a vaccine?

• What delivery strategy should be used to increase vaccination coverage, e.g. fixed sites, mobile teams or campaigns?

• Is targeted or universal vaccination more efficient, e.g. during an influenza pandemic should vaccination be targeted at risk groups or offered to everybody?

• If there are multiple vaccines that are directed against the same disease (e.g. human papillomavirus, rotavirus, pneumococcal and, influenza vaccines), which one should be used, and at what price differential are they equivalent?

• Should a current vaccine be replaced with another directed to the same condition and population but with different characteristics, e.g. should live oral polio vaccine (OPV) be replaced with risk-free inactivated polio vaccine (IPV) or the currently used measles vaccine replaced with a thermostable measles vaccine?

• Is a combination vaccine more efficient than a combination of vaccines, e.g. DPT-HepB or DPT and HepB separately?

• What would be the cost-effectiveness of introducing a new vaccine alone compared to introducing it in combination with other existing preventive health interventions, e.g. HPV vaccine alone vs. in combination with cancer screening, or malaria vaccines alone vs. in combination with insecticide-treated bed-nets?

• Is there an investment case for developing a new vaccine e.g. against a disease with pandemic potential such as SARS?

3.3 Type of evaluation

It is important to state and justify the type(s) of economic evaluation chosen from the types listed in section 2.1 above. As has been described, the different types of analysis serve different purposes (26). The appropriate analysis to use should depend on the budget holder and its priorities (37). Fig. 2 offers an algorithm to decide on the most appropriate kind of analysis to use in different situations, with the boxes in green indicating what most country-specific guidelines currently recommend. Sometimes several different analyses may be needed to inform separate decision makers (e.g. Ministry of Health, Ministry of Finance, external donors etc.).

The preferred analysis for the optimal allocation of a health care budget is cost-utility analysis (CUA), performed from a societal perspective. CUAs aim to maximise a generic measure of health utilities (such as QALYs or DALYs) within a fixed health care budget, so they facilitate comparisons both between vaccines and with health care interventions more generally. If only costs to the health care provider are considered, then a payer or provider perspective is used. This is the narrowest form of analysis, but it is widely used because many jurisdictions give the budget holder an explicit remit to maximise health within a given budget. If costs falling to other budgets (such as other government departments, employers or households) should be considered then a societal perspective is used. Of course analysts can also opt to perform the analysis from different perspectives to provide complementary information (e.g. both the health care payer and the societal perspective).
Fig. 2. Appropriate type of economic analysis to use for a vaccine evaluation
(Note that this flow diagram only discusses the economic analysis; the choice of epidemiological model to capture the health impact of vaccination should follow the guidelines in Chapter 6.)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the impact of vaccination on the wider economy besides the individuals protected (either directly or indirectly) and their families important to consider?</td>
<td></td>
<td></td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Will vaccination be compared to non-health interventions and funded from a general budget rather than to health interventions only and funded from a healthcare-specific budget?</td>
<td></td>
<td></td>
<td>3a</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the broader effects of vaccination on welfare beyond health, financial impact and productivity important to consider for the specific analysis?</td>
<td></td>
<td></td>
<td>4a</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the economic effects of vaccination related to disease in individuals protected, beyond the payer or budget holder important?</td>
<td></td>
<td></td>
<td>5a</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost-utility analysis (societal perspective)</td>
<td></td>
<td></td>
<td>6a</td>
<td></td>
</tr>
<tr>
<td>Cost-utility analysis (payer perspective)</td>
<td></td>
<td></td>
<td>6b</td>
<td></td>
</tr>
<tr>
<td>Cost-consequences or multi-criteria decision analysis within a deliberative process</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This does not mean that other analyses should not be conducted. Cost-consequences (38) and multi-criteria decision analyses (39, 40) which present multiple desirable outcomes (such as efficiency, equity, acceptability and broader impact) rather than a single quantity to be maximised (such as a cost-effectiveness or benefit-cost ratio) are encouraged as this will increase the potential usefulness of the analysis. They can then be used within a deliberative process involving decision makers or stakeholders, in order to either (i) assign weights to each outcome to derive an overall pooled outcome for an intervention, or (ii) consider each outcome qualitatively to reach a decision by deliberation. Other types of analysis not normally integrated into cost-effectiveness or cost-benefit analyses can be conducted to inform these outcomes. For instance, an extended cost-effectiveness analysis presents the impact of an intervention in terms of distributional equity of health gains and finances (financial risk protection and impoverishment) across groups with particular characteristics (such as socioeconomic status) in
the population (41). There may also be important considerations such as social impact and vaccine acceptability that need to be accounted for but are difficult to quantify (42).

Lastly, if vaccines are funded by a wider budget including non-health care interventions, then questions around allocative efficiency exceeding health gains per se are important and a cost-benefit analysis may be appropriate. This aims to optimise allocative efficiency, such as maximising welfare based on the preferences of individuals within the population.

Table 2 shows examples of interventions and appropriate choice of analytic methodology for each according to the flow diagram in Fig. 2.

<table>
<thead>
<tr>
<th>Decision maker</th>
<th>Intervention(s)</th>
<th>Analytical choice</th>
</tr>
</thead>
</table>
| Cabinet (government as a whole) | Stockpiling a pre-pandemic influenza vaccine (27)                                                                                                | 1 → 2a  
An influenza pandemic will have a multi-sectoral impact beyond the individuals and households infected, so macroeconomic evaluation, for instance by using a computable general equilibrium model or production function approach. |
| Ministry of Health | Funding a seasonal influenza vaccine from the healthcare budget (43)                                                                              | 1 → 2b → 3b → 4b → 5a  
Seasonal influenza vaccine will affect health, health care expenditure and productivity of individuals and their families, so cost-utility analysis (societal perspective). If the decision maker is only interested in economic effects on the health care payer then a payer perspective should be used instead (5b). |
| Ministry of Finance | Priority setting about the overall budget allocation for immunisation (44)                                                                      | 1 → 2b → 3a  
Immunisation programmes are being compared to non-health interventions, so cost-benefit analysis. |
| National health insurer | Choosing from a package of interventions to include in a basic benefits package (45)                                                             | 1 → 2b → 3b → 4a → 6b  
Multiple criteria such as efficiency, equity and acceptability are important to consider, so cost-consequences or multi-criteria decision analysis. |

The evaluations discussed above are microeconomic evaluations that consider only the health and economic impact on the individuals affected (either directly through receiving vaccination or indirectly through the population-wide effects of vaccination programs, see Chapter 5), assuming the rest of the economy remains in equilibrium (46). In the highly exceptional case, where a disease has potential large scale impacts on entire sectors of the economy (and as a result also on the entire economy), then a macroeconomic evaluation of vaccination against that disease would be appropriate. Typical examples include emergencies caused by pandemic influenza, ebola or SARS, as well as by increasing prevalence of antibiotic resistance in bacteria. Computational general equilibrium models offer a way to estimate the potential impact of exogenous shocks caused by such disruptive emergencies on labour supply, productivity and
demand in the wider economy. Fiscal Health modelling has been advocated as a less complex method to assess the streams of future costs and benefits from interventions affecting child survival and the government budget. These future fiscal costs include education, social security benefits, and pensions, whereas future benefits are derived from increased taxes through increased labour force participation when more people survive illnesses at a young age (10). Fiscal Health modelling can be seen as a form of cost-benefit analysis, based on financial transfers and with an alternative specific perspective, which can be of interest to government accounts.

### 3.4 Target population

The target population is the group intended to receive the intervention. It can vary by, for example, age, sex, occupation, geography and clinical condition (see Box 1), and has a major impact on the outcome of an evaluation. The target population(s) and expected uptake should therefore be clearly stated. If needed, stratified analyses of smaller, more homogenous sub-groups should be conducted where appropriate, e.g. for different age or ethnic groups. For example, for some vaccines certain groups may have a higher risk of disease than others e.g. injecting drug users and hepatitis B. However, issues such as identifiability, equity and potential stigma need to be considered before targeting a vaccination programme at a subpopulation defined by ethnic, geographical, behavioural or socioeconomic status.

<table>
<thead>
<tr>
<th>BOX 1. EXAMPLES OF TARGET POPULATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
</tr>
<tr>
<td>Infants</td>
</tr>
<tr>
<td>Children</td>
</tr>
<tr>
<td>Adolescents</td>
</tr>
<tr>
<td>Young people</td>
</tr>
<tr>
<td>Older people</td>
</tr>
<tr>
<td>Primary school children</td>
</tr>
<tr>
<td>Secondary school children</td>
</tr>
<tr>
<td>Tertiary school children</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Pregnant women</td>
</tr>
<tr>
<td>Women of childbearing age</td>
</tr>
<tr>
<td>Behavioural risk groups, e.g. commercial sex workers, injecting drug users, men who have sex with men</td>
</tr>
<tr>
<td>People with clinical conditions that may predispose them to severe illness eg. diabetes, asthma</td>
</tr>
<tr>
<td>Different socio-economic groups</td>
</tr>
<tr>
<td>Certain geographical areas</td>
</tr>
</tbody>
</table>

### 3.5 Comparator

The choice of comparators has a fundamental impact on the type of evaluation conducted, the approach to data collection and the interpretation of findings (47). There should therefore be a clear description of the comparators under evaluation. Table 3 summarizes the main comparator options.

As decisions about which vaccines, and health care services generally, to provide are made in the context of what currently happens, the most relevant comparison for new vaccines is usually current practice. However, current practice is not always easy to define because it usually consists of a multitude of different practices. Therefore, in defining current practice one option is to choose the most frequently used interven-
tion(s) for comparison with the new intervention, or alternatively to use several types of care each as single comparators for the new vaccine strategy. A second possibility is to define the comparator as the weighted mix of current interventions, i.e. a package reflecting current practice. The new intervention can then be considered on its own, incrementally to this package (i.e. if the new intervention would be able to replace the whole package), or as an embedded part of the redefined package.

Table 3. Potential options against which to compare vaccines

<table>
<thead>
<tr>
<th>1. Current practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Single principal type(s) of intervention</td>
</tr>
<tr>
<td>b. Mix of interventions</td>
</tr>
<tr>
<td>2. Best available alternatives, e.g. as represented by clinical guidelines or low-cost alternative</td>
</tr>
<tr>
<td>3. Do nothing</td>
</tr>
<tr>
<td>a. Without the new intervention</td>
</tr>
<tr>
<td>b. Without any care, i.e. the null</td>
</tr>
<tr>
<td>PLUS</td>
</tr>
<tr>
<td>4. Alternative levels of scope and intensity for the new intervention</td>
</tr>
</tbody>
</table>

Source: Adapted from Cantor and Ganiats (47).

A second issue to consider is that current practice may itself be inefficient in which case almost any comparison would appear efficient. In that situation, one might choose the best available option or a do nothing option. Two types of do nothing option have been proposed: one that defines ‘do nothing’ as not doing the proposed intervention and the other that defines it as no care at all, i.e. the null. Both are likely to have associated costs and impacts, so zero costs and effects should not be assumed. The latter proposition was also comprised in generalised cost-effectiveness analysis (GCEA), as published in the 2003 WHO guide to cost-effectiveness analysis, under which a hypothetical null scenario is calculated by removing the impact of all currently implemented interventions (48).

When the objective of the decision maker is to develop a package of interventions against a particular disease, non-vaccine interventions such as screening and treatment should also be considered as comparators whenever feasible. For instance, improved sanitation and access to oral rehydration may decrease the burden of enteric diseases more efficiently than vaccination.

If a new vaccine strategy could be run at various levels of intensity, e.g. targeted or universal vaccination, different levels of coverage or different number of doses, these alternatives should be added to the potential range of comparators.

Box 2 provides some examples of comparators against which childhood vaccination against HBV might be compared.

Once the options for comparison are selected, a description of each one should be provided. This helps ensure that all the resources used are identified and allows others to understand exactly what was evaluated, which is important for considering the generalizability of the results. Drummond et al. (26) suggest that analysts need to ask (and answer): who, does what, to whom, where and how often (see Box 3 for an example).
Box 2. Examples of Comparators for Vaccination Against Hepatitis B Virus

The costs and consequences could be compared against one or more of the following:
- doing nothing, i.e. not vaccinating against HBV and not treating cases
- doing nothing, i.e. not vaccinating against HBV but treating cases
- universal childhood HBV vaccination with a birth dose but not treating remaining cases
- universal childhood HBV vaccination with a birth dose and treating remaining cases
- universal childhood HBV vaccination without a birth dose and not treating remaining cases
- universal childhood HBV vaccination without a birth dose but treating remaining cases
- vaccinating only health workers against HBV and not treating remaining cases
- vaccinating only health workers against HBV and treating remaining cases
- vaccinating only sex workers against HBV and not treating remaining cases
- vaccinating only sex workers against HBV and treating remaining cases

The above options can then be compared to other non-HBV options that compete for the same resources:
- introducing another vaccine, e.g. vaccinating against Hib
- extending coverage of existing vaccines

If there are more than two options being evaluated, then a full incremental analysis of all possible options should ideally be conducted. For a cost-effectiveness analysis, the most effective non-dominated option with a cost-effectiveness ratio below the threshold is generally the option to recommend. When accounting for uncertainty (see Chapter 8) this translates into the option which is on average most cost-effective (e.g. has the highest expected (=average) net benefit).

Box 3. Example of a Description of Alternatives for Evaluation

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who?</strong></td>
<td>Village health workers (VHWs) &amp; nurses</td>
</tr>
<tr>
<td><strong>Does what?</strong></td>
<td>Vaccinate newborns (VHWs) and infants (nurses)</td>
</tr>
<tr>
<td><strong>To whom?</strong></td>
<td>Newborns and infants</td>
</tr>
<tr>
<td><strong>Where?</strong></td>
<td>At facilities or homes (after birth) and vaccination sites</td>
</tr>
<tr>
<td><strong>How often?</strong></td>
<td>Once within 48 hours of birth and three subsequent times</td>
</tr>
</tbody>
</table>
3.6 Perspective

The choice of perspective or viewpoint determines the scope of the costs and benefits. The analysis must reflect the perspective of the persons or institutions who are affected by the outcome of interest and who bear certain costs associated with the programme or intervention being evaluated. The choice of a study perspective might also be constrained by the context of the study. For example, the organisation(s) funding the study (the audience) might want the analysis to reflect their own perspective. Note that it is important that the organisation(s) funding the study are clearly stated.

When an analysis is conducted for a decision that will be made by a national government, the choice of perspective should reflect national guidelines about the reference case for health economic evaluation (Box 5a in Fig. 2). If these do not exist, then analyses should adopt the perspective of society, and include all effects and all related costs, regardless of who benefits from or pays for them (Box 5b in Fig. 2). The costs borne by providers (e.g. donors and governments), patients and their families and others should be separated, so far as possible, to allow judgments to be made from the viewpoints of the various decision-makers. This is particularly important for partially donor-supported programmes (such as vaccination in Gavi countries). Also, costs to families should ideally be presented by household and if possible stratified by relevant household characteristics such as income or wealth quintile. This will allow analyses such as those on catastrophic expenditures and extended cost-effectiveness to be conducted if desired. Of course, the extent to which a range of perspectives can be included in the analysis will depend in part on data availability, and on the resources and time available to conduct the study.

In more affluent settings, where productivity losses can be significant, the perspective chosen can have considerable influence on the findings. For example, Lieu et al. (49) estimated (based on existing knowledge about the vaccine at the time) that from the health care payer perspective pneumococcal vaccination of healthy infants in the United States would result in savings if the vaccine cost $18 or less per dose, but from the societal perspective, the vaccination programme would result in savings if the vaccine cost $46 or less per dose. The economic contribution of non-paid labour (such as housework, caregiving and subsistence agriculture) and of the informal sector should be acknowledged wherever possible. These may be particularly important in LICs and LMICs, and for population groups such as women and the elderly.

3.7 Time frame and analytic horizon

The time frame (the period over which the vaccine(s) is applied) and analytic horizon (the period over which the costs and outcomes that occur as result of the vaccine(s) are considered) should be long enough to capture all relevant positive and negative effects.

This implies that it should be long enough for the modelled incremental cost-effectiveness ratio (ICER) and/or net benefit to attain a plateau, especially when using a dy-

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8 Since 2000, Gavi, the Vaccine Alliance, has helped support the purchase of vaccines in many of the poorest countries. Most countries eligible for Gavi support are required to co-finance part of the cost of vaccine purchase depending on their level of income and financial stability. As country income levels increase, the proportion to be co-financed also increases.
namic model where indirect effects change non-linearly with the number of birth cohorts vaccinated. The ICER and net benefit for vaccination programmes may take a considerable length of time to plateau. Depending on the intervention and the epidemiological characteristics of the infection, it may take from one (e.g. seasonal influenza) to 80 years (e.g. some models for varicella-zoster virus vaccination). Ideally, the analytic horizon should be set as a point in time after this plateau has been reached. This implies that the appropriate analytic horizon in these model-based evaluations should best be determined during and not prior to the analysis, and the exploration of various analytical horizons is encouraged.

We highlight some possibilities, which essentially depend on the effectiveness of the vaccination programme:

- Short-term for a vaccine with a short duration of protection, limited or short-lived herd immunity effects (see Chapter 6) and only one modelled birth cohort. An example is vaccinating children against seasonal influenza; at the current state of knowledge direct or indirect effects of vaccination are likely to last for one or two seasons. Note that even in this case, long lasting consequences from a short term impact (e.g. the years of life gained due to averted mortality in the first year) should be aggregated up to the end of life rather than to the end of the time frame over which vaccination is tracked. This is also the case if the effects of influenza vaccination (such as potential long-term modification of natural immune response by repeated vaccination (50)) are tracked over a long-period.

- Lifetime of the vaccinated cohort if a single-cohort model is being used (see also Chapter 6 on model choices).

- Infinite for an intervention with permanent effects, such as global eradication of measles. Note that the sum of benefits over the infinite time horizon will still be finite if a positive discount rate is applied and that a discount rate of 0% for health effects is problematic for the evaluation of eradication programmes as it may give rise to the eradication paradox (infinite benefits accruing to eradication programs implies we would have to invest first and foremost in eradication programs) (see also Chapter 7 on discounting).

3.8 Scope of benefits

Traditionally, health economic evaluations consider only benefits in terms of improved health, reduced health care costs and resource use (and improved quality of care) and short-term productivity increases to patients and their caregivers. However, “broader” economic benefits of vaccination are being increasingly recognised and valued. Such benefits may include longer-term productivity improvements as a result of better cognition and education due to avoided disease, reduced antimicrobial resistance, impacts of particular economic sectors like tourism, avoiding household catastrophic health expenditures and impoverishment as well as supporting innovation by vaccine manufacturers (25, 51, 52).

There are a number of ways that such benefits can be incorporated into economic evaluations, though none of these are trivial (53). Broadening an economic evaluation to incorporate some or all of these benefits should consider the way vaccines are
funded and the decision-maker(s)’ objectives for such funding (37). If the budget from
which vaccines are funded also funds non-vaccine interventions, then similar bene-
fits should be applied to other evaluations, which may require adjusting the thresh-
old at which an intervention becomes cost-effective. We discuss these types of bene-
fits also in Chapter 9.

3.9 Recommendations

- The study question should be well-defined, stated in an answerable form and
  relevant to the decision the target audience is facing;

- The comparators under evaluation should be clearly described. The most rele-
  vant comparison for new vaccines is usually current practice. If existing prac-
  tice itself appears to be cost-ineffective compared to other available options,
  the analyst should include other relevant alternatives into the analysis, such as
  a best available alternative, a viable low-cost alternative or a do-nothing op-
  tion. Non-vaccine interventions against the same disease should be considered
  where appropriate and should be captured by the current or alternative prac-
  tice comparators;

- The form of economic evaluation should be clearly stated and justified. CUA
  is the preferred type of evaluation (with DALYs or QALYs as outcome meas-
  ures), although CEA, which presents outcomes using natural units as outcome
  measures specific to the vaccine(s) in question is also encouraged;

- The perspective of the analysis should reflect national guidelines if the audi-
  ence is the national decision maker. Where absent they should adopt the soci-
  etal perspective, and include all related effects and costs regardless of who ben-
  efits from or pays for them. However, the costs borne by providers (e.g. donors
  and governments), patients and their families and others should be disaggre-
  gated so far as possible in order to allow judgments to be made from the per-
  spectives of the various decision-makers;

- The institution(s) sponsoring the study and individual authors should be clearly
  stated;

- The time frame and analytic horizon should be clearly stated. Their respective
  durations are contingent on the type of vaccine evaluated, the intervention and
  target population, and thus the type of model developed;

- Broader economic benefits besides improved health, reduced health care ex-
  penditure and short-term productivity gains can be incorporated if consistent
  with the way vaccines are funded and the decision-maker(s)’ objectives.
Chapter 4: Estimating costs

This chapter provides guidance on how to identify, measure and value resources in order to estimate the costs associated with a vaccination programme (i.e. both costs incurred and costs avoided). Remember, the exact nature of the costs assessed will depend on the scope of the analysis and the perspective(s) adopted.

4.1 Approaches to costing

4.1.1 Bottom-up and top-down costing

One of the most commonly used techniques for measuring the costs of vaccination programmes is the accounting approach. Accounting cost studies provide unit cost estimates of, for example, vaccinations sites, sessions or vaccinations themselves which can be divided into two categories. The first uses detailed, bottom-up, step-down analyses of accounting to distribute shared costs across the activities of individual facilities. The second uses a top-down approach, which makes less detailed estimates of high-level average costs based on aggregate expenditure records for multiple facilities/vaccination sites (26).

Step-down costings tend to be detailed and resource-intensive. This inherently limits the number of units that can be examined in any given study. Aggregate data, by contrast, allows more scope for comparing relative performance in terms of average costs, but loses a significant degree of discrimination relative to step-down methods, since one can no longer differentiate resource use between different uses.

4.1.2 Full and incremental costing

There are two broad approaches to costing: full (54) and incremental9 (55) costing. A full cost analysis estimates the costs of all the resources that are being employed in running a vaccination programme, including basic infrastructure. The numerator in an economic evaluation of introducing a new vaccine would thus be the difference between the total costs of the national immunization programme with the new antigen and the total costs of the national immunization programme without the new antigen.

In contrast, an incremental analysis looks at the cost of adding the additional vaccine to the existing programme; it does not attempt to provide cost estimates for the existing immunization programme. An incremental analysis accounts for the major ‘new’ inputs that are required by the new vaccine. However, since it assumes that the organizational infrastructure already exists, an incremental costing may under-estimate gen-

9 Sometimes referred to as marginal costing.
eral administrative costs borne by the programme. It is also more difficult to generalize from incremental cost analyses, unless the prior level of the existing programme and its infrastructure is clearly specified. Thus, when adopting an incremental approach to costing, it is important to provide a clear description of the existing programme, i.e. who, does what, to whom, where and how often? (See section 3.5 above).

Regardless of whether a full or incremental cost analysis is conducted, this guide recommends use of the ‘ingredients’ approach to costing, in which the total quantities of goods and services employed in delivering the vaccine(s) are estimated, and multiplied by their respective input prices (or unit costs). Making costs explicit in this way promotes a clear separation of prices and quantities. Both input prices and quantities can be subject to sensitivity analysis within economic analyses and the extent to which quantities respond to either differences in the relative price of inputs or different scales of production can be considered, to help promote understanding about variation in cost-effectiveness ratios. It also allows analysts and policy-makers to validate the assumptions used and assess the extent to which the estimates can be applied to their settings.

Unit costs of many health inputs vary substantially both within and between countries. This implies that basing cost-effectiveness studies for a region or country on the results of a study of a single facility, or even a small group of facilities, is likely to be misleading (56). Therefore, costs should not rely on single observation estimates when these are likely to vary within and between settings.

4.1.3 Choosing the price level and currency

A traded good is a resource that is known to be imported, or could have been imported. Traded goods, such as vaccines, cold-chain equipment and supplies, are all commodities that are, or could be, available on the international market, and could be available to all countries at an international market price. Goods that do not fall under traded goods are termed non-traded goods; these include labour\(^\text{10}\), utilities, buildings and domestic transport. Non-traded goods are goods that are domestically produced and which cannot by their nature be imported or exported. Non-traded goods should be similarly valued at international prices, taking into account distortions that exist in the domestic goods markets.

In nearly all economies, domestic market price levels are higher than international market price levels (57). Since vaccination programmes often rely on a mixture of domestically and internationally produced goods, it is important for the purposes of consistency to define the price level against which costs are valued, i.e. international or domestic prices. In principle, the rank ordering of interventions should not be affected by the decision to use international or domestic price levels. However, it is often argued that international price levels are the most appropriate starting point for analysis, because ‘...they represent the actual terms on which a country can trade’ (58) and enable comparability of cost estimates between countries. The opportunity costs of goods and services consumed by an intervention can then be determined by considering the changes in foreign

\(^{10}\) Although with globalization labour has become increasingly tradable.
exchange available to the country. The opportunity costs for imported goods can be considered to be the foreign exchange that leaves the country in order to pay for the inputs. Similarly, where an input to an intervention is produced locally but could be exported its value is the value that could have been obtained for it on the international market.

In some countries (typically high-income and some middle-income countries), prices and exchange rates are relatively stable, goods are purchased in local currencies, and logistic and regulatory barriers to international trade are relatively minor. In such settings, domestic price levels can be used as approximations of international price levels. However, in countries where some or all of these conditions do not hold (typically low-income and some middle-income countries), international price levels should be used.

Central to the use of international prices is that any tariffs are excluded from the analysis. Tariffs are considered as transfer payments from one part of society to another, and do not consume resources but simply transfer the power to use resources from one person to another. Consider, for example, a cost analysis of a vaccination programme, which uses vaccines and refrigerators, both imported against a tariff of 25% (Table 4). If vaccine costs are valued against international price levels, so should refrigerators, and any import tariff should be excluded. Conversely, if both goods are valued against domestic price levels, import tariffs should be included.

Table 4. Example calculation of vaccination programme costs in the presence of import tariffs in a hypothetical district

<table>
<thead>
<tr>
<th>Type of good</th>
<th>Quantity</th>
<th>Imported</th>
<th>Tariff</th>
<th>International prices</th>
<th>Domestic prices</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Price level</td>
<td>Total costs</td>
</tr>
<tr>
<td>Vaccines</td>
<td>1,000</td>
<td>Yes</td>
<td>25%</td>
<td>$0.10</td>
<td>$100</td>
</tr>
<tr>
<td>Syringes</td>
<td>1,000</td>
<td>No</td>
<td>NA</td>
<td>$0.008</td>
<td>$8</td>
</tr>
<tr>
<td>Refrigerators</td>
<td>1</td>
<td>Yes</td>
<td>25%</td>
<td>$500</td>
<td>$500</td>
</tr>
<tr>
<td>Nurses (FTE)</td>
<td>2</td>
<td>No</td>
<td>NA</td>
<td>$400</td>
<td>$800</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>$1,408</td>
<td>$1,760</td>
</tr>
</tbody>
</table>

Source: Adapted from Hutton and Baltussen (57).

In addition to the price level, the analyst must also choose the currency that costs will be reported in. The choice of currency is independent of the choice of price level. However, both decisions depend on whether the evaluation is being performed to inform broad resource allocation decisions.

- **Example 1: Informing a decision by a local-policy maker about whether a new vaccine should be introduced into the country’s national immunization programme.** In this case, a local decision-maker trying to set spending priorities among different interventions has no good reason to base decisions on the real resource comparisons represented by costs reported in international dollars (I$) via the country purchasing power parity (PPP) exchange rates. Setting aside all con-

11 The average import tariff in the country is assumed to be 25%, so the Standard Conversion Factor, which is the ratio of international to domestic price level, is equal to 0.8 (= 1 / (1 + 0.25)).
siderations except cost-effectiveness, the decision-maker will be much more concerned with the cost; and if a non-traded input is relatively cheap in local currency, will want to take that into account. Therefore, comparisons of total costs should be made either in local costs, by converting the dollar cost of traded imports into local currency, or in dollars, by converting the cost of non-traded inputs into dollars; either conversion will use the actual (official) exchange rate rather than the PPP rate.

- **Example 2: Informing a decision by Gavi about whether to supply a vaccine to eligible countries.** In this case, authors should price traded inputs at a uniform international price; price non-traded inputs at local prices; convert those local prices to I$ via the country PPP exchange rates; multiply prices by quantities to get total cost for each input; and add up all the input costs to get total average cost of the intervention, in I$. Costs calculated in this way would represent (a good approximation of) real resource use, in comparisons among countries and regions for a given intervention and among interventions in the same or different regions.

The last consideration for pricing is inflation. All costs should be inflated to a single base year to ensure their comparability. Turner et al. (59) provide useful specific guidance on how to inflate and perform currency conversion in an international context. Inflation should be done using either a GDP deflator or the consumer price index. However, the former is preferred since the basket of goods used to construct the consumer price index differs between countries and does not always reflect changes in the cost of healthcare. Three methods of inflation are suggested, depending on the mix of traded and nontraded resources involved in the intervention being evaluated:

- If the intervention consists mainly of traded goods, then it should be converted into USD (using international exchange rates) or I$ (using PPP exchange rates), then inflated using a US inflation rate (as a proxy for changes to prices of traded goods internationally).
- If the intervention consists mainly of nontraded goods, then it should be inflated using local currency inflation rates, then converted into USD or I$.
- If the intervention consists of a mix of traded and nontraded goods, then the traded goods should be inflated using US inflation rates while nontraded goods are inflated using local currency inflation rates.

### 4.2 Identification: which costs to include?

It is helpful to distinguish between the costs borne by the health sector and those borne by patients and their families, including lost productivity. A third category is the future costs that are a consequence of the intervention. Each of these categories of costs is examined in more detail below. However, it is important to recognize that the choice of which costs to include depends primarily on the perspective of the analysis, and that the perspective, in turn, is influenced by the scope of the analysis and target audience (see Chapter 3).

If a societal perspective is adopted, all resources used to provide the vaccine(s) and all future resources ‘saved’ by the successful immunization of individuals should be included. When a narrower viewpoint is adopted, such as that of the Ministry of Health, changes in resource use outside of the Ministry of Health or elsewhere in the economy are ignored.
4.2.1 Costs for the health sector

The costs borne by the health sector can be divided into the direct costs of providing the intervention (vaccine programme costs) and the costs that may be averted as a result of the intervention (cost offset, i.e. the savings in health care costs thanks to the intervention).

Guidance on how to estimate total vaccination programme costs can be obtained from an ingredients-based approach to estimating the costs (60), or from the guidelines for producing immunization multi-year plans. The incremental **vaccine programme costs** can be estimated using the stepped approach outlined in WHO’s *Guidelines for Estimating Costs of Introducing New Vaccines into the National Immunization System* (55). As stated above, the recommended method for estimating the costs of introducing a new vaccine consists of identifying all the inputs required for the introduction along with their respective quantities and unit costs – the so-called ‘ingredients’ approach to costing. The types of input required depend to some extent on whether the vaccine would be introduced as a combination vaccine where one or more of the vaccines is already present in the system or whether it would be a monovalent vaccine.

A combination vaccine covering multiple antigens, including those already in the program, is simpler to introduce than a new monovalent vaccine, as it does not involve any additional injections. Furthermore, if the combination vaccine is procured in the same vial size as before, the vaccine will not require additional space in the distribution system. If, on the other hand, the vaccine is monovalent, or the combined vaccine is introduced with fewer doses per vial than previously used, or an extra vial for diluent is required, then the vaccine will take up more space in the distribution system, which may necessitate expansion of the cold chain.

Table 5 summarizes the input categories that have to be assessed according to whether a monovalent or combination vaccine is being introduced. For a combination vaccine in the same vial size, the only inputs that need to be assessed – besides the vaccine itself – are disease surveillance, training, stationery and social mobilization. For a monovalent vaccine, inputs such as syringes, waste management and expansion of the distribution system should also be assessed.

With a robust vaccine pipeline, the number of diseases that can be prevented through vaccination, not just in childhood, but across the life course, has substantially increased. In addition, many of the new vaccines target diseases or syndromes that cannot be completely prevented or controlled by the vaccine alone. For example, the introduction of HPV vaccine provides two important opportunities to implement integrated approaches towards disease control and health promotion: 1) the opportunity for countries to develop comprehensive national strategies for the prevention and control of cervical cancer, including cervical cancer screening, treatment and pallia-

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12 The cMYP Costing and Financing Tool was developed to help with the costing and financing of a cMYP. It can be used to estimate the past costs and financing of immunization, and to make projections of future costs, future resources requirements, and future financing needs to achieve programme objectives, as well as to analyse the corresponding financing gaps. The Tool is accompanied by a User Guide which provides an overview of important immunization costing and financing concepts, methodologies and definitions, as well as step-by-step instructions on how to use the costing and financing tool, including how to analyse the data and findings. The materials are available online at the following website: [https://www.who.int/immunization/programmes_systems/financing/](https://www.who.int/immunization/programmes_systems/financing/)
tive care; and 2) the opportunity to provide other health services or health education messages to 9–14 year old children. As a consequence operational costs for delivering HPV vaccines should include the possibility to deliver vaccines through schools or outreach activities for educating school teachers and transporations of vaccines to schools should be included. Similarly, delivery costs of seasonal influenza vaccines should include costs of strategies of delivering vaccines through antenatal care services, or for typhoid vaccines, through routine or one-time mass campaigns. WHO has developed guidelines for several delivery services as well as new life course vaccination programs (61–63). The Global Health Costing Consortium and EPIC are important initiatives that have recently produced detailed cost guidance, relevant for vaccination (see https://ghcosting.org/pages/standards/reference_case and http://immunizationeconomics.org/recent-activity/2019howtocost, respectively).

### Table 5. Inputs to be assessed according to vaccine presentation

<table>
<thead>
<tr>
<th>Type of new vaccine</th>
<th>Combination vaccine with no change in vial size and no extra vials for diluent</th>
<th>Combination vaccine with fewer doses per vial than previously used and/or with extra vials for diluent</th>
<th>Monovalent vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplies to assess</td>
<td>• Supplies: vaccines • Disease surveillance • Other costs: training, stationery, social mobilization</td>
<td>• Supplies: vaccines and reconstitution syringes • Distribution system: transport and cold storage • Disease surveillance • Other costs: training, stationery, social mobilization</td>
<td>• Supplies: vaccines, syringes, safety boxes • Distribution system: transport and cold storage • Waste management • Personnel • Disease surveillance • Other costs: training, stationery, social mobilization</td>
</tr>
</tbody>
</table>

*Source: Adapted from Kou (55).*

In terms of **treatment costs and treatment cost savings**, direct medical costs are defined as the costs of resources incurred for the treatment of a disease and possible side-effects. Typically, these will include the cost of physician and/or hospital visits/stays (including medical staff time), diagnostic tests and pharmaceuticals. These costs might be borne by the health sector and / or by patients and their families (26).

#### 4.2.2 Costs for patients and their families, including lost productivity

Again costs to patients and their families can be divided into costs to access immunization services, and cost offsets as a result of disease averted by vaccination. For the former category, although factors such as travel/waiting time and lost earnings can represent substantial costs affecting the uptake of vaccination services, economic analyses have tended to focus on the costs of providing vaccination services. However, the inclusion of such costs depends on the study question and vaccine being evaluated. For example, the economic evaluation of a new vaccine that will be provided alongside the existing schedule, e.g. Hib vaccines provided alongside the DPT vaccine doses, will not incur additional transportation costs to the families of vaccinated children notwithstanding a potential fee to cover the new vaccine. An economic evaluation of
increasing vaccination coverage rates would, however, include such costs. Such costs should also be considered when comparing the cost-effectiveness of different vaccination delivery modalities, such as fixed sites, outreach sites and mobile teams; each of these modalities will impose different levels of cost on families to get their children vaccinated, because families are required to bring their children to fixed sites, whereas mobile teams and outreach sites bring the services to the community.

With respect to cost offsets, these can include out-of-pocket payments (or payments made from privately-held insurance funds) for items such as user fees for public healthcare, charges for private healthcare (including informal and traditional care), costs of carers to look after sick individuals (or to relieve sick family members with caring responsibilities) and costs for medical-related expenses such as medicine, special food, extra diapers and environmental modifications for disabled patients. Indirect costs include time lost due to sickness or caring for patients (see section 4.5 for its valuation). Broader economic costs of illness can include long-term effects of illness, particularly in children, such as developmental, cognitive or educational deficits which could translate into lost lifetime earnings and opportunities (64). However, these broader costs are difficult to measure (in both monetary and non-monetary terms) because of the need for long-term follow-up and the high probability of confounding, since children who are at high risk of infectious diseases are also more likely to have poorer life prospects.

4.2.3 Future unrelated costs

There is not yet consensus on the issue of how to properly account for costs that are not costs related to the intervention per se, but result from the successful implementation of the intervention, including the net resource costs (for health and for other forms of consumption) that will be incurred due to unrelated events and disease in the future because life is extended (65, 66). Most country-specific and vaccine-specific guidelines have recommended excluding or had no explicit position on the inclusion of such costs. A notable exception is the recent and potentially influential guide endorsed by the second US panel on cost-effectiveness, which was published in 2016, and advised to include such costs (6). It should be noted that the exclusion of unrelated future costs might create a favourable bias towards:

1) interventions aimed at persons at an increased risk of unrelated illnesses over interventions for healthy persons (e.g. interventions in frail and/or elderly persons over most general prevention programmes, including many vaccines);

2) interventions aimed at persons further removed from death over interventions for persons closer to their time of death, provided they run the same risks for unrelated diseases.

Most guidelines recommend that such costs should not be included, and cite practical difficulties of estimation, because one would need to take account of heterogeneity in risks for unrelated disease and death. For many countries the required data may not be available to researchers to make such estimates, and their inclusion may involve ethical issues around differences in income, especially when considering non-health care costs. The present guide endorses excluding future unrelated costs for these reasons. If, however, an analysis is made for a policy maker, who wants these costs included as part of a reference case for a particular jurisdiction, then we recommend to
present the results with and without including these costs. The same methods for estimating unrelated costs should then be used in that jurisdiction for all interventions, not only for those that include vaccination.

4.3 How to measure resource use?

4.3.1 Costs for the health sector

When it comes to measuring the (incremental) resources associated with the introduction of a new vaccine, clearly much depends on whether the evaluation is being performed *ex ante* or *ex post*. An *ex post* evaluation, in which a new vaccine has actually been introduced into part or all of the national immunization programme, provides the opportunity to observe the change in total costs over past practice, i.e. before the introduction of the new vaccine. However, it is more common for analysts to attempt to measure what additional resources were associated with introducing the new vaccine. Both approaches will involve the allocation of shared resources to the new vaccine. These ‘joint’ costs might be shared by other health services (e.g. staff) and/or other vaccines (e.g. staff, the cold-chain). For example it is unlikely that any staff will work exclusively on a particular new vaccine with the exception of campaigns and/or new delivery systems dedicated to immunization programmes. Personnel costs should therefore be assessed on the basis of time allocations, which may be done through interviews or time-and-motion studies.

An *ex ante* evaluation, on the other hand, requires a picture of the incremental resources to be constructed; WHO’s *Guidelines for Estimating Costs of Introducing New Vaccines into the National Immunization System* (55) enables analysts to do this based on data and assumptions regarding the vaccination coverage rate, birth cohort, wastage rate, cold-chain capacity, etc.

Data on wastage rates are particularly important given the relatively high cost of most new vaccines. 50% wastage, not uncommon for the traditional EPI vaccines, doubles the cost per dose administered. Wastage rates depend on the number of doses in a vial, whether or not the country in question has an open vial policy, the duration and frequency of immunization sessions, any cold chain and distribution failures, and the number of vials discarded due to expiry. Wastage rates are calculated by comparing the number of doses administered with the number of vials opened for use and with the number of closed vials that are discarded because of cold chain failure, vaccine vial monitor indication or expiry. Wastage rates may differ in various settings, depending on factors such as population density and delivery strategy (e.g. fixed site versus outreach). The national wastage estimate for a particular vaccine should be a weighted average of the wastage rates for different settings. If a new vaccine is combined with one of the existing vaccines and if there is no change in vial size, wastage rates for the existing vaccine can be used. Otherwise assumptions regarding the wastage rate of the new vaccine should be clearly stated.

It may be necessary to expand the capacity of the distribution system in order to make space for additional vaccines and syringes. The costs can be separated into those of transport and vaccine storage (often referred to jointly as the cold chain). If there is considerable spare capacity in existing refrigerated storage at one or more levels of the system it should not be necessary to expand the storage space. If there is limited spare
capacity it may be possible to shorten the supply interval at one or more levels so that the volume required for storage is reduced and the transport requirement is increased.

In respect of treatment costs, there are a number of potential sources of data on resource use including randomized controlled trials (RCT), administrative and clinical databases (unlikely to be an option in most low-income and many middle-income countries), and medical records. The issue of how to measure these resources has tended to be seen in terms of economic analysis alongside RCTs versus economic modelling that combines data from a potentially wide range of sources. This is a misleading dichotomy because economic analysis alongside RCTs will almost invariably involve elements of modelling and economic modelling will generally utilize data from trials (should suitable data be available).

However, economic analysis is increasingly favouring economic modelling over economic analysis alongside RCTs. There are two main advantages to this: first, the evaluation can be designed to address precisely the choices faced by decision-makers, which RCTs often do not; second, economic models can utilize information from a wide range of sources as opposed to from a single study. This means that the analysis is not subject to the data limitations of any one particular study. The second advantage is clearly not without its dangers and analysts must be very careful when selecting which data to combine. Nevertheless, there is probably greater scope for manipulation of the eventual outcome in terms of cost-effectiveness in a model than there is with economic analysis alongside an RCT.

Assuming that a study is going to collect some primary data rather than rely wholly on secondary sources, there are a variety of methods by which these data can be collected other than alongside an RCT. Medical records can be an invaluable source of data. Unfortunately, there are frequently problems with missing and/or poor quality data. Where adequate records are unavailable, questionnaires given to physicians, patients or their carers can be a means of documenting past resource use. Of course, questionnaires administered to patients or their caregivers are dependent on recall, which may be biased and, in the absence of good response rates, unrepresentative.

Patient diaries can be a good way of identifying resource use outside of facilities, where detailed records may not be kept, but a high level of compliance is needed if the data are to be representative (67). In addition, diaries work best when the patient has regular contact with members of the research team and if the data collection period is not too long. Best practice guidelines, e.g. Integrated Management of Childhood Illness, as well as the literature can also provide information about patients’ resource use. Whatever the source(s) of data on resource use, a general lack of good quality data is a feature of many studies. Studies are always constrained by the resources available for data collection and difficult judgments must be made about where best to invest these scarce resources.

4.3.2 Costs for patients and their families, including lost productivity

Depending on the type of health system in place, treatment costs may be borne by patients and their families; several of the methods described above can be used to measure these costs. For example, patient diaries and questionnaires administered to patients and/or their carers can be a means of documenting out-of-pocket expenses and lost productive (and leisure) time due to accessing vaccination services as well as due to an illness episode.
4.4 Valuing resources

A number of approaches can be used to estimate unit costs depending on the data available, required level of precision, and the resources available for the study. The different levels of data collection intensity are most pronounced for costs per hospital day and outpatient visit.

1) National price lists. Many countries maintain price lists for medications used by public hospitals and clinics. Since these prices are based on large volume government purchases, the prices may approximate actual economic costs. These prices may not be an appropriate source of information if they are subsidized by the government. Price lists should be available from hospital or clinic administrators.

2) Purchase price. If standardized national prices are not available, actual purchase prices maybe used. Prices should include any discounts and delivery/shipping charges. Purchase prices can usually be obtained from the accounts departments of the ministry of health, the hospital or central pharmacy board.

3) Market prices. These should be determined from a sample of private facilities. Likely to include large profit margins and so to over-estimate true costs.

4) In the absence of a national price list or reliable data on purchase prices, standardized international price lists may be used – see for example the Management Sciences for Health International Medical Products Price Guide (http://mshpriceguide.org), which includes many common medications. UNICEF’s supply division and PAHO’s Revolving Fund operate as vaccine procurement mechanisms for a number of developing countries. Current vaccine prices can be obtained from UNICEF and/or PAHO (https://www.unicef.org/supply/ and https://www.paho.org).

In this guide, we define hospital costs per bed-day as the cost per patient day of hospital personnel, the building, equipment, maintenance, administration, laundry, food, cleaning, etc. Cost per bed-day does not include the patient-specific costs of diagnostic tests, medications and medical supplies. There are three different approaches that can be used for estimating the costs per hospital bed-day. These methods differ in their intensity (i.e. the financial and time resources required to carry them out) as well as in the accuracy of the estimates they produce. The method chosen in a particular study should be selected based on the purpose and scope of the study and the needs of decision-makers. The alternative methods described below are presented in order of increasing intensity:

1) Standardized WHO-CHOICE estimates. As a part of its CHOICE project, WHO has developed estimates of the unit costs of a hospital bed-day, outpatient department (OPD) visit and health centre visit in different settings using a regression model. In the model, country estimates are a function of GDP, ownership (public/private), level of the facility for hospital bed-day and OPD unit costs (primary, secondary and tertiary), the level of capacity utilization and whether or not capital and food costs are included (for hospital bed-days). The estimates are given in international dollars, which can be converted to local currency. Estimates are based on an occupancy rate of 80% (http://www.who.int/choice/costs/).

Admitted patients will usually spend their time in one or more of the following wards: general, isolation, paediatric or intensive care unit. The intensity of resource use will vary in these wards, e.g. an intensive care unit bed-day typically costs 2–3 times that of a bed-day in a general ward.
2) *Existing unit cost data.* In some countries, estimates of the cost per hospital bed-day, OPD visit and health centre visit may be available for some facilities. These estimates may be from administrative sources or previous costing studies. In order to be used, the costs should include all relevant cost components (facilities, equipment, maintenance, administration, personnel, etc.). However, care should be taken to make sure that the sample is representative and that adjustment is made for inflation if the cost data were collected in years prior to the one chosen for the study.

3) *Full costing study.* This approach is the most intensive in terms of both time and resources. The costs of all of the facility’s activities are estimated separately and all cost items are divided into capital and recurrent costs. This detailed approach should only be used if very precise estimates are considered worth the additional investment of effort and resources needed to produce them. Remember that unit costs vary within countries or settings, hence the generalizability of a full costing study from one facility, or even a sample of facilities, might be limited (42).

4.5 Valuing productivity losses/gains

The most common means of valuing the loss of time borne by an individual, household or society due to morbidity or premature mortality, seeking and providing care for an individual (e.g. informal care in the family), or accessing vaccination services, is the human capital approach, which values lost time using an individual’s gross earnings (26). The underlying justification is the assumption that employers continue hiring labour until the value of the marginal contribution to output by an individual worker is just matched by the cost of employing them. Of course, many individuals in developing countries may not be formally employed nor earning an income, i.e. they may be subsistence farmers. Where individuals are from rural areas and would otherwise have been employed in agricultural production, the opportunity cost can be taken to equal the value of lost production. An indirect way of estimating this is to use the rural wage rate, adjusting for seasonality. At some times of the year, this might be close to zero. Where individuals are from urban areas, productivity losses can be approximated by estimates of annual incomes in the urban informal sector. The urban formal sector wage rate is likely to be an over-estimate, especially where minimum wage laws apply. In the absence of data, analysts might use estimates of the gross national income (GNI) or GDP per capita to value lost time.

The main alternative approach to valuing lost time/production gains is the friction cost method, which explicitly recognizes that output is in many circumstances only lost temporarily, for example where a replacement can be hired from a pool of unemployed workers (68). As a consequence, this approach produces lower estimates of production lost/gained. Although this approach appears conceptually more appropriate, especially for long term illness, it is not used as often as the human capital approach because the data it requires are less readily available. The importance of the perspective should also be noted. Lost productivity will be borne by the households affected and society more broadly. As recognized by the friction cost method, in economies with large pools of unemployed, these costs can be more easily offset at the societal level. Indeed, even at the household level, some proportion of short-term lost productivity, i.e. during an illness episode, can most likely be made up by the individuals themselves or by friends and family. However, long-term productivity losses, e.g. due to
the sequelae of bacterial meningitis, cannot be offset at an individual/household level in the same way as they can at the societal level.

There is still debate over whether and to which extent production gains should be taken into account given concerns about double counting productive time with QALY or DALY valuations. There seems more support for including productivity costs in theory than currently seems to transpire from practice and from country guidelines for economic evaluation, possibly because estimates of the value of time tend to vary widely (69–72). If assessments of cost-effectiveness were routinely to take into account such effects, one implication would be that more productive groups or economies would tend to be given priority over less productive groups or economies. However, within low-income countries, where indirect costs have been measured and valued, studies have shown that such costs can be substantial relative to the direct costs of health care (73). As a result, ignoring these costs may lead to the costs and benefits of different vaccines being greatly under-estimated. However, data collection difficulties are if anything more formidable here than in the case of direct costs, since few data are routinely collected. Therefore, because of the challenges and controversy regarding how best to measure and value time and lost earnings, such costs – if they are considered in line with a specific perspective (see Chapter 3) – should be separately reported. Similarly, the results in terms of cost-effectiveness or cost-utility should be presented separately, with and without these costs.

### 4.6 Vaccination-specific costing issues

The optimal level of coverage, compared to using the resources for other interventions, depends on what happens to the cost-effectiveness ratio as vaccination is expanded (or contracted). While our understanding of some of the key features of different vaccination programmes is becoming increasingly sophisticated, little information has been compiled on how costs vary with the scale of production. Country-specific empirical evidence detailing the division between government and private costs, and on how vaccination programme costs change as coverage changes is, despite its importance for policy decisions, scarce (74, 75).

Most cost and cost-effectiveness analyses of vaccination programmes are evaluated at a set level. While this approach may be justified given the general lack of information available beyond a single point in time, it suffers from two major shortcomings. First, these studies often report only the average cost of operations without any further analysis of the marginal cost. Second, they usually only consider cost at the current level of operations without estimating how changes in scale of operation will affect average costs. Even when studies have attempted to ascertain the costs of increasing coverage rates, most have assumed a linear increase in costs, i.e. the studies assume that the programme exhibits constant returns to scale (76). This is done by taking the unit cost associated with a programme and multiplying this by a factor reflecting activity at a larger scale (e.g. if the unit cost per fully vaccinated child is $10, the cost increase for expanding vaccination services for another 50 children is $500). However, given the existence of some fixed costs and some rising marginal costs, “U-shaped” cost curves of falling and then rising average costs should be expected. This suggests that current estimates of costs could be significantly biased.
The calculation of marginal costs requires an understanding of how costs change with the number of people vaccinated. Unfortunately, vaccination studies generally report static analyses of costs that have not been performed in conjunction with coverage surveys. Therefore, in reality this is rarely observable. The following describes some of the methodological stances adopted in the wider economics and health economics literature.

One approach examines the relationship between total, capital and recurrent costs, and the number of people vaccinated in each facility. Over (77) suggests that the expansion of programme activities results in diseconomies of scale that are not captured by constant average cost projections of recurrent costs: he uses a combination of data and knowledge about a project to consider the costs of scaling-up a project. He establishes a minimum efficient scale of production for the programme and then derives unit costs from this. However, this requires a working knowledge of each programme in a country-specific context.

An alternative approach uses statistical methods to identify the behaviour of marginal costs at different output levels, and thus to draw conclusions regarding the existence and importance of returns to scale. A problem common to both types of accounting studies described in section 4.1.1 is that they have an implicit underlying cost function represented by the sum of the products of the quantity of each input, multiplied by its respective price. Thus, although accounting studies generate a point estimate of total costs at an observed output, they do not provide information about what is likely to happen with changes in the price or quantity of an input. Inferences therefore cannot be made about economies of scale and scope, as average cost will only coincide with marginal cost under conditions of constant economies of scale. In contrast to cost analyses, statistical approaches can provide a more realistic depiction of how total costs change in response to differences in service mix, inputs, input prices and scale of operations. Statistical methods therefore allow for substitution between inputs as their relative prices and marginal productivity change. Indeed, emerging evidence based on the application of data envelopment analysis suggests that the cost of vaccinating each additional child may change with the scale of production (78).

However, it does not follow that vaccination will become less cost-effective when coverage is expanded, because the increase in effectiveness may be even greater than the increase in costs. This can happen because incidence is higher among the unprotected population, as with diarrhoea among children without access to safe water. It can also happen because, for a common risk of incidence, severity is greater among the unprotected population. Measles incidence in the absence of vaccination may be roughly equal for all children, but undernourished children are much more likely to die as a result; vaccinating them is thus likely to be more cost-effective than average for the intervention. Most previous analyses have also failed to consider potential changes in effectiveness of vaccination at different levels of coverage, through indirect protection of populations (“herd immunity”) above a critical threshold of coverage. For measles, extremely high coverage levels are required to achieve elimination – in the order of 95% or higher (79). The costs of attaining this level of coverage will be high, but could be offset by avoiding the costs of responding to measles outbreaks, which continue even at coverage levels of 85–95%. Therefore, the economic evaluation of the same programme at two points in time should be undertaken when the opportunity presents itself, as such an analysis will shed empirical light on how costs, effects and cost-effectiveness vary with the scale of production.
Finally, there may be efficiency gains when introducing combination vaccines or a combination of vaccines (economies of scope), particularly when they are given alongside the existing schedule. For example, costs associated with training, stationery and social mobilization can be shared among different antigens, rather than incurred separately for each individual vaccine. However, it is also important to recognize that changes in child mortality caused by, for example, rotavirus vaccination may influence the incidence of, for example, Hib, i.e. the benefits of vaccinating against multiple diseases may not be additive.

4.7 Recommendations

- The methods used for the estimation of costs should be clearly stated;
- A summary should be provided of the expected resource use and unit costs for each alternative. This should include specifying the assumptions behind calculations of costs, e.g. amounts and types of health service use with and without the alternative, given a specific coverage of the alternative and indicating actual and potential ranges of each estimate;
- A full costing study should only be considered if precise estimates are needed and it is considered worth the additional effort involved. Otherwise, it is recommended that standardized WHO-CHOICE estimates be used or existing country-specific cost data if available;
- Costs for patients and their families, including lost productivity if considered, should be reported separately. This guide recognizes that several methods exist for valuing lost productivity; analysts should therefore make clear and justify why a particular method was chosen and set out its pros and cons;
- Future unrelated costs should not be included, both because of the practical difficulties of estimation and because their inclusion involves conceptual and ethical issues concerning differences in incomes, unless it is a requirement of the reference case for the local policy maker, for whom the analysis is meant. In that case, we recommend presenting the results with and without including these costs.
- Costs should be reported in local currency units, ideally using the most recent year as the base-year, converted to US$ using official exchange rates for the base-year in question or also converted to I$ using purchasing power parity (PPP) exchange rates for the purposes of regional or global comparison.
Chapter 5: Assessing the effects of the vaccination programme

This chapter discusses the concepts involved in estimating the impact of vaccination. Specifically, the terms efficacy and effectiveness are described and background is provided on the extrapolation of vaccine efficacy data to produce vaccine effectiveness estimates. This chapter also includes a discussion of sources of data for estimating vaccine uptake (or coverage) and possible adverse events of vaccination. Lastly, the various possible outcome measures, and their strengths and weaknesses, are listed. The choice of outcome measure(s) will largely be determined by available information and the type(s) of economic evaluation being used to answer the study question.

5.1 Vaccine efficacy

The intended impact of vaccines on people who are vaccinated has different facets, depending on the properties of the vaccine itself, and that of the pathogen. These may be any or a combination of the following (80–82):

- Vaccination may reduce the probability, severity and/or speed of progression of clinical disease (including towards mortality) in vaccinated persons.
- Vaccination may reduce susceptibility to infection of vaccinated persons upon exposure.
- Vaccination may modify infectivity of vaccinated persons to others. That is, when vaccinated persons acquire natural infection they may be less infectious than non-vaccinated persons who acquire an infection.
- Vaccinated persons may immunize non-vaccinated persons indirectly by shedding vaccine-induced viral load (irrespective of whether these vaccinated persons have been exposed to natural infection).

Each of these facets may be such that (80–87):

- A proportion of vaccinated persons experience the intended effects and the remainder of vaccinated persons do not. This is sometimes referred to as “Take” (indicating that in this proportion of vaccine recipients the vaccine “takes hold”). For example, a vaccine with 90% “take” would then produce the intended effect in 90% of vaccinated persons, and not in the remaining 10%.
- Vaccinated persons in whom the vaccine “takes” may experience the intended effects to a certain degree. For example a vaccine with 90% “degree” would produce
the intended effect in 90% of vaccinated persons in whom the vaccine “takes hold”. Note that it is possible that a proportion of vaccinated people are completely protected, and the remainder is not at all (i.e. when degree is 100%), or that every vaccinated person receives protection to some degree (i.e. when take is 100%).

• They remain constant over lifetime or wane as a function of time since vaccination (and here various evolutions of decline in protection are possible, e.g. an exponential decay is often assumed). Note that the detectable levels of antibodies are not always a good correlate for vaccine-induced immunity, as some vaccines have been shown to induce cellular immunity in the absence of detectable antibodies.

In addition, it is well known that the efficacy of vaccines depends on the age at administration and adherence with the vaccination schedule (compliance and spacing between doses). That is, the immune system shows different responsiveness based on the vaccine recipient’s age (along with other biomedical aspects). Similarly, it responds differently when a single dose is given, or two or three etc. of the same vaccine (depending on the vaccine). Since compliance with the full schedule may be problematic in some settings, these differences need to be considered when estimating effectiveness (see below).

In principle, many of these effects could be estimated in specific studies. There are well established study designs for estimating the efficacy of health interventions (basically RCTs, case-control studies and cohort studies, for a succinct review of these see Grimes and Schulz (88)). The gold standard is the RCT, but often, when an intervention (including vaccines) is known to have some beneficial effect the possibility of conducting further RCTs could be considered unethical.

“Efficacy” is defined as the intended impact on measurable end-points (biological markers, clinical disease stages) observed in the controlled setting of a trial, with obvious limitations associated with the choice of measured end points, and length of the trial. Over a given time period, \(N_V\) vaccinated individuals are observed, and \(C_V\) of these become cases; “a case” is then defined in relation to relevant measurable end-points that one wishes to avoid, e.g. level of detectable antibodies below a defined threshold (often termed “seroconversion threshold”), mild clinical cases, severe clinical cases, physician consultations, hospitalizations, deaths. Over the same period, \(N_U\) unvaccinated individuals are observed, and \(C_U\) of these become cases. Vaccine efficacy (\(VE\)) is then typically derived as:

\[
VE = 1 - \frac{C_V}{N_V} \frac{C_U}{N_U}
\]

Note that this definition does not take account of the infectious nature of the diseases against which vaccines are aimed. That is, this definition is valid under the assumption that the infectious nature of the disease does not influence the observations in the trial setting. The extent to which the assumption is met, depends on the above four facets of impact along which the vaccine works (as not all vaccines work along all these facets), the size of the trial population relative to local population size (or in clusters thereof)
and on environmental factors such as the force of infection. For instance, a vaccine reducing susceptibility to infection will be shown to be more efficacious in a trial conducted in an area where the force of infection is high, if natural boosting improves long-lasting protection against clinical disease in vaccinated persons who initially responded poorly to vaccination. Fig. 3 illustrates the processes at work in persons vaccinated against an infectious pathogen, which circulates in their environment.

**Fig. 3. What happens when an individual is vaccinated?**

Vaccinated persons end up in the dashed rectangle after receiving vaccination in one of three compartments with probabilities $a$, $b$ or $c$ (note that for some vaccines some of these probabilities may be zero).

- $a$ – probability of being fully protected after vaccination;
- $b$ – probability of being not protected after vaccination;
- $c$ – probability of being partially protected after vaccination.

After vaccination vaccinated persons will flow among the three compartments, depending on their contacts with other vaccinated and infectious persons in their environment.

- $t$, $w$, $y$ – rates to improved immunity by exposure to natural infection (as a function of the force of infection) or more rarely by exposure to vaccinated persons shedding viral load;
- $u$, $v$, $x$ – rates to reduced immunity by loss of vaccine-induced immunity (as a function of time since vaccination).
In a trial, what is observed is not usually linked to the three compartments depicted in Fig. 3. Both the “partially immune” and the “not immune at all” compartments may contribute to the number of observed cases, $C_V$. For this reason, and because transmission of infection is influenced by contextual factors (e.g. how and how frequently people interact, biological transmissibility under the influence of climate), pooling results from vaccine trials across geographic areas may require more care than pooling results from therapeutic drug trials. This remains, however, a problem that the economic analyst can hardly deal with, other than by taking care while interpreting vaccine trial results, considering at the same time the transmission properties of the pathogen, the immunological characteristics of trial participants, the likely biological mechanisms of the vaccine and the context and design of the trial. There is substantial literature on mathematical approaches that aim to acknowledge these specific issues for quantitative estimates of efficacy from vaccine trials (82, 89–102). Additionally, trial designs have been proposed to estimate indirect effects from vaccination (103–105).

Source estimates of vaccine efficacy for economic evaluation should preferably be based upon systematic reviews of the available literature. These may be available for a number of vaccines at The Cochrane Library (https://www.cochranelibrary.com). When a systematic review is not available, analysts should strive to derive estimates on vaccine efficacy from trial data using formal meta-analytic techniques (106–109). Alternatively, analysts can use a range identified from trials of vaccine efficacy. When a vaccine has not yet been developed or data on vaccine efficacy are not in the public domain, analysts should clearly state their assumptions and/or sources (e.g. unpublished data from industry sponsored trials) regarding vaccine efficacy and subject them to sensitivity analyses (see below).

The separation of vaccine efficacy into “take” and “degree” can be influential in economic evaluation. They can be estimated by using statistical models to fit to vaccine trial observations and to explore which estimates of take and degree best explain the observed cases and non-cases in the vaccinated and unvaccinated trial groups (usually this requires assuming that the force of infection is identical in both these groups). See also section 5.2.3 on duration of protection.

Note also that some vaccines act only against one or a selection of “variations” of a pathogen (i.e. serotypes, serogroups, genotypes). For example, seven-valent pneumococcal conjugate vaccine reduces nasopharyngeal carriage of seven out of more than 90 known pneumococcal serotypes. The geographic distribution of circulating “variations” and associated clinical disease is not uniform. That is, people are infected by different “variations” of the same pathogen in different parts of the world, and the associated clinical disease and health care utilization is then not only a function of contextual characteristics, such as health care system organization, but also of biological properties. For example, HPV types 16 and 18 are oncogenic whereas many other known HPV types are not. At the same time some HPV vaccine types may exert cross reactivity to non-vaccine types (110). The analyst could make proportionate adjustments based on epidemiological data, i.e. using the prevalence of circulating “variations” in both the trial setting, and the country of analysis. Clearly, extrapolating a trial result in a particular geographic setting to other settings must be done with care, and the possible implications of the extrapolation should be carefully delineated. This type of extrapolation leads to estimating real-world impact, i.e. effectiveness rather than efficacy.
5.2 Vaccine effectiveness

“Effectiveness” is defined as the intended impact on measurable end-points (minimum level of biological markers, clinical disease stages) observed in a real world setting (as opposed to the trial settings in which efficacy is measured). Thus, effectiveness is dependent on the extent to which widespread vaccination affects the occurrence of infections and disease episodes both in vaccinated (including unprotected, partially and fully protected vaccinated persons) and unvaccinated persons. The latter group’s exposure is affected by the reduced circulation of the pathogen when vaccinated and unvaccinated persons mix in the same population. Thus in addition to direct effects through the protection of successfully vaccinated persons, indirect effects in unvaccinated or unsuccessfully vaccinated persons contribute to the total effectiveness, or impact, of vaccination in a population.

Real world post-licensure observational studies have been important to inform vaccine effectiveness estimates for economic evaluations of vaccines. This entails (a) comparing the same population before and after a vaccination program was implemented (see for instance (111)), or (b) comparing different (sub)populations, some in which a vaccination program was implemented and some in which it was not (see for instance (112)). In both these instances, given the implementation of a vaccination program, some individuals were vaccinated and some were not. In all these cases the comparisons made to derive an estimate of vaccine effectiveness inevitably is done on the basis of a number of common assumptions. First, it is assumed that vaccination status and the disease, infection or medical care endpoints of interest are measured in a consistent manner for all individuals in the various groups or time periods under comparison (113). Second, if these post-licensure study designs are used to come up with a direct estimate of vaccine efficacy (and not effectiveness) in individual vaccine recipients to use as a model input, it is important, given the study’s context, to consider how realistic it is to additionally assume that vaccinated and unvaccinated persons experience identical levels of susceptibility and exposure. Stratification in age and risk groups is important to limit the impact of these assumptions. In any case, such studies can be informative to understand the potential impact of herd immunity, by comparing the efficacy observed in previous trials with effectiveness in the real world.

Given a number of conditions, many aspects of the indirect effects in unvaccinated, or unprotected and partially protected vaccinated persons, such as herd immunity, serotype replacement or antimicrobial resistance, could be ignored for the purposes of economic evaluation, although this is not best practice. We will return to this issue in the next chapter (Chapter 6), and provide guidance there on the consequences of ignoring indirect effects and of applying different types of infectious disease models when conducting economic evaluations.

5.2.1 Vaccine delivery and uptake (coverage)

Vaccine effectiveness also depends upon a number of service delivery factors, such as the potential loss of vaccine potency due to heat or freeze exposure, use of vaccine beyond expiry date, and other administrative errors, such as improper dosing. To maintain the potency and safety of vaccines, immunization programmes have established a cold-chain that extends from vaccine production facilities to remote health centres and beyond. This requires qualified health workers trained in planning, operating,
and maintaining a chain of refrigerated storage and transport equipment that prevents excessive heat exposure to vaccines and protects freeze-sensitive vaccines from sub-zero temperatures. Unfortunately, much of the cold-chain in developing countries is old and in disrepair, or must be replaced due to new environmental regulations. Difficulties in maintaining the cold-chain between the 2 °C and 8 °C desired for most vaccines can result in delivery of sub-potent vaccine due to undetected heat or freeze damage. It is therefore essential to estimate vaccine doses lost to delivery, and include them on the cost side of the analysis. Since vaccine uptake, including compliance with vaccine schedules, has a great impact on vaccine effectiveness, this needs also to be accounted for.

There are two main sources of data used to assess coverage of vaccination programmes worldwide: health service delivery records and household-based surveys. Countries are requested to report their vaccination coverage estimates every year to WHO and UNICEF using the WHO/UNICEF joint reporting form on vaccine-preventable diseases; data from these forms are officially reported data. Methods and strategies for collection and reporting of these data are specific to each country. The source of data for official reports can include service registries, surveys, or a combination of both. The target population in which vaccination coverage is assessed can also vary between countries, taking into account either yearly number of births, number of infants that survive their first year of life, or the number of children within a specific age range. Furthermore, a country might change its methods for obtaining estimates from year to year. The absence of standardization in data sources and methods of collection decreases the comparability of officially reported data between countries and over time. Officially reported data tend to be the primary source of information for assessment of vaccination coverage, and thus it is essential to analyse their validity.

To overcome some of these biases, WHO and UNICEF annually review the officially reported data from countries, together with any available data from the published and grey literature and bringing in local expert knowledge of other factors that may have influenced immunization coverage. They estimate annually, based on the data available, consideration of potential biases, and contributions from local experts, the most likely true level of immunization coverage.\(^\text{14}\)

The “effective coverage” of vaccines is the product of vaccination coverage (based on relevant sources depending on the type of programme) adjusted for non-compliance by vaccine efficacy adjusted for loss of potency due to heat and freeze exposure, where such data are available.

5.2.2 Adverse events following immunization (AEFI)

Adverse events following immunization (AEFI) may give rise to health care costs, i.e. medical care, non-health care costs, as well as an adverse quality of life impact. If these adverse events are caused by vaccination, and likely to have a substantial impact on the results of the analysis, they should be included on both the costs and effects side of the analysis. The significance of the impact depends both on their likelihood of occurring as a consequence of vaccination and their severity.

\(^\text{14}\) https://www.who.int/immunization/monitoring_surveillance
At the time of licensure not all (rare) side effects may have been documented.

When many people are vaccinated as part of the implementation of a country-wide vaccination program, some serious events that occur too rarely to be observed in clinical trials, may be observed in the real world setting. It is often very challenging to establish whether vaccination is the cause of an adverse event, or is merely associated with it. That is, the rare event in question may occur with the same likelihood in unvaccinated people, but in that case it is not reported as a serious event not following vaccination, and may remain off the records. Careful analysis of risks in both vaccinated and unvaccinated people to establish causation is therefore pivotal.

The reputation of a vaccine and vaccination in general can be negatively affected by AEFI to such an extent that vaccination uptake drops. Some vaccines have been withdrawn from use at least partially for AEFI. For instance, the rotavirus vaccine Rotashield was found, after licensure in the United States, to be associated with intussusceptions and was consequently taken off the market by the manufacturer (114).

The use of whole cell pertussis vaccination is known to be associated with side effects, which has under some circumstances been justified to switch to acellular pertussis vaccines (115). Furthermore the choice of switching from OPV to IPV is partly based on concerns over the occurrence of side effects from the vaccine, especially as – due to the success of the vaccination programme – the natural disease itself was often no longer present (116).

Cochrane reviews of vaccines contain data on the risk of adverse events, and in addition to the latest scientific literature provide an important base for documenting adverse events for inclusion in economic analyses. Since vaccines that cause frequently adverse events are highly unlikely to be licensed or marketed, the inclusion or exclusion of AEFI tends to have a minor impact on the outcomes of economic evaluation, simply because their risk of occurring, as it is known at the time of the analysis, tends to be very low compared to the risks of morbidity and mortality vaccines reduce. Nonetheless, analysts should document potential AEFI, preferably through available systematic reviews. When AEFI are likely important relative to the disease burden vaccination aims to prevent, their costs (of treatment, surveillance and control) and consequences (impairments in terms of morbidity and mortality) should serve as inputs for the economic evaluation.

Note that many countries may not have the resources to set up pharmacovigilance systems, and the surveillance costs they represent may be high. As such, if setting up surveillance is a prerequisite for the introduction of a specific new vaccine, then those costs would need to be attributed at least partially – and depending on the specificity of the safety signals being monitored perhaps even completely – to the implementation costs of the vaccination program (see also Chapter 3).
5.2.3 Duration of protection

Data from trials typically allow estimating a measure of vaccine efficacy over a relatively short period of time (usually in the order of a few years), compared to the period of time over which vaccine protection is projected to affect a successfully vaccinated person (usually in the order of 5 years to 100 years). The duration of protection is, however, in many economic evaluations highly influential. It can be estimated either by (a) using statistical models to fit to vaccine trial observations and project the observed trend forwards (see for instance (117)); or (b) using vaccine trial data in mechanistic mathematical models to simulate between-host transmission (see for instance (118)) or within-host immunological response processes (see for instance (119)) that allow extraction of parameters for further projections of the efficacy over time in simulation models.

Since the estimation of the duration of efficacy, inferred from clinical trials, is influential for the projected effectiveness and cost-effectiveness of vaccination programs, the duration of protection over time should be as much as possible data driven, made completely transparent and subjected to thorough uncertainty analysis (see Chapter 8).

5.3 Choosing and valuing outcomes

The strengths and weaknesses of different outcome measures are described in Table 6. Many vaccine-preventable diseases affect infants and children. Yet, quality of life (QoL) estimates for short-term diseases in young children, particularly those under four years of age, are virtually non-existent and the appropriate methodology for doing this is subject to debate. In addition, the impact of a child’s illness on the QoL of caregivers can be substantial, just as it is for life threatening and severe chronic diseases such as cancer; such indirect QoL losses are typically not accounted for. Because additionally the DALY is the only summary measure for which consistent estimates are available across all parts of the world, this guide recommends using DALYs, if suitable QALY weights are not readily available. It is noted though, that in the literature QALYs are far more popular and seem increasingly used to conduct economic evaluations over a wider range of countries (120), and that increasing attention is given to developing consistent valuation of health states for children.

The use of either QALYs or DALYs in economic evaluation can inform allocative efficiency decisions within health care (see Chapter 3). Analysts should first present estimates of burden in natural units—cases, deaths, years of life lost (YLL) and years lived with disability (YLD) or impaired health-related quality of life, before these units are converted to DALYs or QALYs. The global burden of disease estimates using DALYs have been presented both with and without age weighting, and with and without discounting (see also Chapter 7) (121). When DALYs are used in cost-utility analysis, like QALYs they should not be subjected to social weighting, such as age weighting, unless explicitly desired by the policy maker the analysis is meant to advise. We refer to other sources for further comparisons between QALYs and DALYs (122), and details on how to estimate DALYs (123–125) and QALYs (12, 13, 21, 26).
## Table 6. The strengths and weaknesses of different outcome measures

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process outcomes, e.g. number of children (fully) vaccinated</td>
<td>• Ease of collection; these measures are part of routine monitoring&lt;br&gt;• Reflects technical efficiency of programme&lt;br&gt;• Can identify most efficient method of delivery</td>
<td>• Routine statistics may be unreliable, incomplete or biased&lt;br&gt;• No measure of impact on disease transmission</td>
</tr>
<tr>
<td>Intermediate outcomes, e.g. number of children immunized</td>
<td>• Relative ease of measurement and interpretation&lt;br&gt;• May give some indication of impact, even though final health status unknown&lt;br&gt;• Reflects technical efficiency of programme&lt;br&gt;• Can identify most efficient method of delivery</td>
<td>• Require studies to measure serological status&lt;br&gt;• No measure of impact on disease transmission, unless repetitively performed</td>
</tr>
<tr>
<td>Disease-specific outcomes, e.g. measles cases averted</td>
<td>• Comparisons across different prevention strategies are possible&lt;br&gt;• DALYs or QALYs can be derived with adequate information on mortality and life expectancy</td>
<td>• Unable to compare across health interventions&lt;br&gt;• May not include indirect consequences of intervention</td>
</tr>
<tr>
<td>Quality-adjusted life years (QALY) gained</td>
<td>• Cross-vaccine and cross-sector comparisons are possible&lt;br&gt;• Ability to assess impact of combined clinical management and prevention strategies&lt;br&gt;• Quantity and quality effects combined in one measure</td>
<td>• Health Related Quality of life (HRQoL) estimates for short-term diseases in young children, particularly those under five years of age, are virtually non-existent and the appropriate methodology for doing this is subject to debate</td>
</tr>
<tr>
<td>Disability adjusted life years (DALY) averted</td>
<td>• Cross-vaccine and cross-sector comparisons are possible.&lt;br&gt;• Ability to assess impact of combined clinical management and prevention strategies&lt;br&gt;• Morbidity (years of life lived with a disability – YLDs) and mortality (years of life lost – YLLs) effects combined in one measure</td>
<td>• Possible over-simplification&lt;br&gt;• Debate over their validity&lt;br&gt;• Not widely recognized outside the health sector</td>
</tr>
<tr>
<td>Socio-economic measures, e.g. bed-days, OPD visits</td>
<td>• Indicate to what extent resource savings will offset intervention costs&lt;br&gt;• Indicate those interventions which increase national income</td>
<td>• Difficult to measure and value gain in labour time&lt;br&gt;• Information on the saved costs of treatment and gains in production are usually not routinely available&lt;br&gt;• Indicators used do not reflect the primary aim of health interventions, namely health improvement</td>
</tr>
</tbody>
</table>
5.4 Recommendations

- Estimates of vaccine efficacy should be based upon systematic reviews of the literature where available, taking account of the biological characteristics of the pathogen in question and how its infectious nature may have influenced the efficacy estimates derived from trials.

- The effective coverage of vaccines should be calculated by multiplying vaccination coverage (based on relevant resources depending on the type of programme) adjusted for non-compliance, by vaccine efficacy adjusted for loss of potency due to heat and freeze exposure, where such data are available.

- The population effectiveness (or “impact”) of vaccines should be calculated using empirical information on both the direct and indirect effects of the vaccination program, where this is available, and requires integrating this information in a mathematical model (see also Chapter 6).

- If adverse events from immunization are likely to have a substantial impact on the results of the analysis, they should be included on both the costs and effects side of the analysis. The significance of the impact depends on both their likelihood of occurring as a consequence of vaccination and their severity.

- Since the estimation of the duration of efficacy, inferred from clinical trials, is influential for the effectiveness and cost-effectiveness of vaccination programs, the duration of protection over time should be as much as possible data-driven, made completely transparent and subjected to thorough uncertainty analysis, in line with recommendations in Chapter 8.

- Estimates of burden should be presented in natural units—cases, deaths, years of life lost (YLL). Also years lived with disability (YLD), or years lived with impaired health-related quality of life are informative, and necessary to estimate either DALYs or QALYs lost as recommended final outcome of burden of disease.

- **This guide recommends the use of QALYs.** If suitable QALY weights are not readily available, it is recommended to use DALYs for cost-utility analyses.

- When DALYs are used in cost-utility analysis, like QALYs they should not be subjected to social weighting, such as age weighting, unless explicitly desired by the policy maker the analysis is meant to advise.
Chapter 6: Modelling

This chapter will examine modelling concepts and approaches. It begins by describing the various parameters of particular importance when modelling a vaccine-preventable disease, before considering the impact of vaccines (see also Chapter 5). Next, the basic types of infectious disease models are described and a flow chart provided to help analysts determine the types of infection and target groups for which a dynamic model is required, or preferred and/or a static model is acceptable. Lastly, the chapter focuses on approaches to validating models.

6.1 Specific parameters for infectious disease epidemiology

This section is largely based on three references, and gives a brief and simplified overview of parameters that are specific to infectious disease transmission (79, 126, 127).

6.1.1 The reproduction number

The effective reproduction number Rt is defined as the number of secondary cases a single infectious individual causes on average in a population at time t, and can be formally written as follows:

\[ R_t = pcD \frac{X_t}{N} = pcDx_t \]

where:
- \( p \) – probability of transmission following exposure;
- \( c \) – average number of new contacts made by an individual host per unit of time;
- \( D \) – duration of infectiousness;
- \( N \) – Host population size;
- \( X_t \) – Number of susceptible hosts at time \( t \);
- \( x_t \) – Proportion of susceptible hosts at time \( t \).

The above expression represents the simplified case of a homogeneously mixing population, without immigration or emigration. The value of the reproduction number depends on both infectious disease characteristics (\( p \) and \( D \)), and population characteristics (\( c \) and \( x \)). Consider at time 0 a population that is completely susceptible. In this case \( x_0 = 1 \) and the basic reproduction number \( R_0 \) can be defined as the number of secondary cases an average infectious individual causes in a completely suscepti-
ble population. $R_0$ is therefore a measure of the intrinsic capacity for an infection to spread in a naive population:

$$R_0 = pcD$$

The effective reproduction number equals the basic reproduction number, adjusted for the proportion of the population that remains susceptible (assuming a negligible proportion of the population is infectious, in addition to one infectious person that is introduced in this population):

$$R_t = R_0 x_i$$

The value of $R$ indicates whether the number of new infections per generation time (i.e. the average duration of infectiousness in an infected person) is increasing ($R_t > 1$), decreasing ($R_t < 1$), or stable ($R_t = 1$). Even without vaccination, most epidemics eventually fade out, because during epidemics natural infection usually immunizes more people than the number of new susceptible people that are brought into the at-risk population through birth, immigration, and loss of immunity. After an epidemic fades out, the number of susceptible persons builds up again, usually when the birth rate is higher than the infection rate, until the epidemic threshold is reached – when $R_t$ once again equals one – and the next epidemic can start. If on average $R_t$ attains the value $R_t = 1$ for a prolonged period of time, it means that endemic transmission of the infectious agent is sustained. This is the case for most infections that have been around for a long time, in the absence of vaccination. The infection is then said to be at endemic equilibrium.

$R_0$ is an independent disease- and population specific number, which does not change within a particular population, as long as the population characteristics and the infectious agent itself do not change.

The basic reproduction number can be estimated directly or indirectly. A direct estimate requires knowledge of the number of contacts per unit of time (ranging from sexual partnership change to casual conversations). At the invasion phase $R_0$ can be derived indirectly from case notifications, if one assumes that the population is completely susceptible at the start of invasion, e.g. for SARS, see Wallinga and Teunis (128). For vaccine-preventable diseases it is more usual to estimate $R_0$ from cumulated age-specific notification or serological data at endemic equilibrium prior to vaccination. Assuming a stable population in which incidence and mortality rates are both independent of age and the population’s age distribution is rectangular, the basic reproduction number can be approximated by:

$$R_0 = \frac{L}{A}$$

Where $L$ is the average life expectancy in the population, and $A$ is the average age at which the infection is contracted in the given population.
This is a simplified intuitive representation, departing from the assumptions given above. It would for instance be more accurate to take the period of protection from maternal antibodies ($M$) into account, particularly when $A$ is low (e.g. measles infection in developing countries):

$$R_0 = \frac{L - M}{A - M}$$

It is beyond the scope of this guide to give specific advice on how to estimate $R_0$. Clearly this will need to be done differently if the above outlined assumptions do not hold (129, 130). Therefore, in models in which the estimate of $R_0$ forms a direct input, as with other parameters, the basis for the estimation of $R_0$ should be clearly described, by outlining important assumptions (e.g. assumptions regarding mixing, survival and heterogeneity) and specifying the defining equations.

### 6.1.2 Incidence and the force of infection

The force of infection ($\lambda$) is defined as the probability per unit of time that a susceptible person becomes infected (131). In other words, it is the per-susceptible rate of infection. The net transmission rate or incidence of new cases ($I$) is given by the force of infection acting on susceptible persons:

$$I = \lambda X = pc \frac{Y}{N} X$$

where $X$ is the number of susceptible people, $Y$ the number of infectious people, $N$ the total number of people in the population, $p$ the probability of transmission given contact, and $c$ the number of contacts between susceptible and infectious people.

The force of infection can be derived from the ratio of changes in the proportion of susceptibles to corresponding changes in age. These derivations have often been based on the assumptions that $\lambda$ is piecewise constant in ad-hoc determined age intervals or independent of age, that the population size is constant, that everybody is susceptible at birth, that infection induces life-long immunity, and that infection does not influence mortality of infected individuals (132). The last decade has seen an increase in the application of modern statistical methods that relax these assumptions, especially with regards to age-specificity. Current status biomedical data, such as seroprevalence data, are generally the most accurate way of determining age-specific susceptibility in a population, provided the above assumptions hold. However, for some diseases it would make sense to use case notification data – for instance if the current interpretation of serological data is ambiguous (e.g. Respiratory Syncytial Virus (RSV)), or if the transmission of infection is likely to have changed over time. For instance, the improvements in hygiene have altered the transmission of hepatitis A virus (HAV) in many populations over time. However, notification data alone can be insufficient in that the true number of infections is typically underreported, even if the disease is easily and reliably diagnosed. Estimating the degree of underreporting is often impossible. Moreover, diagnosis can sometimes be difficult, and may become less reliable the rarer the disease. This also implies that the reliability of diagnoses may change.
over time. For instance, an apparently easily identified infection like measles is today less reliably diagnosed in most European countries than 40 years ago when measles was still a common childhood infection (133, 134), especially at the start of outbreaks. Furthermore for diseases with subclinical infection at the time infection occurs, this approach links only part (or none) of the infections to the correct time and age at infection, e.g. HBV, hepatitis c (HCV), Human Papillomavirus (HPV) and HIV. Additionally, reporting systems are likely to differ geographically or – as a result of changing case definitions – over time, compounding the difficulty of making comparisons over time and between places (regions or countries).

There are various methods for performing this derivation in practice using serological or case notification data. Several parametric and nonparametric approaches have been proposed (135). Text books are available, with some providing code to implement these methods (136–138).

In calculating the force of infection $\lambda$ on the basis of cross-sectional seroprevalence studies, two important assumptions are made:

1) the overall transmission of the infection has not changed over time (neither in relation to population behavioural characteristics, nor in relation to the properties of the infection itself);

2) there is no significant disease-specific or background mortality.

The first assumption can be problematic for infections that have undergone changes in transmission, e.g. HAV, for which the incidence generally declined over time and was shifted to older age groups as a result of improvements in hygiene. The second assumption is particularly hard to maintain when the disease is very lethal in the short run, or when background mortality interferes significantly. Using age-specific seroprevalence data can then be problematic because people who die are removed from the numerator as well as from the denominator for the calculation of susceptibility. If one (or both) of these assumptions is violated, the estimated force of infection can turn out to be negative, which is in contradiction with the above definitions.

### 6.2 Impact of vaccination

The impact of mass vaccination on the epidemiology of an infection can generally be expressed in three ways: (1) the incidence of infection decreases; (2) the average age at infection increases; (3) the length of the inter-epidemic period increases. The extent to which this occurs is closely related to the four facets along which the vaccine in question operates (see Chapter 5). In this section we will briefly describe the theoretical underpinnings of these characteristics.

Vaccines which reduce infectivity and/or susceptibility to infection protect not only vaccinated individuals, but also to some extent those that remain susceptible. This last group is indirectly protected because as the proportion of infectious people (or the duration of the infectious period) decreases, so will over time the force of infection. Indeed, if they are vaccinated, susceptible people will experience a shorter infectious period when they are exposed, or bypass it completely. Therefore as relatively more people are vaccinated, the proportion of infectious people will decrease, and
hence so will the probability that a susceptible person comes into contact with an infectious person. Immunization may also reduce the proportion of susceptibles in the population if vaccination immunizes more susceptibles than, on balance, new susceptibles enter the population (mainly by birth). Subsequently, the incidence also declines because it is directly related to the proportion of susceptibles in the population (see above). This indirect protection of susceptible people in a largely vaccinated population is commonly known as herd immunity, or community immunity.

Vaccination reduces the proportion of susceptibles \( (x) \), while \( R_0 \) remains constant. Therefore, on average \( R_t \) will be reduced as well. If \( R_t \) can be kept lower than 1 by preventing new susceptibles from entering the host population (for instance by vaccinating upon entrance), the generation of secondary cases remains insufficient to maintain the infection in the community and eventually the infection will be eliminated. If the infection is controlled but not eliminated by vaccination, in the long run the infection will settle around a new equilibrium state. At the peak of an epidemic \( R_t = 1 \), so that the threshold density of susceptibles, \( x^* \) can be written as:

\[
x^* = \frac{1}{R_0}
\]

Where \( x^* \) represents the critical proportion of susceptibles to maintain transmission. If the proportion of susceptibles can be kept lower than \( x^* \), the infection cannot maintain itself and will eventually be eliminated.

A formal description of herd immunity can be obtained by the expression of \( x^* \) given above. As long as \( x > x^* \) each primary case will infect on average more than one susceptible person. For \( x = x^* \) one primary infection will result in exactly one infection in a susceptible person. Therefore the herd immunity threshold \( (H) \) is attained when the proportion of immunes is so high that the number of susceptibles is below the epidemiologic threshold, implying that the incidence will decrease. So if vaccination reduces the proportion of susceptibles to less than \( x^* \), susceptibles will be insufficiently present in the population to sustain transmission.

\[
H = 1 - x^* = 1 - \frac{1}{R_0}
\]

Now we can define the critical effective immunization level (or critical proportion to be immunized) \( p_c \) as the minimum effective immunization level required to eliminate the infection from the population.

\[
p_c \geq 1 - \frac{1}{R_0}
\]

The greater \( R_0 \), the greater the level of effective immunization required to move from a situation where transmission persists to a situation where the infection is eliminated. Table 7 shows the epidemiological parameters for a number of childhood infec-
tions using the simplified relationships in the above equations. Note that these properties can differ substantially for the same disease between different populations. It should also be noted that $p_c$ is the level of effective immunization, which means that the actual vaccination coverage should be greater than the effective level of immunization, because the protective efficacy of a vaccine is usually imperfect (take and/or degree are less than 100%) and it is not always injected at birth or immediately after maternal immunity has waned (as implicitly assumed).

### Table 7. Illustration of the relationship between important epidemiological parameters (for certain childhood infections)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Average age at infection ($A$)</th>
<th>Basic reproduction number ($R_0$)</th>
<th>Critical proportion ($p_c$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>5.0–8.0*</td>
<td>9.3–15.6</td>
<td>89–94%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>4.5–6.5**</td>
<td>10–17.5</td>
<td>90–94%</td>
</tr>
<tr>
<td>Mumps</td>
<td>5.7–9.9</td>
<td>7.4–14.4</td>
<td>86–93%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>10.4</td>
<td>6.1</td>
<td>84%</td>
</tr>
<tr>
<td>Polio</td>
<td>10–14</td>
<td>5–7</td>
<td>80–86%</td>
</tr>
<tr>
<td>Rubella</td>
<td>10.2–10.8</td>
<td>7.2–7.3</td>
<td>86%</td>
</tr>
</tbody>
</table>

* In small and large families in the USA (1957), the average age at infection was 8 and 5.5 years, respectively. In England and Wales (1948–1968) the overall average age at infection was 5 years.

** In rural areas in the USA (1908–1917), the average age at infection was substantially higher than in urban areas (6.5 years versus 4.9 years), or than the overall average age in England and Wales in 1944–1978 (4.5 years).

Sources: (79, 126).

The sooner susceptible people are immunized, the greater the ensuing reduction of susceptibles in the population. Assuming again a rectangular age distribution, the required level of effective vaccination is given by Anderson and May (139):

$$p_c = \frac{1 + V}{1 + A}$$

where $V$ is the average age at vaccination. For $V < A$, the closer the average age at vaccination to the average age at infection, the higher the proportion required to be immunized. For $V > A$, the infection cannot be eliminated, implying that the most effective vaccination programmes are those that target age groups that are below the average age at infection.

Apart from being subject to seasonal fluctuations, the number of acute childhood infections in a population oscillates around an average with a constant period between the peaks when the infection is at quasi-equilibrium. The oscillations occur because the pool of susceptibles decreases (by infection) and increases (mainly by birth) at regular intervals. The intervals are determined by the time lag between the exhaustion of old susceptibles and the supply of new susceptibles. On the basis of the mass action principle, the inter-epidemic period $T$ can be described in relation to the genera-
tion time ($K$, the sum of the latent and infectious period) and the average age at infection ($A$), as follows:

$$T = 2\pi \sqrt{AK}$$

This equation is considered a useful description of the inter-epidemic period for acute childhood infections that confer life long immunity against reinfection. It can be interpreted as follows. The longer the generation time, the longer it takes to generate $R_t$ new cases and the slower the epidemic rises. The greater the average age at infection, the lower the birth rate (for a particular $R_0$) the slower the pool of susceptibles will be replenished. Vaccination will decrease $\lambda$, which implies that the generation time increases, which in combination with a higher age at infection lengthens the inter-epidemic period.

Note that when vaccines reduce infection of only a part – and not all – of the circulating variations in a species of a pathogen (e.g. serotypes, genotypes), then the impact on incidence, age at infection and interepidemic period is modulated by the extent to which the vaccine covers the range of variations in a pathogen (e.g. pneumococcal, meningococcal and human papillomavirus vaccines). The impact on disease burden is then further complicated by the different levels of severity of illness and lethality that different variations in a species of a pathogen may exert on their host upon infection.

Though the elegant relationships between the basic reproduction number, the average age at infection and the critical vaccination level offer highly interesting general guidance, they are not sufficiently accurate to be used casually for quantifications. As set out above, the assumptions regarding the independence of age and homogeneity of population generally do not hold in practice for most infections. Indeed, the derivation based on the mass action principle assumes that susceptible and infectious persons mix at random, i.e. homogeneously, across all relevant mixing groups (including age groups) and seasons. In reality, these various mixing groups each show different within- and between-group contact patterns, and include different numbers of susceptibles. A vaccination programme that fails to reduce the number of susceptibles in key subgroups or in relatively large general clusters (leaving some important pockets of susceptibles unprotected) could not eliminate the infection despite a generally high proportion of immune people.

In order to account for age-dependency, complex age-structured models have been developed (see below). Similar models structured for various subgroups other than age have also been developed for specific diseases. By introducing age-dependent or group-dependent elements, the relationships between the various epidemiological parameters predicted by such models have lost the simplicity of the general formulations given in this section. Indeed, the crude estimates of $R_0$ (and $p_c$) have been shown to be overestimations if transmission is greatest among young people and declines with age, and underestimations if transmission increases with age (140). For instance, the critical proportion of measles immunization estimated by age-dependent models seems to be lower than with the simplified model described above. Furthermore, models analysing seasonality indicate that transmission can be most easily interrupted during low incidence seasons (when the herd immunity threshold is lower) (141).
Measuring the impact of a vaccination programme is therefore unique for each population and infectious disease. This is also demonstrated by the general formulations given here. The introduction of time, age, seasonal and spatial variations seriously add to the complexity of such formulations (and the amount of required data to make them). We discuss in the sections below at what level of complexity which types of epidemiological models are sufficiently accurate to be used for the economic evaluation of various vaccination strategies.

6.3 Modelling infectious diseases

Economic evaluations of vaccination programmes tend by necessity to be based on modelling. General observations and guidelines formulated for model-based economic evaluation apply for both vaccine- and non-vaccine-related health care interventions (142–144). There are however some specific issues related to mathematical models for infectious diseases as an integral part of model-based economic evaluation (145–153). The main specific issues will be further highlighted in this section.

At the population level, mathematical models for infectious diseases are mainly developed with the aim of estimating:

1) the disease burden of an infectious disease;
2) the impact of vaccination on the disease burden of an infectious disease.

There exists a large body of literature on estimating prevalence, incidence, attributable mortality and the burden of disease in general (154). For infectious diseases, the difficulty lies in attributing observed clinical disease to a particular infection, e.g. distinguishing the etiologies of severe meningitis, whilst distinguishing primary from secondary causes of illness and mortality. This is particularly difficult for common diseases with many potential causes, e.g. pneumonia and otitis media, or if there are long time lags between infection and the associated clinical disease, e.g. cirrhosis and cancer caused by HBV and HCV, subacute sclerosing panencephalitis caused by measles. Appropriate interpretation of registration and surveillance systems would be required to assess the quality of the existing evidence base on disease burden. In addition, epidemiological and demographic data and markers for infectious disease, e.g. based on representative cross-sectional and/or longitudinal samples of, for example, blood, urine or saliva, might be needed to quantify the local and national disease burden. It may thus be necessary to model the natural course of illness in order to infer the attributable clinical burden from infection data. Relying predominantly on expert opinion to estimate the disease burden has clear limitations one should be aware of.

Disease burden estimates form an integral part of model-based economic evaluation (such as cost-effectiveness analysis). The aim of economic evaluation is to assess the impact of various options for vaccination on the disease burden of an infectious disease, in terms of both economic costs and epidemiological effects.

6.3.1 Basic types of infectious disease models

In most infectious disease models, the population is made to flow between mutually exclusive compartments of susceptible (S), infectious (I) and recovered (R) (sometimes
referred to as removed (immune) people). This basic structure (S-I-R) can be adapted, for instance, to include a latent phase with an Exposed (E) compartment (S-E-I-R), or an explicit phase of Maternal antibody protection (M) to make (M-S-E-I-R). When infection does not induce lifelong immunity, it would be important to revert to an S-I-S structure. For instance, an analysis of measles vaccination would minimally require a S-I-R structure (as after measles infection, one is immune for life), whereas pneumococcal conjugate vaccination would require an S-I-S structure (as one can be reinfected after infection with pneumococcus, and can therefore be considered to be susceptible again). These compartments are the minimal set that govern the infectious disease processes, but for decision analysis, additional compartments are often useful, e.g. distinguishing compartments of people who died from the disease in question, or died from other causes.

An important distinction must be made between ‘static’ and ‘dynamic’ models. In a dynamic transmission model, the force of infection (the probability that a susceptible person acquires infection per unit of time) can change over time. As more people are vaccinated, and the vaccine prevents transmission of the pathogen from infectious persons to susceptible persons (and/or reduces the infectious period of vaccinated people who still get infected), the proportion of infectious people in the population will decrease. Consequently, the force of infection acting on those remaining susceptible declines as well. A dynamic model takes this into account by cyclically or continuously recalculating the force of infection from the proportion of infectious people it projects at each point in time. In a static model the force of infection remains constant; i.e. although it can be defined as being age-dependent, in a static model the force of infection is assumed to be independent of the proportion of infectious people in the (age-specific) population at various time points. In dynamic models the transitions between health states are typically estimated by solving sets of differential equations with continuous age and/or time (i.e. at every moment) variables. Alternatively, for practical reasons, discrete age and/or time variables (i.e. when events are assumed to occur over discrete time and/or age intervals, e.g. one year, instead of on a continuous basis) are often applied, especially to model the ageing process in dynamic models. In static models, time and age is typically equalized (by modelling a single ageing cohort), and is defined over discrete intervals, e.g. the observed incidence over one year is used to estimate the number of cases as the cohort ages by one year, in one discrete step (or “cycle” in a Markov model).

One of the most popular types of model in health economics in general is the static decision tree model, in which the target group is apportioned instantaneously (in a single time step) to different relevant states, such as mild case, moderate case, hospitalised case, or death. When many decision trees need to be run through in sequence, for instance when the probability of acquiring a disease stage upon infection is age-specific, a cohort model becomes a more efficient modelling tool. Another popular health economics model simulates events on an aggregate basis in a single closed static cohort, ageing over time – typically from birth until death – but without interacting with other cohorts. It is also possible to model the entire population in a static or a dynamic framework. Such models are often termed to be “open” because they have an inflow of newborns into the population. In dynamic systems this inflow is often assumed to equal the outflow of deaths.
Static and dynamic models can be either deterministic or stochastic. In the context of infectious diseases, we define a model here as deterministic if there is no randomness in the calculations of the acquisition of infection, implying the transition rates between compartments are pre-defined (and averaged out based on aggregate population data, see below). In the real world, individuals come in whole entities (and cannot be averaged out to fractions) and the acquisition of an infection can be regarded as a process that is subject to chance. However, one can assume that this process can be adequately mimicked with average rates (i.e. in a deterministic model) if the population at risk is large and the infection is not close to elimination or global eradication, e.g. polio, measles. For small populations, e.g. small islands, or in order to simulate the rise of an emerging infection, or the demise of a rare infection that is close to elimination, stochastic models are more suitable because they take account of the importance of random transmission events in these particular situations.

Stochastic processes can also be built into models to govern chance events other than infectious disease transmission itself. A well-known example is that of second order (or parameter) uncertainty, which is most commonly explored by Monte Carlo simulation as a form of probabilistic sensitivity analysis (see Chapter 8 below). Strictly speaking, a static model can then be termed stochastic. However, in this section we focus on specific issues relating to modelling infectious diseases, as opposed to non-infectious diseases. This means we focus here on how the disease transmission process is modelled.

Transmission parameters in models should take on values according to characteristics that determine the force of infection. For instance, for airborne infections these characteristics can often be limited to age, whereas for STIs they may need to include age, gender and sexual activity class, because typically within each age category a small group of people has many sexual contacts and high rates of partner change of one or both sexes. Such core transmitter groups make greater than average contributions to the overall spread of infection. Thus, models can be developed by structuring the population in groups (as is usually the case today), and treating transitions on an aggregate basis, or alternatively as a system of inter-acting individuals. In the latter case, in an individual-based model (sometimes referred to as agent-based or microsimulation model) the individuals that make up a population (of human or non-human hosts) are each defined in relation to a number of relevant characteristics – e.g. age, gender, susceptibility, location, household membership, travel habits – that govern the events that lead to transmission of infections on an individual basis. Such models offer greater flexibility as well as an intuitively appealing basis for dynamic stochastic transmission processes. However, they require more computing power and time and the outcomes are more difficult to validate and interpret. They are increasingly applied integrated with economic evaluation. Most of these applications for vaccines were on HPV, influenza, malaria and pertussis. More detailed information can be found in a systematic review of IBMs for infectious diseases (155).

A further distinction that can be made is whether (compartmental or individual-based) models incorporate dynamic feedback mechanisms related to behavioural change triggered by, for instance, (perceived) risks of disease, risks of adverse events, and information campaigns. In these models in addition to the force of infection, parameters related to social contact behaviour, such as mixing patterns, are adjusted under the influence of changing perceptions on disease burden and on vaccine adverse events or
sickness itself (i.e. persons who develop symptoms have different social contact patterns than healthy persons), when the epidemiology changes over time through interventions. Although the majority of such models currently lack a strong empirical basis, this is a developing area in infectious disease modelling (156, 157). This type of application is of particular interest when vaccination itself or other interventions with which it is integrated, impact on behaviour (e.g. school closure for pandemic influenza).

For economic evaluation, this guide advocates choosing the model that minimally meets the analytical requirements given the pathogen, the endemic situation and the intervention. In view of the many specific advantages and disadvantages of various modelling attributes for specific infections and interventions, we cannot provide a generic “one size fits all” guide that can discern static versus dynamic, deterministic versus stochastic, open versus closed, aggregate versus individual, discrete versus continuous time modelling. Instead we provide guidance mainly on the generally most influential choices of model attributes for the estimated cost-effectiveness ratio of vaccination: choosing between static and dynamic models, and then what the main options are when choosing either one of them. However, as transparency is key in model-based economic analysis, analysts should report on all the above modelling attributes. Therefore, economists should be aware of different model attributes for specific infections and interventions, as there are circumstances where the use of an inappropriate model could lead to erroneous policy decisions. It is therefore essential that analysts make a careful and conscientious assessment of the model they use (in addition to validating it, see below), with the aim of not providing misleading information to policy makers. See also Koopman (158) for an explanation of inference robustness analysis as a way of dealing with this problem.

6.3.2 Choosing between different types of model

6.3.2.1 Static versus dynamic

The pivotal choice in infectious disease modelling that aims to estimate the cost-effectiveness of vaccination is the choice between a static or a dynamic model. Although other choices can be made about how the model is set up, such as deterministic or stochastic, grouped or individual based, open or closed, or how the simulation is performed, these are usually secondary to the static/dynamic choice in the framework of economic analysis of a vaccination programme. These “secondary” choices will also be more important for some situations than for others (as outlined briefly in the previous section). Fig. 4, Fig. 5 and Table 8 indicate the types of infection and interventions for which a dynamic model is preferred and/or a static model is still acceptable. Dotted lines show conceptually less preferred routes versus the alternative solid line at a given choice.

These flow charts provide guidance for good modelling practice. These are also intended to make analysts, who might not be fully accustomed to the specificities of vaccination programmes, more aware of the limitations of standard modelling practices in health economics when they are applied to infectious diseases.

These flow charts are designed to be applicable to a broad range of vaccination programmes aiming to prevent, control, eliminate or mitigate infectious diseases in humans. Their generic nature is both appealing and limiting. It is appealing because it provides an easy to comprehend guidance to make analysts reflect on their model
choices, irrespective of the application they model. However, it may also be limiting in that different aims of model-based economic evaluations may influence which model is chosen for which pathogen and intervention. Additionally, some of the ultimate choices one makes based on these flow charts depend somewhat on self-critical value judgements of what is “epidemiologically influential”, or what are “equivalent results”.

**Fig. 4. Flow chart to help determine when dynamic or static models are appropriate when one of the interventions being compared is vaccination against disease in humans**

In view of this, we provide also some explicit guidance with examples for each of the final model choices one may make. In any case, if the health economic evaluation is meant to directly inform policy, then the modelling choices an analyst makes, should be justifiable based on these flow charts. For instance, if they judge the particular application they model does not involve target groups that are epidemiologically influential, they would need to be able to argue explicitly why that is.
Fig. 5. Flow chart to help understand the limitations of potentially justifiable static models when epidemiologically influential subgroups are directly affected (dashed lines indicate less preferred progressions through the flow chart)

- Previous dynamic models have shown that indirect transmission-dependent effects\(^*\) had negligible impact, or – preferably – formal model comparisons\(^**\) have shown that static and dynamic models lead to equivalent cost-effectiveness results for the interventions being compared in a comparable epidemiological situation.
- Although less preferred, a static model is considered (5a).
- Dynamic model strongly preferred (8).
- Dynamic model required (9).
- It can be expected that negative externalities from vaccination, potentially exceed positive externalities.
- Previous dynamic models have shown that indirect transmission-dependent effects\(^*\) had an important impact on results, or – preferably – formal model comparisons\(^**\) have shown that static and dynamic models lead to inequivalent cost-effectiveness results for the interventions being compared in a comparable epidemiological situation.
- Dynamic model strongly preferred (5a).
- Although less preferred, a static model is chosen (5b).
- Static model acceptable (4).
- Static model shows clearly favourable\(^**\) results for vaccination.
- Observations on externalities from a comparable setting are integrated in the model.
- Static model acceptable to assess whether a vaccination strategy has favourable cost-effectiveness, keeping in mind its benefits are underrepresented. The extent to which this underestimate can differ between different strategies being compared needs to be ascertained (7).
- Results become unfavourable or borderline favourable\(^**\) for vaccination. Of limited use for policy (11).
- Results are clearly favourable for vaccination. Static model could be useful for policy. The extent to which this impact can differ between the strategies, and the externalities are transferable between the comparable settings, need to be discussed (6).
- These results as such are not useful for policy (10).
- Static model shows unfavourable or borderline favourable\(^**\) result for vaccination.
- There are no negative externalities from vaccination, or these are highly likely to be smaller than positive externalities.
- Although less preferred, a static model is chosen (5b).
- Dynamic model strongly preferred (5a).
- Static model acceptable (4).
- Static model shows unfavourable or borderline favourable\(^**\) result for vaccination.
- There are no negative externalities from vaccination, or these are highly likely to be smaller than positive externalities.
- Static model acceptable to assess whether a vaccination strategy has favourable cost-effectiveness, keeping in mind its benefits are underrepresented. The extent to which this underestimate can differ between different strategies being compared needs to be ascertained (7).
- Results become unfavourable or borderline favourable for vaccination. Of limited use for policy (11).
- Results are clearly favourable for vaccination. Static model could be useful for policy. The extent to which this impact can differ between the strategies, and the externalities are transferable between the comparable settings, need to be discussed (6).

\(^*\) Indirect effects such as herd immunity, natural boosting events, and serotype/serogroup dependent phenomena (e.g. antibody-dependent enhancement for dengue, serotype replacement for pneumococcal infections).

\(^**\) Formal model comparisons: model comparisons adhering to guidelines for model comparisons.

\(^***\) By favourable it is meant here that the results (e.g. expressed as incremental cost-utility ratios), compare favourably with some locally defined cut-off expressing willingness to pay for a QALY gained or a DALY averted. If the results are not or only borderline favourable (i.e. by accounting for uncertainty), it means that the static model in these boxes leads to inconclusive results. This by no means implies that we encourage the analyst to look for a model that will produce favourable results, it means simply, that at this stage, the outcome of the static model is not sufficient to enable a policy maker to make an informed decision.
Table 8. The acceptability of static versus dynamic models depending on pathogen (and epidemic situation), target group and vaccine effectiveness

<table>
<thead>
<tr>
<th>Flow chart model choice number</th>
<th>Confidence in decision if based on a static model strong/relatively weak/weak/unacceptable</th>
<th>Examples of vaccination programmes in this part of the flow chart (non-exhaustive)</th>
<th>References to studies with corresponding “good” model choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strong: non-infectious disease</td>
<td>Therapeutic vaccines against cancer (under development)</td>
<td>(159)</td>
</tr>
<tr>
<td>2</td>
<td>Strong: absence of evidence of herd immunity and other indirect effects (e.g. environmental pathogens like tetanus)</td>
<td>Rabies, tetanus, Q fever, Japanese encephalitis</td>
<td>(160, 161)</td>
</tr>
<tr>
<td>3</td>
<td>Strong: target group not influential for transmission</td>
<td>Hepatitis A vaccination of health care workers; influenza, pneumococcal and RSV vaccination of the elderly and pregnant women, varicella-zoster vaccination for adolescents and adults</td>
<td>(162–165)</td>
</tr>
<tr>
<td>4</td>
<td>Strong: previous modelling work has shown that the impact of using a dynamic model is small for the interventions under study, either when a single dynamic model applied for a comparable set of interventions in a comparable setting has shown limited impact of herd immunity, or when a formal model comparison, encompassing both static and dynamic models have shown limited difference in results from the two types of models. Especially strong if static model shows vaccination is cost-effective since a dynamic model will only reinforce this conclusion</td>
<td>HPV vaccination for 9–14 year old girls at high vaccine coverage</td>
<td>(166, 167)</td>
</tr>
<tr>
<td>5a</td>
<td>Weak: can only be justified if one expects the results to be favourable and eventual acceptability depends on characteristics further down the flow chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5b</td>
<td>Weak: depends on transferability of results between comparable settings (e.g. applying real world observations from US to Europe and Asia)</td>
<td>Pneumococcal*, pertussis and <em>Haemophilus influenzae</em> type b vaccination for children</td>
<td>(168)</td>
</tr>
<tr>
<td>6</td>
<td>Relatively weak: cost-effectiveness is attractive and known to be underestimated, dynamic model would remain strongly preferable to allow an incremental analysis of all potential options of vaccination</td>
<td>HPV vaccination of a single cohort of girls; influenza and meningococcal C vaccination for children and adolescents, hepatitis B vaccination for adults in low endemic areas</td>
<td>(169–171)</td>
</tr>
<tr>
<td>Flow chart model choice number</td>
<td>Confidence in decision if based on a static model</td>
<td>Examples of vaccination programmes in this part of the flow chart (non-exhaustive)</td>
<td>References to studies with corresponding “good” model choice</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>8</td>
<td>Unacceptable: negative indirect effects could outweigh positive indirect effects, dynamic model is required</td>
<td>Childhood varicella-zoster, measles, mumps, rubella vaccination</td>
<td>(172–174)</td>
</tr>
<tr>
<td>9</td>
<td>Weak: there is preference for using dynamic models, especially if both targeted and universal strategies are feasible options requiring comparison</td>
<td>HPV vaccination of multiple cohorts of girls (e.g. 12–18 years) versus a single cohort (e.g. 12 years) or other multiple cohorts (e.g. 12–17 years), HPV vaccination of boys and girls versus girls alone, childhood and elderly influenza vaccination versus elderly influenza vaccination alone, childhood hepatitis A vaccination versus hepatitis A vaccination of food handlers in low endemicity areas</td>
<td>(175, 176)</td>
</tr>
<tr>
<td>10, 11</td>
<td>Unacceptable: the use for policy is limited, due to the inconclusive results obtained with a static model</td>
<td></td>
<td></td>
</tr>
</tbody>
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Population group of children <2y currently targeted with pneumococcal conjugate vaccines, which protect against naso-pharyngeal carriage and hence induce herd immunity.

If targeted vaccination is cost-effective versus no vaccination, and universal vaccination is also cost-effective versus no vaccination, then an important and relevant question for policy is whether universal versus targeted vaccination would be cost-effective. If the impact of herd immunity has not been observed in empirical studies for at least targeted vaccination, then a static model would not be helpful to advise on this question.

The references given here are to indicate that these papers made a choice about their model that corresponds – given the time at which these choices were made – to the given choice number. This does not necessarily imply that this guide endorses these studies in their entirety.

The general philosophy behind the preferred and acceptable options depicted in Fig. 4 and Fig. 5 is “to make everything as simple as possible, but not simpler”, while minimizing the risk of doing harm. Hence the use of static models could be justified in contexts where this is feasible given the dominant transmission routes of the pathogen. Note that this may vary by level of endemicity, the current impact of ongoing immunization efforts, the expected properties of the vaccine and the target group for vaccination.

Static models can be sufficient for the evaluation of the impact of vaccination (or potentially of other interventions to which vaccination options are compared) if herd immunity does not play an important role – i.e. when the additional effectiveness per additionally vaccinated person is constant. An obvious example is for vaccination against non-infectious diseases (at least based on current biomedical knowledge), see (1) in Fig. 4. Another example is an intervention targeted at a specific risk group that is not or does not contain an epidemiologically influential group for transmitting the pathogen, see (3) in Fig. 4. Immunizing such groups will not cause nonlinear differences in transmission in the population, provided that the number of vaccinated persons remains relatively small compared with total population size. Examples of vaccination programmes that may fall into this category are hepatitis A vaccination of health
care workers, influenza and pneumococcal vaccination programmes targeted at the elderly or varicella-zoster virus vaccination of (susceptible) pre-adolescents or healthcare workers. For these same pathogens, examples that do not fall into this category are hepatitis A vaccination of children or food handlers, influenza, pneumococcal or varicella-zoster virus vaccination programmes in childhood. Another example where the epidemiological influence is small is where vaccinating humans against an infection will not induce herd immunity, simply because humans are not the main hosts for the infectious agent and its transmission does not depend on the interaction of infectious humans, but is channelled via an environmental or animal reservoir (e.g. tetanus, rabies), see (2) in Fig. 4.

**Dynamic models are required to analyse programmes targeted at epidemiologically influential groups of an infection.** Immunizing such groups would have complex effects on the propagation of the pathogen in the population. These are usually relatively large groups, but also targeted vaccination of core transmitter groups could have a substantial impact on the epidemiology of infection, which cannot be estimated by static models. Examples of such interventions include vaccination against blood-borne and sexually transmitted diseases targeted in injecting drug users and people with high sexual partner change where the main routes of transmission are needle sharing and sexual intercourse (e.g. HIV, HBV). Ignoring herd immunity could then have an important impact on the estimated cost-effectiveness of the programme. For these applications, a dynamic model should be the first choice, as a static model has limited value, and can potentially be misleading for public health policy.

Still sometimes static model use can be justified. If it is known from previous similar evaluations that the difference between static and dynamic model applications for the type of intervention and similar context is negligible, then one could use a static model. The condition is then that it is well established, either through previous dynamic modelling with and without indirect effects, or through formal model comparisons (177), that the static-dynamic choice does not play an important role for the problem at hand, see (4) in Fig. 5.

If, on the other hand, a substantial difference in cost-effectiveness results between static and dynamic model applications has been demonstrated, then a dynamic model is strongly preferred, as we know then that a static model (5a) will always be limited in terms of the conclusions that can be drawn.

When there are no such previous comparisons, likewise a dynamic model is preferred. The usefulness of static models in these situations (5a and 5b) will then be conditional on knowledge about the likely net effect of positive and negative externalities (indirect effects) from vaccination, as well as the results of the static model. If it is likely that negative externalities from vaccination outweigh positive externalities, then a static model is unacceptable and a dynamic model is required, see (8) in Fig. 5. If there are no negative externalities from vaccination or these are likely to be smaller than positive externalities, then a static model can be attempted, although a dynamic model remains preferable, see (9) in Fig. 5.

For diseases that are more benign the older the age at infection (or indeed the severity of which is independent of the age at infection), ignoring herd immunity will un-
derestimate the benefits of vaccination – i.e. there will be positive externalities. Such a programme would more than proportionally reduce the incidence of infection and shift the average age at infection to ages at which the disease is less (or equally) severe. Examples of such programmes include childhood pertussis, RSV and Hib vaccination. When the evaluation of such vaccination programmes yields favourable results with sufficient certainty, the analyst can assume that it will be more favourable in reality. Hence, the associated simplification from using a static model should not have changed the recommended decision. Although a static model could thus be acceptable for such applications, dynamic models are still preferred, especially when different subgroups are targeted by the interventions and herd immunity effects are larger for one group than for another, see (7) in Fig. 5.

Some infections however, cause more severe disease the older the age at infection. Hence it is important to assess whether the net effect of herd immunity is positive or negative. In the extreme case, at intermediate levels of vaccination coverage, vaccination programmes could, for some diseases, cause more harm than good. Examples of these include childhood varicella-zoster virus and rubella vaccination. Clearly, before such programmes are initiated it is vital to have a reliable estimate of expected vaccination uptake. The use of static models to evaluate these programmes can only be justified if a sufficiently high level of vaccination coverage can be attained during the first year of the programme and if coverage can be maintained at such high levels. At high vaccination coverage (possibly with a catch-up/mop-up campaign in multiple age groups), the proportional shift in the average age at infection (see section 6.2) would still occur but the number of cases would decrease in all age groups, including the older age groups. This means that the shift in the age at infection would not cause a greater burden of disease, even in the age groups that are at risk of more severe disease if infected. Immunity due to natural infection would then simply be replaced by vaccine-induced immunity in newly introduced (i.e. by birth) susceptible persons. If, in a static model, vaccine protection is assumed to be of limited duration or to wane over time, the model should also generate a shift in the age at infection. However, it would not capture the shift resulting from the vaccine impact on transmission dynamics, as observed in reality or produced by dynamic modelling. Furthermore widespread vaccination may have other externalities related to competition between variations in pathogens (e.g. serotypes, see also Chapter 5) that can only be estimated by dynamic transmission models that simulate interactions between the age cohorts that make up the entire population.

If then, allowing for uncertainty, the results are borderline favourable or unfavourable, the information provided by a static model analysis will only be of very limited value to the decisionmaker, see (10) in Fig. 5, as it could potentially lead to wrong or even harmful policy decisions. Note that the plausibility of achieving “favourable results with sufficient certainty”, hinges on the assumed vaccination costs (mainly consisting of the vaccine price and the delivery costs), implying these results are conditional on the vaccination costs assumed. These vaccination costs would need to be realistic, and be complemented by estimates of vaccination costs at which the static model no longer yields a clearly favourable cost-effective result (see also Chapter 8).

Sometimes observations from a similar setting are available and can be used as a ready estimate in a static population model (this has for instance been the case for the ob-
servations on childhood pneumococcal conjugate vaccination in the United States of America (111) being used in some of the European analyses (178). When indirect effect data (such as herd immunity, serotype replacement and antibiotic resistance) from comparable settings are integrated as a correction factor in a static model to adjust the “static (constant force of infection)” estimates, the interpretation of comparability between settings is very important and needs to be assessed and discussed by analysts. In this case, again we can have a situation where results are clearly favourable, or not. In the latter case, the static model is not useful, see (11) in Fig. 5. In the former case, a static model can be useful, but again the reliability of incremental cost-effectiveness estimates of different strategies depends on the comparability of the data that were transferred from other settings to the setting at hand and the strategies being considered, see (6) in Fig. 5.

6.3.2.2 Basic static model options

Basic choice options for a static model can be distinguished by considering whether or not people can be assumed to be subjected to instantaneous risks in a single time step, or ongoing risks over time (see Fig. 6). In case of the former a decision tree structure can be considered (e.g. influenza vaccination of the elderly in a single (“average”) influenza season), in case of the latter a cohort model would be more appropriate (or else the analyst may end up modelling many decision trees in sequence). In case of a cohort model, when there is the possibility that relevant risks of cohorts are differentially affected by age and time, there could be benefit in using a multiple cohort model instead of a single cohort model. For instance, because vaccine efficacy in elderly over 65 years is both age and time dependent it would be more efficient and more accurate to model potential pneumococcal vaccination strategies at age 65–75 and age 75+, using a multiple cohort model for the entire population aged 65+, over single year ages, instead of repetitively using a single cohort model with a particular starting age.

For relevant literature on these common types of health economic models we refer to text books (e.g. (179)).

6.3.2.3 Basic dynamic model options

There are many challenges to modelling infections beyond herd immunity effects for a single pathogen, which is the situation we have implicitly emphasized in Fig. 4 and Fig. 5. Historically, dynamic models have been used sparingly for some vaccines, sometimes due to a limited understanding of what the biomedical transmission effects were of some of the new vaccines (e.g. rotavirus), sometimes due to a lack of essential data in many countries (e.g. nasopharyngeal carriage in the general population of bacteria such as *Streptococcus pneumoniae*). Since the previous version of this guide (2008), a substantial rise in dynamic model applications both with and without economic evaluation occurred. This can be attributed to scientific communication about these models becoming more internationally transparent, but also to relevant mixing pattern (180) and case-notification and serological data becoming more readily available. Most dynamic model applications for economic evaluation involve deterministic compartmental models, usually assuming individuals mix at random. Alternative assumptions can be made in this respect, for instance by using network
models (181) in the context of sexually transmitted infections, or smaller communities with heterogenous mixing like hospital wards.

**Fig. 6. Basic static model structure options**

In addition to herd immunity, the consideration of variations (e.g. serogroup, serotype, genotype) of infectious agents, which may or may not be competing with each other, might be important. Indeed, cross protection (where protection against one type would offer some degree of protection against other types), type replacement (where the reduced circulation of vaccine types is gradually replaced by increased circulation of non-vaccine types), mutation (where the biological characteristics of the pathogen are subject to change) and rising antimicrobial resistance are concerns that might be relevant to model for specific infections, but for which empirical evidence is not always available to allow this. For instance, modelling various strains and types jointly would basically require an expansion of the unique characteristics of individuals (in an individual-based dynamic model) or of compartments (in a compartmental dynamic model). Indeed, this implies that (groups of) individuals might be susceptible for one type and immune for others, and that the model should be able to distinguish groups or individuals on this basis. This would further increase the computational burden of such models, and substantially increase the data requirements. The desirability to do so depends on the availability of solid epidemiological data and the additional expected information gained from such an analysis (i.e. with the aim of performing economic evaluation). When risks for relevant infectious disease states are substantially different between many small groups in the population, irrespective of age and time as covariates of risks, then it might be useful to consider individual-based models. Both compartmental and individual-based models can be deterministic or stochastic, depending on whether risks are at least partially defined by chance events (see Fig. 7). Chance may play an important role, and require a stochastic model, for instance when disease
transmission is rare, such as at the emerging stages of a new pathogen (e.g. SARS), or the near-elimination stages of an existing pathogen (e.g. polio, measles), or when the modelled population is small and/or not well connected (e.g. islands, hospitals).

Note that Fig. 7 like Fig. 6, presents some broad categorisations, without specifying that other model types or combined/hybrid models are also possible and useful, like network models, metapopulation models and stochastic Markov models. These figures are added in an effort to clarify and raise awareness of some main modelling features, but not to provide any strict guidance (in contrast to the earlier Fig. 4 and Fig. 5 on static versus dynamic models).

Fig. 7. Distinguishing stochastic versus deterministic, and compartmental versus individual-based model structures

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6.4 Practical implementation options of static and dynamic models

Table 9 provides an overview of the main practical differences for the implementation of static and dynamic models. While Table 9 lists some examples of ready to use software, this is not an exhaustive list. There is an increasing trend to use basic statistical, mathematical or multi-purpose coding languages, such as R (https://www.r-project.org) or C++ (http://www.cplusplus.com), that require direct programming, with the advantage of great flexibility, and potential maximum transparency. These are increasingly used to develop the common static, as well as the more complex dynamic model applications for vaccination decisions. In this respect, an expanding number of R libraries are available for use with health economic models, and a number of existing dynamic models can be accessed with source code openly published for peer use,
extension and validation. This guide encourages an open science approach for both models and data.

Social mixing pattern data are increasingly made publicly available for scientific use (see [http://www.socialcontactdata.org](http://www.socialcontactdata.org) and [http://www.sociopatterns.org/data-sets/](http://www.sociopatterns.org/data-sets/)). A freely available R package, “socialmixr”, can be used to derive social mixing matrices from survey data (see [http://sbfnk.github.io/socialmixr/](http://sbfnk.github.io/socialmixr/)). Furthermore approximative, synthetic contact matrices can be generated using different methods, drawing on the characteristics of social contact patterns from countries for which such primary data were collected. For instance data from the 8 POLYMOD-study countries (180) have been used to infer synthetic contact matrices for other countries, using demographic and sociological data such as household structure, school entry ages or work force participation data. Such resulting synthetic matrices have been made available as part of these studie (182, 183).

Table 9. Practical differences of static versus dynamic models for economic evaluation

<table>
<thead>
<tr>
<th></th>
<th>Static</th>
<th>Dynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical population in which costs and effects are monitored</td>
<td>A single ageing cohort (with removal of deaths from all causes through time), or – more rarely – a multicohort model covering part of, or the entire population</td>
<td>The entire population (with introductions of births and removal of deaths from all causes through time)</td>
</tr>
<tr>
<td>Development complexity</td>
<td>Easy to develop, single cohort model embedded in traditional health economic methods</td>
<td>Not part of the traditional toolbox of epidemiologists and health economists</td>
</tr>
<tr>
<td>Ready to use software(^{a})</td>
<td>Spreadsheets, e.g. • MS Excel™ • @Risk™ • TreeAge Pro™ • Crystal Ball™</td>
<td>• Berkeley Madonna™ • Model Maker™ • Stella™ • Vensim™</td>
</tr>
<tr>
<td>Required data</td>
<td>Requires (usually age-specific) data on epidemiology, demography, course of illness, vaccine efficacy, costs</td>
<td>Same as with static models + average duration of infectiousness + information on relevant(^{b}) social contact patterns between infectious and susceptible people + probability of transmission per contact</td>
</tr>
</tbody>
</table>

\(^{a}\) Non-exhaustive list. Note that both static and dynamic models can also be programmed directly in basic programming languages or more generic software (e.g. C++, Matlab, Visual Basic, S-plus), including open source software (e.g. R, OpenBUGS, CPython).

\(^{b}\) relevant in the sense that these are instrumental in facilitating transmission of the pathogen from an infectious to a susceptible person (e.g. a conversation and touching for airborne infections, sexual intercourse for STIs). These mixing and transmission probabilities could be estimated partially from prevalence data alone, but not completely without making some simplifying assumptions. Hence the increased use of direct social contact surveys to document social mixing patterns.
6.5 Model validation

In principle, there is no difference between model validation for vaccination programs and for other interventions that inform policy. Based on the principles of validation literature, four broad types of validation for health economic evaluation have been distinguished: (a) conceptual validation (i.e. the analytical approach or model is conceptually fit for purpose), (b) data validation (i.e. input data are appropriate, accurate, sufficient as well as properly transformed before use), (c) computerized model validation (i.e. the model is correctly implemented and coded in line with its concepts), and (d) operational validation (i.e. the model’s behavior is sufficiently accurate) (184). Analysts should strive, as much as possible, to explore the various facets of validation outlined in this section. The literature shows that validation efforts are often not undertaken or not reported as part of journal articles, even if they have been performed (185). There is a role for publishers to accommodate appendices on validation efforts as part of journal articles.

In addition to using the validation assessment tool “AdViSHE” (184) for health economic evaluation in general, it is recommended to consider the validity of the model, by undertaking some or all of the actions described in this section, with an absolute minimum of model verification.

6.5.1 Model verification and calibration

Model verification (“debugging”) is done to check whether (changes in) the outputs produced, conditional on (changes in) the inputs, are in line with what is known. An easy way to check whether the model behaves as intended is to change input values so that the output, or the impact on the output is perfectly predictable. For instance, setting vaccine efficacy to zero, should result in zero cases prevented and zero deaths prevented, and setting disease-specific mortality to zero should result in zero deaths from the infectious disease. Just as increasing the costs of vaccination should make vaccination less attractive in terms of cost-effectiveness, increasing the disease-specific mortality rate should make the cost-effectiveness ratio of vaccination versus no vaccination more attractive. Clearly there are numerous disease- and intervention-specific variations to this theme, and analysts should try to check all that they can.

Note that when, as in static models, herd immunity is ignored, while at the same time constant returns to scale are assumed (i.e. the same vaccination costs per vaccine recipient at any level of vaccine uptake), changes in vaccination coverage will have no impact on the cost-effectiveness ratio (186). For instance, vaccinating 1% of the target group will then have the same incremental cost-effectiveness ratio as vaccinating 70%, or 100%. However, this result is not a sign of an erroneous model, as this is simply a consequence of the basic structure that was chosen for the model. Whether or not this choice corresponds reasonably with reality depends on the infectious disease and intervention under analysis.

Model verification also implies checking the results of the model versus unrelated observations (unrelated in the sense that they were not used as parameters in the model). This is often done through visual inspection (with or without formal estimates for the goodness of fit). Results of this type of verification analysis should be presented with
the main analysis, and if not, it should be clarified why not (eg, no unrelated observations available).

The term validation is sometimes confused with calibration. Calibration is meant to mean that unknown parameters in the model are estimated by searching for their values that yield the best fit of the model results to unrelated observations. That is, calibration is in this context a method for parameter estimation, and the data used for calibration are then no longer unrelated to the model parameters, so they do not serve in a strict sense as a source for model verification. An example of such fitting for Meningococcal C vaccination is provided in Trotter et al. (187). Unrelated observations could for instance come from vital statistics or health care utilization data, e.g. cancer registry data to fit models for HPV (188).

6.5.2 Convergent validity

Convergent validity relates to checking whether models developed by different analysts and/or at different moments in time show similar results and if they do not, whether their differences can be logically explained on the basis of different inputs or structure. Clearly, this type of validity requires the existence of other models. Moreover, the observation that different models show similar results may be a consequence of them all being based on the same structural assumptions and is therefore not conclusive evidence that they are correct.

In the field of infectious disease there are several examples of dynamic models reaching substantially different results to static models for reasons explained higher in this chapter (see for instance (186, 189–191)). Comparing a static model to a dynamic model is not straightforward, because dynamic models typically show accumulated results in unvaccinated and vaccinated cohorts after vaccinating multiple cohorts, whereas the static models are typically restricted to results in a single vaccinated cohort. In other words, when an analysis based on a static cohort model presents an incremental cost-effectiveness ratio (ICER) accumulated over 10 years, the intervention costs typically contain only the costs of vaccinating a single cohort, and other costs and effects are estimated only for that same cohort. In a dynamic population model, the results accumulated after 10 years typically contain the sum of vaccination costs for 10 consecutive cohorts, and the other costs and effects are estimated not only for the vaccinated cohorts, but also for all other people in the population. The ICER of a dynamic model should not be divided by the time span (10 years in this case) to obtain an ICER comparable to that of a static cohort model. One more reliable approach would be to sum the costs of 10 static cohort models in a row and sum the effects separately (both with appropriate discounting) for each option for intervention, and work out the ICER for these 10 accumulated cohorts. This would provide an easy basis for comparison between results from an existing static and an existing dynamic model. Guidelines are available that enable standardizing comparisons between different infectious disease models (192), and it is expected that this type of validation activity will increase over time, partially as an approach to deal with model structure uncertainty (see also Chapter 8).
6.5.3 Face validity
Face validity means that the results of the model are not counter-intuitive and can be logically explained. Although the absence of face validity should raise concerns, its presence should not be taken to be a strong reason for considering the model to be valid.

6.5.4 Predictive validity and post-implementation economic evaluation
Predictive validity can be problematic as circumstances tend to change. Vaccine prices, for instance, have been known to fluctuate significantly and many other factors might be subject to change. This makes it all the more apparent that model-based economic analysis should be seen as an aid to decision making by showing what would happen if a range of conditions are met, and how foreseeable changes in these conditions, affect the outcomes.

There is, however, a rising interest to perform post-implementation economic evaluations, with the aim to evaluate past decisions and ongoing programs. In addition to serving as a validation for economic evaluations that were made pre-implementation, it can be a basis for pay for performance type contracting with vaccine manufacturers (193). Although such evaluations try to minimise the impact of modelling, they often cannot completely avoid some modelling, despite the benefit of hindsight, partially due to surveillance and accessible government databases not generating data that are sufficiently specific (194).

6.6 Recommendations

The mathematical model should be:

- Transparent in that the structure and implicit or explicit assumptions are all clearly described and motivated.
- Static, if vaccination is unlikely to change the force of infection in susceptibles or as a means to make a conservative estimate when indirect transmission-dependent effects cannot on the whole be adverse.
- Dynamic, if vaccination is likely to change the force of infection in susceptibles, and a static model would not yield a conservative estimate, or if the conservative estimate from a static model does not lead to an outcome which would be considered favourable by decision makers.
- Stochastic, if chance plays an important role in the transmission process of the pathogen.
- Validated, in as many facets of validation (verification, calibration, face validity, predictive validity) as possible, but at least verified.
Chapter 7: Discounting

Discounting is the reduction of the value of future consumption (and health, where relevant) in an economic evaluation at a pre-specified rate, on the basis that individuals and societies value present consumption more than future consumption. The consequence of discounting is that costs and benefits are considered less important, the further they arise in the future. Discounting can be regarded as a technical correction, which puts costs and benefits occurring at different points in time on the same basis of comparison. In cost-effectiveness analysis, both costs and health effects are often discounted.

7.1 Why vaccination programmes are sensitive to the choice of discount rates

For curative therapies, most benefits accrue immediately or shortly after the intervention is initiated, and the cost-effectiveness of these interventions is therefore largely independent of the discount rate. Conversely, the cost-effectiveness of many vaccination programmes can be highly sensitive to discounting due to the much longer time horizons that are involved. This is because (i) there are often long delays between the vaccination event, the time that an infection is averted by vaccination, and the time when disease is averted by vaccination, (ii) vaccination often protects against childhood diseases which can cause death or long-term disability, implying many future life-years are affected by vaccination, (iii) the population-level externalities of vaccination (such as herd protection and pathogen strain replacement) can persist for a long time, and sometimes even beyond the lifetime of the vaccinee, and (iv) vaccination allows the possibility of eradicating a disease, which in principle produces a stream of benefits indefinitely.

7.2 Equal or differential discounting

Currently most countries with pharmacoeconomic reference cases advocate discounting health effects and consumption at an equal rate, although Belgium, the Netherlands and Poland advocate differential discounting (https://tools.ispor.org/peguidelines/). A review of the vaccine literature found that the majority (but not all) cost-effectiveness analyses of vaccines in the literature used equal discounting in their base case (195).

Several theoretical reasons have been raised to argue that the discount rate for consumption and for health outcomes should be equal, but all of them have been disputed (195). More recently, it has been argued that differential discounting is valid if the decision maker is seeking to maximise health (rather than consumption) within a fixed
health care budget, and the value of health changes over time (196). In addition, philosophical and ethical objections to equal discounting (or even discounting health at all) have been made on the grounds of intergenerational equity (197, 198), because health grows at a slower rate than consumption in most societies, and because uncertainty about catastrophic risk is smaller on a societal level on which vaccination operates (199, 200).

O’Mahony et al. (201) have shown that multi-cohort models (such as most transmission dynamic models) can produce inconsistent results when differential discounting is used.

This guide recommends initially using the rate used in the country in question. In the absence of national guidelines, two analyses using the following discount rate schemes are recommended to be used: (i) 3% and 0% discounting for consumption and health respectively, (ii) 3% discounting for both health and consumption (202).

### 7.3 Other discounting schemes

Other discounting schemes have been proposed to correct perceived inadequacies of conventional discounting methods for long-term interventions such as vaccination (see Jit and Mibe (195) for a review). These include:

- "Slow" or non-constant (e.g., hyperbolic) discounting: Changing the discount rate over time, usually by decreasing the rate for events far into the future.
- Two-stage discounting: Discounting health effects in the same individual back to a common age at one rate, then back to a common time at another rate.
- Delayed discounting: Discounting health gains from an intervention to a different time from the time at which the intervention is introduced.

### 7.4 Recommendations

- Discount costs and effects initially using the rate in the country in question (for studies to inform local decision-makers) and also using WHO recommends schemes of (i) 3% and 0% discounting for consumption and health respectively in the base case, (ii) 3% discounting for both health and consumption.
Chapter 8: Estimating, presenting and interpreting cost-effectiveness data under uncertainty

This chapter considers the summarizing measures used to report economic evaluations and how they can be used to inform decision-making. It also considers the sources of uncertainty inherent in any economic evaluation and describes how decisions can be made in the context of uncertainty. This chapter also looks at more sophisticated types of sensitivity analysis and explains how they might help with the interpretation of cost-effectiveness data and the identification of important areas for future research.

8.1 Why accounting for uncertainty?

First, even if we would only be interested in the average value for the cost-effectiveness ratio of one strategy versus another, it is important to account for uncertainty in order to estimate this average correctly. Indeed, the average value for the cost-effectiveness ratio is not necessarily equal to the value obtained when using the average value of each input parameter (203). This is also a reason to argue against the use of a base case analysis when such analysis refers to calculating cost-effectiveness based on average or selective “most likely” (often termed “base case”) values of all input parameters.

Second, by accounting for uncertainty in health economic evaluations, we can assess whether there is value in obtaining further information on uncertain aspects, and if so, identify the key aspects on which further information would be most valuable (203).

8.2 How should costs and effects be linked?

Having assessed the costs (Chapter 4) and effects (Chapter 5 and Chapter 6), the next step in an economic evaluation is to bring together these results to provide an overall indication of cost-effectiveness in a way that will inform decision-making. This can be done by calculating a cost-effectiveness ratio, and/or by calculating the net benefit.

Depending on the study question and comparison undertaken, there are three types of cost-effectiveness ratios:

- Average cost-effectiveness ratio (ACER): an ACER deals with a single intervention and evaluates that intervention against its baseline option, e.g. no program-
me or current practice. It is calculated by dividing the total cost of the intervention \( (C) \) by the total number of health outcomes prevented by the intervention \( (E) \).

\[
ACER = \frac{C_{\text{Intervention A}}}{E_{\text{Intervention A}}}
\]

- Marginal cost-effectiveness ratio (MCER): the MCER assesses the specific changes in cost and effect when a programme is expanded or contracted, e.g. the additional costs and effects of vaccinating an additional child. In practice it is rare for output to change by one unit, so the marginal cost-effectiveness ratio of a particular programme is often approximated by dividing the additional costs associated with a larger change in production than one unit by the change in production. An example might be the cost of extending the same vaccination service to another village and dividing this by the additional number of vaccinations in order to approximate the marginal cost per additional child vaccinated.

\[
MCER = \frac{C_{\text{Intervention A+1}} - C_{\text{Intervention A}}}{E_{\text{Intervention A+1}} - E_{\text{Intervention A}}}
\]

- Incremental cost-effectiveness ratio (ICER): an ICER compares the differences between the costs and health outcomes of two alternative interventions that compete for the same resources, and is generally described as the additional cost per additional health outcome. The ICER numerator includes the differences in programme costs and can include in addition the averted disease costs and averted costs of productivity losses depending on the choice of perspective. Similarly, the ICER denominator is the difference in health outcomes.\(^{15}\) When more than two alternative interventions are considered, an ICER can be obtained for each intervention compared to the baseline intervention (no programme or current practice).

\[
ICER = \frac{C_{\text{Intervention A}} - C_{\text{Intervention B}}}{E_{\text{Intervention A}} - E_{\text{Intervention B}}}
\]

Due to the properties of a ratio, the interpretation of results becomes problematic in case of negative incremental cost-effectiveness ratios. We cannot tell from a cost-effectiveness ratio if an intervention results in health loss and/or cost savings. A negative ICER can either mean that an intervention results in health gains and cost savings, or that an intervention results in health loss and a cost to pay (Table 10). Also, when considering more than two strategies, it is not straightforward to determine the most optimal strategy (see further). This is why the net benefit approach has been introduced (204).

\(^{15}\) Some consider an ACER to be a specific type of ICER in which the implicit comparator is doing nothing. Furthermore, it should be noted that the terms MCER and ICER are often used interchangeably in the literature.
Table 10. Incremental costs and effects and the corresponding ICER, INMB and INHB, assuming an arbitrary willingness-to-pay value of €30 000 per unit health gain

<table>
<thead>
<tr>
<th>Incremental costs</th>
<th>Incremental effects</th>
<th>ICER</th>
<th>INMB</th>
<th>INHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 000</td>
<td>10</td>
<td>20 000</td>
<td>100 000</td>
<td>3</td>
</tr>
<tr>
<td>200 000</td>
<td>-10</td>
<td>-20 000</td>
<td>-100 000</td>
<td>-17</td>
</tr>
<tr>
<td>-200 000</td>
<td>10</td>
<td>20 000</td>
<td>500 000</td>
<td>17</td>
</tr>
<tr>
<td>-200 000</td>
<td>-10</td>
<td>20 000</td>
<td>500 000</td>
<td>-3</td>
</tr>
</tbody>
</table>

The incremental net monetary benefit (INMB) and the incremental net health benefit (INHB) are calculated as follows, with WTP referring to the societal willingness-to-pay value for a unit health gain:

\[
INMB = \left( E_{\text{Intervention A}} - E_{\text{Intervention B}} \right) \times WTP - \left( C_{\text{Intervention A}} - C_{\text{Intervention B}} \right)
\]

\[
INHB = \left( E_{\text{Intervention A}} - E_{\text{Intervention B}} \right) - \frac{C_{\text{Intervention A}} - C_{\text{Intervention B}}}{WTP}
\]

8.3 Which uncertainties to account for?

After setting the health economics framework and having decided on all the options for intervention to be compared, the next step of any health economic evaluation is to gather all information available on the disease and interventions that is needed for the evaluation (including incidence, vaccine effectiveness, treatment and intervention costs). Many, if not most, of the aspects of the disease and intervention will be to some extent uncertain, as rarely studies exist that measure exactly what is needed for the economic evaluation. For instance, average treatment costs are often based on only a sample of the population under study, or are extrapolated from another country than the one under study. Accounting for these uncertainties is necessary to calculate the expected costs, effects and cost-effectiveness of an intervention correctly (203). Furthermore, it allows assessing the impact of the uncertainties around the disease and the interventions under study.

In paragraph 8.3.1 the different possible types and sources of uncertainty are described. Paragraph 8.3.2 provides guidance on which uncertainties (not) to account for in an economic evaluation, paragraph 8.3.3 on how (large) to quantify uncertainties, and paragraph 8.3.4 concludes with how to be transparent about this.

8.3.1 Types and sources of uncertainty

Table 11 summarizes the terms used in the literature to describe various types of uncertainty, which we propose fall into 3 broad categories, encompassing uncertainty around methodological choices, the structure of the model, and the true values of the model parameters (22).
Table 11. Types of uncertainty in health economic evaluations and why they may arise
(adapted from Bilcke et al. MDM 2011 (22))

<table>
<thead>
<tr>
<th>Methodological:</th>
<th>Examples:</th>
</tr>
</thead>
</table>
| Which normative modelling approach should be used? | • Discount rate and procedure  
• Time horizon  
• Perspective (health care provider, societal)  
• Means of valuing health gains; Age weighing of utilities |
| Possible sources of uncertainty: | • Different normative views about what constitutes the ‘correct’ approach for policymaking, with the aim of optimising some desirable quantity (e.g. social welfare) within given constraints |
| Other descriptions in the literature: | • Uncertainty around values of parameters related to analytical methods (such as discount rate and time horizon) has been classified as parameter uncertainty |

<table>
<thead>
<tr>
<th>Structural:</th>
<th>Examples:</th>
</tr>
</thead>
</table>
| What structural aspects should be incorporated to capture the relevant characteristics of the disease and intervention being investigated? | • Disease states to include  
• Static or dynamic transition rates  
• Type of function used to extrapolate data into the future  
• Type of function used to represent intervention efficacy in different subpopulations (e.g., age groups)  
• Extrapolation of intervention effect to a different setting |
| Possible sources of uncertainty: | • Lack of evidence on particular characteristics of the disease and/or intervention being investigated  
• Lack of resources to obtain such evidence and/or to construct a suitably realistic model |
| Other descriptions in the literature: | • Model uncertainty  
• Uncertainty about model structure (model type, model substructure, and structural assumptions) and modeling process  
• Uncertainty about model structure and model process  
• Uncertainty about model type and model structure |

<table>
<thead>
<tr>
<th>Parameter*:</th>
<th>Examples:</th>
</tr>
</thead>
</table>
| What is the true value of each model parameter? | • True value of the parameter  
• Reliability of its estimated value (bias)  
• Value of the parameter when extrapolated to a different setting |
| Possible sources of uncertainty: | • There is no direct or indirect evidence on the parameter value (or no resources to obtain it)  
• There is evidence about the parameter value, but its quality is not clear  
• There is evidence available about the parameter value, but only for a sample and not for the entire population of interest  
• The parameter value is estimated indirectly by combining a number of other parameter values because no direct evidence is available |
| Other descriptions in the literature: | • Uncertainty about parameters that could (in principle) be observed  
• Uncertainty about generalizability and transferability of evidence |

* We refer to a ‘parameter’ as a true unknown, the value of which can be estimated using either a Bayesian or a frequentist approach.
Uncertainty around methodological choices arises when there are different normative views about what constitutes the “correct” approach for optimum decision-making. Examples for economic evaluations include the decision-making perspective taken (e.g. health care provider, third-party payer, society), the discounting procedure, the way health gains are valued, the inclusion of health loss for caregivers, the types of disease outcomes (e.g. mortality, morbidity, loss of well-being, economic costs) to capture and the extent to which macroeconomic consequences are considered. Methodological uncertainty also includes uncertainty around parameters related to normative views about analytical methods, such as the time horizon and discount rate of an analysis.

Uncertainty about the structure of the model refers to uncertainty about the extent to which structural features of the model adequately capture the relevant characteristics of the disease and intervention being investigated. It refers to doubts about the natural history of the disease as well as uncertainty about the correct method for combining the parameters of the costs, consequences and/or combinations of costs and consequences. We distinguish between uncertainty related to the general structure of the disease model and structural uncertainty on a lower level. Chapter 6 gives guidance on which disease model to choose. If there is only a single disease model of choice that can be clearly justified, it is acceptable to assume no uncertainty around the general structure of the disease model. However, there will be likely structural uncertainties on a lower level, i.e. when a parameter value is estimated indirectly by combining a number of other parameter values because no direct evidence is available about the parameter value (i.e., no study exists that directly measures the parameter of interest). In this case, the uncertainty around the parameter value is a combination of: (1) parameter uncertainty (see next paragraph), i.e. the uncertainty around the values of the other parameters from which the parameter of interest is derived and (2) structural uncertainty, i.e. the uncertainty around the way these other parameters are combined (i.e., the submodel) to obtain the parameter of interest. An example is the uncertainty around how vaccine efficacy may wane over time. For instance, annual data on live attenuated herpes zoster vaccine efficacy were available for up to 10 years after initial vaccination. Different models can be fitted to these data to estimate how vaccine efficacy changes over time (e.g. exponential waning model, logarithmic waning model, etc.). Hence, in this case the total uncertainty in relation to waning is a combination of (1) the uncertainty around the vaccine efficacy at the 10 annual time points, as well as (2) the uncertainty around the statistical or mathematical model that is used to combine these data points (e.g. (117, 205)).

Structural uncertainty arises because of limitations in the availability and/or quality of supporting evidence in one of the following ways:

- Lack of evidence: There is no empirical evidence on particular characteristics of the disease and/or intervention being investigated. This may occur either because 1) relevant studies (published or unpublished) are imperfect or nonexistent or 2) there is no opportunity to investigate or synthesize all existing evidence and/or to construct a suitably realistic model because of resource constraints (time, budget, expertise, current state of technology, etc.). As a result, simplifying and inherently uncertain assumptions are often necessary.

- Conflicting or unclear evidence: There is empirical evidence on particular characteristics of the disease and/or intervention being investigated, but its quality is
unclear. Several shortcomings in evidence can affect its quality. For instance, the means by which the evidence was obtained and the adequacy of the study design may be unclear (possibly due to poor reporting). Evidence may have been obtained in one setting (e.g. population, country, time period) but may need to be used to model a different setting, hence leading to uncertainty about the transferability (external validity) of the evidence. In such cases, it may be uncertain whether to incorporate a particular structural aspect based on the strength of available evidence.

**Uncertainty about the model parameters** refers to the uncertainty about the value for each parameter within the model, with respect to its true value. Often, consideration of parameter uncertainty is restricted to second-order uncertainty (uncertainty that arises when a parameter is estimated from a sample). However, the value of a parameter can be uncertain for a number of other reasons. There may be no evidence, direct or indirect, about the parameter value or no resources to obtain it, so the value has to be assumed and is therefore highly uncertain. Or there may be evidence about the parameter, but its quality is not clear, for the same reasons described above that the quality of evidence about a structural aspect of the model may be unclear. As mentioned above, when a parameter value is estimated indirectly by combining a number of other parameter values, the uncertainty around the parameter value is a combination of 1) the uncertainty around the values of the other parameters from which the parameter of interest is derived and 2) the uncertainty around the submodel used to obtain the parameter of interest (117, 205). A special case of this, could be parameters, which are at the core of a model, and are not necessarily adapted for each new application of the model, e.g. so-called 'deep' parameters of transmission-dynamic models, such as social contact rates used to estimate the transmission coefficients in a “who acquires infection from whom” matrix (see also Chapter 6) (126, 180).

### 8.3.2 Which uncertainties (not) to account for?

Ideally, all uncertainties pervading in an economic evaluation should be accounted for. As a minimum, at least the uncertainties for which it is expected or unsure that they will impact on the results of the economic evaluation should be accounted for. Particular attention should be given to methodological and model uncertainties as they are often more likely than parameter uncertainties to impact on the results, to the extent of changing the optimal decision. Methodological and model choices determine largely which parameters are included, and in which way. Therefore, analysts should always assess the sensitivity of the results to the following variables: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant) and vaccine price.

### 8.3.3 How (large) should the uncertainties be specified?

Uncertainties can be quantified in a deterministic or a probabilistic way.

- **Deterministic**
  The different plausible methodological choices, model structures and/or model parameter values are here just listed (Table 12), as they are presumed in a next step to be run through the model as scenarios (see section 8.4.1).
Table 12. An example of specifying plausible methodological choices, model structures and parameter values in a deterministic way

<table>
<thead>
<tr>
<th>Type of uncertainty</th>
<th>Uncertain aspect</th>
<th>Justifiable* choices/values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodological</td>
<td>Perspective</td>
<td>Health care payer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Societal</td>
</tr>
<tr>
<td></td>
<td>Discount rate</td>
<td>3% / 3%</td>
</tr>
<tr>
<td></td>
<td>costs/effects</td>
<td>5% / 5%</td>
</tr>
<tr>
<td>Structural</td>
<td>Waning function</td>
<td>Exponential</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Logarithmic</td>
</tr>
<tr>
<td>Parameter</td>
<td>Vaccine price</td>
<td>$1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$3</td>
</tr>
</tbody>
</table>

* Justifiable within the decision maker’s context

### Probabilistic

Not only the plausible model structures and/or model parameter values are specified, but also the probability that each of them is true. One way of obtaining the probability of different model structures is by calibrating to an external data source. That is, estimating the likelihood of each structural option being true, given the data. Based on this, a single best-fitting submodel can be selected (“model selection”), or results can be averaged over all submodels, weighted by their goodness of fit (“model averaging”) (e.g. (206)). The input parameters of the model can be represented as distributions instead of as point values. The distributions should reflect the uncertainty around the estimated average of an input parameter, and hence should be informed by the sample standard error, not the sample standard deviation. Indeed, the normal distribution with as its mean the sample mean and its standard deviation the sample standard error is appropriate to reflect the uncertainty around any input parameter if sample size is large enough. If sample size is small, different distributions are generally appropriate for different types of variable (179, 207). Of correlated parameters the correlation structure should be taken into account. A special case of uncertain parameters in economic evaluations of immunization programs are the ‘deep’ parameters of transmission-dynamic models (e.g. force of infection, reported social contact rates, ...), which are usually correlated, because they are estimated together by fitting the model to data. To estimate the uncertainty around transmission-dynamic model parameters jointly while taking into account the goodness of fit to data, various methods can be used such as rejection sampling and profile likelihood approaches. However, Markov Chain Monte Carlo (MCMC) is a particularly attractive and statistically robust method (for examples see (208, 209)).

Note that the uncertainty that is easiest to quantify (i.e. sample size uncertainty of single parameters) has rarely the biggest impact on the results of the economic evaluation. When no information is available, no standard ways exist to specify uncertainty ranges or distributions. At least the most extreme, but plausible values/structures should be specified. For parameters that are naturally bounded (e.g. proportions, such as the case-fatality ratio are bounded between 0 and 1), a distribution can be chosen that spans these natural boundaries. A uniform distribution is an option but one
should be careful to consider if the resulting mean (i.e. the midpoint of the boundaries of a uniform distribution) is plausible. For instance specifying the uncertainty around the case-fatality ratio as a uniform distribution between 0 and 1 results in an average case-fatality ratio of 0.5. The uncertainty distribution for parameters for which no information is available can also be informed by expert opinion, or by using similar parameters for other (similar) diseases and or interventions. A general rule one should keep in mind is that the width of the uncertainty ranges considered in the analysis, should reflect the data (not) available. In other words, a parameter for which no information is available should always have a wider uncertainty distribution than a similar parameter based on a large sample from the population under study. Wide uncertainty ranges for some parameters may increase the uncertainty around the cost-effectiveness of a strategy to a large extent. But this should not make the decision about which strategy to adopt more difficult. Indeed, decisions need to be made in the context of uncertainty, and the strategy of choice should be the one yielding the most attractive expected cost-effectiveness, irrespective of the uncertainty around this expected value (210). This is discussed in more details in section 8.5.2.2, but the take home message here is that 'assuming a fixed value because no information available' is never a good justification to ignore uncertainty for a parameter. However 'a single assumption because the parameter is unlikely to impact on the results' (e.g. cost of vaccine injection equipment when it is known to be a very small part of the total vaccination cost and its uncertainty may not be so influential) can be an acceptable justification, especially if this assertion is also confirmed in sensitivity analysis.

8.3.4 How to be transparent on the uncertainties (not) included?

Analysts should provide all information that is needed so that any other person can reconstruct the analysis, including reproducing the same model structures, model parameter values and/or distributions.

This includes:

1) An overview of the model structures, parameter values and/or distributions that are used in the evaluation. For parameter distributions, both the type of distribution and the parameters of the distribution needs to be reported (e.g. utility weight ~ Beta (a = 20, b = 105)).

2) The information that was used to inform each of these (e.g. reference to publication, database). In some cases additional information should be provided:

   a) For parameters for which the input value and distribution cannot be extracted unambiguously from the referenced publication/database, analysts should report how they came from the values presented in the referenced publication/database to the final model parameter values and distributions used for the economic evaluation (e.g. any adjustment or transformation done or any other assumption made).

   b) Analysts should explicitly state for which parameters they used a proxy (e.g. delivery costs of measles vaccine as proxy for delivery cost of typhoid vaccine, treatment costs of influenza-like-illness as proxy for treatment costs of influenza, or treatment costs from a neighbouring/similar country used in the absence of treatment cost from the country under evaluation).
c) Analysts should justify all aspects of the model that are assumed fixed (no uncertainty accounted for).

8.4 Propagating the uncertainties into the results of the economic evaluation

Uncertainty around methodological choices, model structure and model parameters should always be reflected into the results of the economic evaluation. Methodological uncertainty should always be shown in a deterministic way, while propagating model structure and parameter uncertainty can be done in a deterministic and/or a probabilistic way. Ideally, analysts should account for all uncertainty at once by conducting a probabilistic cost-effectiveness analysis (section 8.4.2). However we acknowledge that this sometimes may be difficult and that it may not always be necessary (see section 8.5.1). Therefore we describe also a ‘minimum analysis’. As a minimum, analysts should always include an extreme (best/worst) case scenario analysis (see section 8.4.1 and section 8.4.3), show the full range of potential cost-effectiveness results.

8.4.1 Propagating uncertainty in a deterministic way

When all uncertainties are specified in a deterministic way (e.g. Table 12), ideally all results should be obtained for each combination of uncertain methodological choices, model structures and parameters values. For the example presented in Table 12, there are 24 possible combinations of the uncertain options and values. A single combination of options and values is often referred to as a ‘scenario’, and the exploration of these different combinations as “scenario analysis”.

Hence, the result of deterministic analysis will be, for any comparison between two strategies, a set of n cost-effectiveness ratios and/or net benefit values, with n being the number of different combinations of input values, model structures and methodological choices that were used.

With deterministic sensitivity analysis it is usually not possible to vary more than 4 to 5 parameters/models/methodological options at the same time over their entire range: probabilistic sensitivity analysis is required to assess the impact of simultaneous variation of many input parameters/models (see next paragraph). As a minimum, analysts should present the results for the set of extreme circumstances across methods, models and parameters, also known as a ‘max-min’ analysis or ‘worst/best’ case analysis. In this case the methodological choices, model structures and parameter values that yield the worst (highest)/best (lowest) cost-effectiveness ratios are combined.

8.4.2 Propagating uncertainty in a probabilistic way

When the input parameters of the model are represented as distributions instead of as point values, uncertainty can be propagated in a probabilistic way: (1) a set of input parameter values is drawn by random sampling from each distribution, and (2) the model is ‘run’ to generate outputs (incremental costs and effects), which are stored. This is repeated many times (typically 1000 to 10 000 iterations), resulting in a distribution of outputs. This way of propagating uncertainty into the results of an economic evaluation is referred to as probabilistic sensitivity analysis (PSA).
The result of probabilistic sensitivity analysis will be, for any comparison between two strategies, a number \( n \) of cost-effectiveness ratios and/or net benefit values, with \( n \) being the number of samples drawn from the probability distributions/iterations from the model.

### 8.4.3 Deterministic and probabilistic sensitivity analysis combined

Note that probabilistic sensitivity analysis only accounts for the uncertainty that can be expressed as a distribution, and may not be feasible to account for particular model structure uncertainties and is not recommended for methodological uncertainties. In such cases, a combination of probabilistic and deterministic sensitivity analysis may be the best way to reflect all uncertainty inherent to the economic model. Ideally, probabilistic sensitivity analysis can be done for all scenario’s, resulting in a set of distributions for incremental costs and effects for each scenario. As a minimum, probabilistic sensitivity analysis should be done for the best and worst case scenario’s (see 8.4.1).

### 8.5 Determining the most optimal strategy

A major goal of any health economic evaluation is to determine the most optimal strategy, sometimes referred to as the 'preferred', the 'most attractive' or 'most cost-effective' strategy. The most optimal strategy in terms of cost-effectiveness is the strategy that is on average more cost-effective (e.g. highest expected net benefit) than other strategies. The next paragraphs explain how to determine the most optimal strategy distinguishing between the deterministic (section 8.5.1) versus probabilistic (section 8.5.2) approach to cost-effectiveness analysis.

Whether or not an intervention is cost-effective depends almost always on two key factors: (1) vaccine price, and (2) the amount a decision maker is willing-to-pay for a health gain. Bertram et al. (211) elaborated on the pros and cons of different fixed willingness-to-pay thresholds, emphasizing that such thresholds defined in a top-down manner based on GDP per capita are not recommended by WHO. The general rule for representing results under uncertainty is that, if no willingness-to-pay value is recommended/available for a given country, cost-effectiveness results should always be shown for a range of willingness-to-pay values and should always be presented together with the vaccine price (or vaccination costs) on which they are based.

### 8.5.1 Deterministic cost-effectiveness analysis (DETCEA)

We refer to deterministic cost-effectiveness analysis, when all methodological and model choices and parameter values are specified and propagated in a deterministic way, i.e. a single or a set of options/values is specified without probabilities assigned to each of the options/values.

#### 8.5.1.1 DETCEA: Does the intervention result in net cost savings and/or health losses?

As a first step, it is informative to determine whether an intervention results in net cost savings (i.e. the cost of the intervention is less than the treatment costs saved by avoiding cases when the intervention is introduced) and/or net health losses (i.e. health losses induced by the intervention (adverse events) exceed its health gains). When usu-
al practice is no vaccination, it is rare for this to be more effective than vaccination but it might, on balance, be less costly. But for instance, consider a decision to move from universal to targeted vaccination: in this instance it is probable that usual practice, i.e. universal vaccination, would be more effective. Furthermore, depending on the cost of organising a targeted vaccination programme in some contexts, universal vaccination could also be less costly.

The cost-effectiveness plane can be used to depict whether an intervention results in net cost savings and/or health losses (Fig. 8) (212), with incremental costs on the Y-axis, and incremental effects plotted on the X-axis. ICERs or INBs cannot be used for this purpose. As discussed above, the interpretation of ICERs becomes problematic when ICERs are negative (reflecting either health loss or cost savings). INBs do not suffer from this interpretation problem, but the same INB values can reflect different combinations of incremental health effects (gains or losses) and incremental costs/savings (Table 13).

Fig. 8. Concepts of decision-making shown on a cost-effectiveness plane
Table 13. Incremental costs, incremental effects and corresponding incremental net monetary benefit (INMB) and incremental net health benefit (INHB), assuming an arbitrary willingness-to-pay value of €30 000 per health gain

<table>
<thead>
<tr>
<th>Incremental costs</th>
<th>Incremental effects</th>
<th>INMB</th>
<th>INHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>295 000</td>
<td>10</td>
<td>5000</td>
<td>0.2</td>
</tr>
<tr>
<td>-305 000</td>
<td>-10</td>
<td>5000</td>
<td>0.2</td>
</tr>
<tr>
<td>100 000</td>
<td>10</td>
<td>200 000</td>
<td>6.7</td>
</tr>
<tr>
<td>-50 000</td>
<td>5</td>
<td>200 000</td>
<td>6.7</td>
</tr>
<tr>
<td>-295 000</td>
<td>-10</td>
<td>-5000</td>
<td>-0.2</td>
</tr>
<tr>
<td>305 000</td>
<td>10</td>
<td>-5000</td>
<td>-0.2</td>
</tr>
<tr>
<td>100 000</td>
<td>-10</td>
<td>-400 000</td>
<td>-13.3</td>
</tr>
<tr>
<td>-200 000</td>
<td>-20</td>
<td>-400 000</td>
<td>-13.3</td>
</tr>
</tbody>
</table>

8.5.1.2 DETCEA: What is the most optimal option from two interventions?
When the choice is between vaccination and usual practice, which is often no vaccination, the analyst should begin by applying the principle of dominance (sometimes called ‘strong’ dominance). Dominance favours a strategy that is both more effective and less costly (for example see section 8.5.1.3). Either the vaccine or usual practice may be preferred using this principle.

When a strategy is both more effective and more costly, the dominance principle provides no guidance. The decision-maker must decide if the greater effectiveness justifies the cost of achieving it. This is done by calculating a cost-effectiveness ratio.

The cost-effectiveness ratio represents a measure of how efficiently the proposed intervention can produce an additional unit of effect, e.g. DALY averted or QALY gained. By using this standard method, the cost-effectiveness of alternative vaccines can be compared, helping policy-makers decide which vaccines they should adopt. The goal of the decision-maker is to adopt all vaccines – and health interventions more generally – that represent efficient ways of averting morbidity and/or mortality or conversely of gaining health.

8.5.1.3 DETCEA: What is the most optimal option from more than two interventions?
In studies that compare multiple mutually exclusive vaccine strategies (i.e. only a single strategy can be implemented at the same time), an additional dominance principle should be applied. As is the case when comparing two interventions, the analyst should first apply the principle of strong dominance: any of the competing interventions is ruled out if another intervention is both more effective and less costly. The analyst should then apply the principle of extended dominance (sometimes called ‘weak dominance’). The list of interventions, trimmed of strongly dominated alternatives, is then ordered by increasing effectiveness. Each intervention is compared to the next most effective alternative by calculating the ICER. Extended dominance rules out any intervention that has an ICER that is greater than that of a more effective intervention. A rational decision-maker would prefer the more effective intervention with a lower ICER.
Prioritising the more effective interventions with better ICERs over less effective and less cost-effective ones allows good health to be purchased more efficiently.\textsuperscript{16} It is important to note that while this approach is technically correct if the sole aim is to maximise measurable health outcomes in the population, other criteria (see section 9.3 below) shape vaccine policies in addition to efficiency. In particular affordability in light of the available budget may oftentimes trump the logic of cost-effectiveness, such that if a decision-maker has insufficient funds to introduce a more cost-effective vaccine, they may decide to choose a less costly but also less cost-effective, or even dominated, vaccination programme that they can afford without having to change the disposable budget.

Table 14 and Fig. 9 illustrate the differences between the three types of cost-effectiveness ratio (presented in section 8.2), and the principles of strong and weak (or extended) dominance, using a hypothetical example of three different ways to deliver immunization.

\textbf{Fig. 9. Average, marginal and incremental cost-effectiveness and intervention choices – comparison of three ways to deliver vaccination}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig9.png}
\caption{Average, marginal and incremental cost-effectiveness and intervention choices – comparison of three ways to deliver vaccination}
\end{figure}

\textit{Source:} Musgrove & Fox-Rushby (213)

\textsuperscript{16} Dominance principles can also be applied by ranking interventions in the order of their cost, with the same end result. Dominance principles can also be applied when outcomes are measured in units other than QALYs and DALYs.
Point X describes the status quo of a current intervention, delivering vaccination by means of fixed facilities. At point X, the intervention achieves a total effect \( E_2 \) (measured as coverage or as disease reduction, e.g. DALYs averted or QALYs gained) at a total cost \( C_2 \). The ratio \( C_2 \) to \( E_2 \) is the ACER, shown by the slope of the line 0–X. Beyond point X, expanding coverage by means of fixed facilities becomes very costly, perhaps because the population not yet vaccinated is dispersed and hard to reach. Expansion to point X1, which increases the cost from \( C_2 \) to \( C_3 \), yields only a small increment \( E_3–E_2 \) in effect. The slope of the line X–X1 represents the MCER of that expansion, which would raise the ACER to line 0–X1. A reduction in coverage from X to X2 would improve the average cost-effectiveness (to \( C_1/E_1 \)) because marginal costs are rising steeply near point X. The MCER of the reduction in coverage is the ratio of \( C_2–C_1 \) to \( E_2–E_1 \).

The use of mobile vaccination teams, intervention Y, would result in higher coverage rates. The combination of fixed facilities and mobile teams allows the effect to be increased to \( E_4 \) at a total cost of \( C_4 \). The ICER of the mobile teams is shown by the slope of the line X–Y and the resulting overall or combined ACER by the slope 0–Y. Adopting intervention Y would clearly be preferable to trying to expand coverage through intervention X by building and staffing more fixed facilities, X1.

An alternative might subsequently be developed that is even better than Y, represented by point Z, e.g. community-based vaccination teams that could operate either near or far from fixed facilities because they use heat-stable vaccines that do not require a cold-chain. The ICER of opting for that choice, represented by the line X–Z, is not only more favourable than intervention Y, but is even better than the current ACER, and preferable to intervention X at any coverage level beyond X2.

Table 14. Average, marginal and incremental cost-effectiveness and intervention choices – comparison of three ways to deliver vaccination
(Note: numbers are for illustration purposes)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Total costs</th>
<th>Total effects</th>
<th>ACER</th>
<th>MCER</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>100</td>
<td>10</td>
<td>= 10\times(100/10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>X1</td>
<td>180</td>
<td>12</td>
<td>= 15\times(180/12)</td>
<td>( = 40 ) compared to X, i.e. ( (180–100)/(12–10) )</td>
<td>—</td>
</tr>
<tr>
<td>X2</td>
<td>63</td>
<td>7</td>
<td>= 9\times(63/7)</td>
<td>= 12.3 compared to X1, i.e. ( (100–63)/(10–7) )</td>
<td>—</td>
</tr>
<tr>
<td>Y</td>
<td>250</td>
<td>20</td>
<td>= 12.5\times(250/20)</td>
<td>—</td>
<td>( = 15 ) compared to X, i.e. ( (250–100)/(20–10) )</td>
</tr>
<tr>
<td>Z</td>
<td>125</td>
<td>20</td>
<td>= 6.25</td>
<td>—</td>
<td>( = 2.5 ) compared to X, i.e. ( (125–100)/(20–10) )</td>
</tr>
<tr>
<td>Z2</td>
<td>100</td>
<td>16</td>
<td>= 6.25</td>
<td>—</td>
<td>( = 6.25 ) compared to Z (assumes that intervention Z is perfectly divisible and exhibits constant returns to scale)</td>
</tr>
</tbody>
</table>

Z2 weakly dominates Z because it has the same cost but is more effective.
If intervention \( Z \) is divisible (meaning that it can be operated at any desired scale, such as \( Z_2 \)), then it is preferable to \( X \) at a cost of \( C_2 \) because of the additional effect \( E^{2*} - E_2 \). Compared with intervention \( X \), intervention \( Z \) is better in both dimensions (same cost and greater effectiveness), so it is to be preferred through extended dominance, and is said to weakly dominate \( X \). However, intervention \( X \) would dominate any other treatment that is both more costly and less effective. If a maximum acceptable willingness-to-pay threshold value for the ICER is determined, then any intervention that falls below it would be acceptable, and any that falls above it would not be (Fig. 8). However, uncertainty about the estimates of cost, effects and hence cost-effectiveness means that the classification of cost-effective and cost-ineffective interventions should not be made on the basis of such point estimates of cost-effectiveness.

8.5.2 Probabilistic cost-effectiveness analysis (PROBCEA)

We refer to probabilistic cost-effectiveness analysis, when uncertainty around model choices and parameters are specified and propagated in a probabilistic way, i.e. probabilities are assigned to each of the model choices/parameter values.

8.5.2.1 PROBCEA: Does the intervention result in net cost savings and/or health losses?

As for deterministic cost-effectiveness analysis, it is informative to plot the incremental costs and incremental effects of each intervention in the cost-effectiveness plane. Whereas in case of deterministic cost-effectiveness analysis (ignoring uncertainty) this results in a single point on the cost-effectiveness plane for each intervention, in case of probabilistic cost-effectiveness analysis, this results in a cloud of points for each intervention (Fig. 10).

**Fig. 10. Cost-effectiveness plane using probabilistic cost-effectiveness analysis**
(with 2 of 10 possible frontiers shown)
8.5.2.2 PROBCEA: What is the most optimal option from a set of interventions?

The concepts of dominance and extended dominance are not straightforward to use when uncertainty is accounted for in a probabilistic way, instead the most optimal strategy is the strategy which is on average most cost-effective (e.g. resulting in the highest average net benefit). The rationale for this is explained in the next paragraphs (based on Briggs et al. (214)).

Let us continue with the example explained in section 8.5.1.3 but assuming only interventions Y and Z are considered as alternatives for the current intervention X, as well as two other interventions P and Q which are increasingly more effective than intervention Z, but at a higher cost (Fig. 10).

As mentioned before, one of the main outcomes of a probabilistic cost-effectiveness analysis are $n$ incremental cost and incremental effect values for each intervention compared to the current situation (with $n$ being the number of samples drawn from the input distributions/the number of model iterations). For each intervention, these $n$ incremental cost and effect values can be plotted on the cost-effectiveness plane, resulting in a cloud of points (Fig. 10 above). For each of the iterations of the model, the frontier can be identified (Fig. 10 above). It is clear that intervention Y would not be preferred over intervention Z, P or Q based on cost-effectiveness, as all the points of Y fall to the left and above all the points of the three other interventions. However, for interventions P and Q it is not so clear, because they may form part of the frontier in some of the samples. In Fig. 10 intervention Q forms part of the frontier based on sample 1, but does not form part of the frontier based on sample 2. Table 15 summarizes the proportion of frontiers of which a particular intervention forms part of, when for each of the ten samples a frontier is constructed (Fig. 10). For instance, in Fig. 10 the green intervention is part of the frontier based on sample 1, but not part of the frontier based on sample 2.

Table 15. For each intervention the % of frontiers they are part of

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Percentage of frontiers (out of 10 in Fig. 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>100%</td>
</tr>
<tr>
<td>Y</td>
<td>0%</td>
</tr>
<tr>
<td>Z</td>
<td>100%</td>
</tr>
<tr>
<td>Q</td>
<td>40%</td>
</tr>
<tr>
<td>P</td>
<td>70%</td>
</tr>
</tbody>
</table>

Intervention Q forms part of the frontier in 40% of simulations, but it is not so clear how to use this information for decision making. However, given a WTP value, the most optimal strategy can be identified for each model iteration. That is, for each sample the frontier can be identified, and incremental cost-effectiveness ratios can be calculated along each frontier. Then, given a WTP value, the most optimal strategy can be identified by comparing their incremental costs and effects for each frontier (i.e. using the same approach as explained above for deterministic cost-effectiveness analysis).

However, the net benefit framework offers a more straightforward approach to determine which strategy is the most optimal. The average incremental net benefit between any 2 strategies can be calculated from the difference between their individual average net benefits. This is not true for average cost-effectiveness ratios. Therefore, given a willingness-to-pay value, the strategy of choice from all the interventions under evaluation will be the strategy resulting in the highest expected net benefit.
(average) incremental net benefit. Different plots can be used to identify and/or present the strategy of choice for a range of WTP values. The expected incremental net benefit plot shows for each strategy the expected incremental net benefit for a range of WTP values (e.g. \( (215) \)). As such, for a given WTP value, the strategy with the highest expected incremental net benefit can be identified. The cost-effectiveness acceptability frontier shows the strategy of choice (most optimal strategy) over a range of willingness-to-pay values (see also section 8.5.2.4). The expected net loss frontier shows for a range of WTP values the strategy that minimises the expected net loss or equivalently, the strategy that maximises the expected incremental net benefit \((216)\). The optimal strategy may change when the willingness to pay threshold value changes. Note that the strategy of choice cannot be identified from cost-effectiveness acceptability curves (CEACs, see section 8.5.2.4).

8.5.2.3 PROBCEA: How certain are we that an intervention is the most optimal option from a set of interventions?

The proportion of samples in which a strategy results in highest INB among the \( n \) iterations of the model, provides information on the strength of evidence in favour of that strategy. This is also plotted as part of cost-effectiveness acceptability curves and the cost-effectiveness acceptability frontier (see section 8.5.2.4).

8.5.2.4 PROBCEA: Cost-effectiveness acceptability curves and the cost-effectiveness acceptability frontier

Cost-effectiveness acceptability curves (CEACs) plot the proportion of times a strategy has the highest net benefit, for all strategies \((204, 217)\). The cost-effectiveness acceptability frontier (CEAF) plots the proportion of times a strategy has the highest net benefit, only for the most optimal strategy \((218)\). The most optimal strategy is the strategy that is on average the most cost-effective (i.e. has highest average INB, see section 8.5.2.2). This takes into account the magnitude of the expected net benefit. CEACs only show the probability that a strategy yields the highest net benefit, but do not show how high this net benefit is. Hence, CEACs should not be used to identify the most optimal strategy (except when the INBs follow a symmetrical distribution\(^1\)). Indeed, the strategy with the highest average INB has not necessarily the highest probability to result in the highest INB \((218)\).

This is illustrated by the example in Table 16. Table 16 shows the incremental net benefit of two strategies compared to the current situation. Uncertainty is accounted for in a probabilistic way, which is why there are four INB values for each strategy (four iterations of the model in this example). For each strategy, the average INB is simply the average of the INB values for all iterations. Table 16 shows that intervention option 2

\(^{17}\) Note that this assumes risk-neutral decision-makers. Other decision criteria have been proposed to identify the optimal strategy from a set of interventions, e.g. the strategy with the maximum median INB (Claxton, Journal of Health Economics 1999) or with a 95% probability to result in highest INB (Basu and Meltzer, Medical Decision Making 2018), instead of the strategy with maximum expected (mean) NB.

\(^{18}\) CEACs can be used to identify the most optimal option if the \( n \) INBs for each strategy follow a symmetrical distribution. In that case the average and median INB will be the same, and the strategy with highest average INB will also have highest probability to result in highest INB.
results in the highest average INB, i.e. $2225. Hence, intervention option 2 should be preferred over intervention option 1.

To assess how certain we are about intervention option 2 being preferred, we need to calculate probabilities. Table 16 shows that intervention 1 has a 75% probability to be the most cost-effective: in 3 out of 4 samples it has the highest INB. Intervention 2 has a 25% probability to be the most cost-effective.

Table 16. Results of a hypothetical cost-effectiveness analysis comparing two intervention options to the current situation, at a willingness-to-pay value of $200 per DALY averted. Uncertainty is accounted for in a probabilistic way, which is why there are n incremental net benefits (INBs) for each intervention option (n = 4 for this example)

<table>
<thead>
<tr>
<th>Iteration/sample</th>
<th>INB intervention option 1</th>
<th>INB intervention option 2</th>
<th>Intervention with highest INB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1600</td>
<td>1500</td>
<td>option 1</td>
</tr>
<tr>
<td>2</td>
<td>1950</td>
<td>1900</td>
<td>option 1</td>
</tr>
<tr>
<td>3</td>
<td>2300</td>
<td>3800</td>
<td>option 2</td>
</tr>
<tr>
<td>4</td>
<td>1800</td>
<td>1700</td>
<td>option 1</td>
</tr>
<tr>
<td>Average INB</td>
<td>1913</td>
<td>2225</td>
<td>option 1: 3/4 = 0.75</td>
</tr>
<tr>
<td>Probability to result in highest INB</td>
<td></td>
<td>option 2: 1/4 = 0.25</td>
<td></td>
</tr>
</tbody>
</table>

Hence, intervention option 2 is preferred, although it has only 25% probability to be the most cost-effective. This is because also the magnitude of the expected INB is accounted for: intervention option 2 has 25% probability to yield very large INBs ($3800). If we would choose intervention option 1, because it has the highest probability to be the most cost-effective, we would not maximize our net benefit: our expected INB would be $2188 although it could be $2450.

Based on the information from Table 16, we can construct the CEACs and the CEAF (Fig. 11). Only two dots and a single dot is plotted for the CEACs and CEAF, respectively, as Table 16 showed the results for only a single willingness-to-pay value. When considering results over a range of willingness-to-pay values, CEACs and CEAF form curves (which connect the dots for the different willingness-to-pay values considered). This is illustrated in Fig. 12 and Fig. 13. The next paragraphs explain how to interpret the CEACs and CEAF.

Fig. 12 shows the CEACs for the current strategy (no vaccination) and three different vaccination strategies. The green line crosses the black line at a willingness-to-pay value around US$ 1900 per DALY averted. This means that if a decision maker is willing-to-pay US$ 1900 or more per DALY averted, the green vaccination strategy has the highest probability to have the highest net benefit (i.e. a higher net benefit than the no vaccination strategy (black) and the blue and red vaccination strategies). If a decision-maker is willing-to-pay less than US$ 1900 per DALY averted, the current strategy (no vaccination, black) has the highest probability to have the highest net benefit. However, if we look at Fig. 13, the green strategy is the most optimal strategy.
(has the highest expected (or average) net benefit) from a willingness-to-pay value of US$ 950 per DALY averted. Hence for this example, if a decision-maker is willing-to-pay US$ 1000 per DALY averted, and s/he had to choose between keeping the current situation (no vaccination, black) or implementing one of three vaccination strategies (red, blue or green) based on current information on cost-effectiveness alone, s/he would choose the green vaccination strategy (i.e. based on Fig. 13). However, the uncertainty around this decision is substantial, as for a WTP value of US$ 1000 per DALY averted, the probability that the green strategy has the highest net benefit, is only about 25% (Fig. 12 and Fig. 13).

Fig. 11. Example of a fragment cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) when only considering a single willingness-to-pay threshold (i.e. US$ 200 per DALY averted), as shown in Table 16

![CEAC and CEAF](image1)

Fig. 12. Example of cost-effectiveness acceptability curves: probability highest net benefit for the current strategy (no vaccination, black) and three different vaccination strategies (highlighted in blue, red and green), for a range of willingness-to-pay values

![Cost-effectiveness acceptability curves](image2)
CEACs can be constructed using both the ICER or INB, but when there are more than two intervention strategies to choose from, the INB approach is easier to implement and interpret (204). For more guidance on how to construct and interpret cost-effectiveness acceptability curves, see for instance Briggs et al. (214).

In summary, the most optimal strategy for a given willingness-to-pay value is the strategy with the maximum expected net benefit (210), which can be identified from the cost-effectiveness acceptability frontier. The frontier additionally shows the probability that the most optimal strategy has the highest net benefit among the competing interventions evaluated. If for a range of plausible willingness-to-pay values, there is more than one preferred intervention and/or the probability that the most optimal strategy results in highest net benefit is relatively low, it is worth looking further in what causes this uncertainty, see section 8.6.

8.5.2.5 PROBCEA: Is there value in conducting further research?

If there exists substantial uncertainty about which strategy should be chosen given current information on cost-effectiveness, it may be worthwhile to assess the value of obtaining more information (179, 210, 219). The expected value of perfect information (EVPI) is the price that one is willing to pay to have perfect information regarding all uncertain aspects of the disease and interventions under study that influence which strategy is preferred based on cost-effectiveness analysis. In other words, EVPI is the value (in monetary terms) of eliminating all uncertainties of a cost-effectiveness analysis. EVPI is calculated as the difference between the expected net benefit of a decision...
made with perfect information (no uncertainty) and with current information (with uncertainty). It accounts for both the probability of making a wrong decision (cfr. CEAC) and the cost of making a wrong decision. If EVPI is larger than the cost of designing and conducting studies to obtain perfect information on all uncertain aspects of the disease and interventions under study, then further research may be justified (this is a necessary but not sufficient condition). The EVPI can be calculated for a range of willingness-to-pay values based on the results of a probabilistic cost-effectiveness analysis (i.e. a set of incremental costs and incremental effects for each strategy).

Note that if the cost-effectiveness of a strategy is subject to much uncertainty, this does not necessarily imply that the choice of the preferred strategy (i.e. which decision to take) at a particular willingness to pay value is also subject to a similarly large uncertainty.

In practice, it will rarely be possible to obtain perfect information about all uncertain aspects in a new study, i.e. to eliminate uncertainty completely. It may then be more relevant to calculate the expected value of sample information (EVSI). The EVSI estimates the value of a decision to collect additional sample information. Typically, additional research reduces, rather than eliminates uncertainty (i.e. perfect information will almost never be available). EVSI can be utilized to help determine the optimal research design (study population, comparisons to be tested, sample size) to maximize both the reduction in uncertainty and the value to society of conducting the study (220).

The EVPI and EVSI can also be calculated for each uncertain parameter separately and/or for groups of uncertain parameters. This is discussed further under section 8.6.4.

8.5.3 Deterministic and probabilistic cost-effectiveness analysis combined

This occurs when part of the uncertainty is specified in a deterministic way (e.g. two different scenarios: health care payer perspective and societal perspective) and part of the uncertainty is specified in a probabilistic way. In this case, the most optimal strategy should be identified for each scenario (as described in section 8.5.2).

8.6 Identifying what causes (decision) uncertainty

If substantial uncertainty exists about whether a (set of) strategy(s) is optimal, it is worthwhile to identify which of the uncertain characteristics of the disease and intervention under study are the major drivers of this uncertainty. Substantial uncertainty exists for instance when the most optimal strategy for a given willingness-to-pay value (i.e. the strategy with the highest expected net benefit) has a relative low probability to be the most optimal one (i.e. has the highest net benefit in only a small percentage of all simulations) and/or when for a plausible range of willingness-to-pay values, more than one strategy is optimal.

Identifying what causes (decision) uncertainty can be useful for different reasons. Depending on the question of interest, different methods exist.

1) To understand the impact of individual variables/models on the outcome of interest. This helps to understand the analyst’s own model and to identify the conditions under which the results may change.
• How does the outcome of interest change when using different input parameter value(s), or when using a different model or methodological choice? → univariate and multivariate sensitivity/scenario analysis:
  – Which (combination of) input parameter values cause health losses, or which (combination of) input parameter values cause savings? → threshold analysis;
  – What are the minimum conditions for an intervention to become cost-effective? → threshold analysis.

• How influential are model choices for the results? → multi-model comparisons, potentially involving different research teams.

• Which uncertain aspects of the disease and interventions under study induce most uncertainty in incremental costs, incremental effects, cost-effectiveness ratios and/or net benefits? → variable importance measures.

2) To set future research priorities.

• Which uncertain aspects of the disease and interventions under study induce most decision uncertainty? → expected value of information for parameters.

The methods that can be used to get insight in each of these questions, are described in the next paragraphs.

8.6.1 How does the outcome of interest change when using different input parameter value(s), and/or different model(s) and/or methodological choice(s)?

Deterministic sensitivity analysis (DSA) is a method that can be used to investigate the sensitivity of the results from a model-based analysis to variations in a specific input parameter, set of parameters and/or model structures. One or more parameters and/or model structures are manually changed (usually across a pre-specified range/set of options) and the results are analysed to determine to what extent the change has an impact on the output values.

The principal methods for handling uncertainty in a deterministic way are (142):

• One-way (univariate) sensitivity analysis: parameter estimates are varied one at a time, keeping all others constant, in order to investigate the impact on study findings. Threshold analysis is a particular form of one-way sensitivity analysis;

• Threshold analysis: the value of a parameter is varied to find the “tipping point”, i.e. the level at which the results change, e.g. the price per dose at which an intervention becomes cost-effective compared to the current situation – this would determine the threshold, sometimes referred to as the switching price. Threshold analysis can also be used to find the value of an uncertain input parameter at which the results change (e.g. the minimum value of disease incidence at which an intervention becomes cost-effective). One particular type of threshold analysis that is useful in economic evaluation of vaccines is the break-even analysis, which determines the price per dose at which the intervention becomes cost-saving, i.e. at which the cost of a programme is offset by treatment cost savings. However, because the overall
uncertainty in the cost-effectiveness ratio depends on the combined variability of several factors, multi-way sensitivity analysis can be useful;

- Multi-way (multivariate) sensitivity analysis: this type of analysis explores the impact on the results of changing the value of two or more parameters at the same time, e.g. disease incidence and vaccine price. Scenario analysis is another type of multi-way sensitivity analysis;

- Scenario analysis: two types of scenario analysis are considered here. The first is the analysis of the set of extreme circumstances across parameters, also known as a ‘max-min’ analysis or ‘worst/best’ case analysis. In this case the parameter values that yield the worst (lowest)/best (highest) INB are combined. The second is the use of an agreed ‘reference case’ of methods and conceptual choices, and how these should be varied (e.g. different perspectives, different sets of discount rates). Such reference cases are increasingly available at a per-country level. The best known reference case is described by Gold et al. (221), who set out the methodological guidance from the report of the Panel on Cost-Effectiveness and Medicine in the United States; it is particularly aimed at increasing the quality and comparability of results across interventions and reducing what Briggs et al. (223) call ‘methodological uncertainty’. While the present guide does not go quite so far in terms of defining a reference case, adherence to the recommendations contained herein should improve the quality and comparability of economic evaluations of immunization programmes;

- Sensitivity analysis on varying the structure of the model (to explore model structure uncertainty).

The results of DSA are usually expressed as line graphs or bar charts. A ‘tornado chart’ refers to a summary (stack) of bar graphs representing univariate sensitivity analyses for a wide range of input values, ordered according to the extent (spread) of variation of the resulting model output value (with the widest variation on top).

Univariate sensitivity analyses is however not recommended for input parameters which are correlated. The impact of such parameters should be evaluated together. Also, in principle ‘any arbitrary value’ can be used in univariate sensitivity analysis if the aim is to explore the model (i.e. not to generate results for decision makers). However, in order to communicate the results, the ranges of input values should reflect ranges informed by the available evidence or a wide range in case no evidence is available (i.e. not arbitrary 50% up and down).

8.6.2 How much do the model choices impact the results?
Another approach to sensitivity analysis involves comparing the results of different model structures, potentially involving models of different research groups. Input values are chosen to be the same/similar for all models, so that the outputs produced by the different models mainly reflect structural differences between the models (177, 222, 224).

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19 See their Appendix A and applications of the reference case given in Appendices B and C in Gold et al. (221).
8.6.3 Which uncertain aspects of the disease and interventions under study induce most uncertainty in incremental costs, incremental effects, cost-effectiveness ratios and/or net benefits?

With deterministic sensitivity analysis, the results focus on the most influential parameters (e.g. univariate sensitivity analysis). Whereas with PSA all uncertainty is shown at once in the results, and further methods are needed to identify the most influential uncertainties. Variable importance measures quantify the impact of the uncertainties incorporated in the PSA on the incremental costs, effects and cost-effectiveness (e.g. standardized regression coefficients, coefficients of determination, or variable importance lists (22, 179). The larger the variable importance measure, the more the uncertain input parameter causes uncertainty in incremental costs, effects and cost-effectiveness.

8.6.4 Which uncertain aspects of the disease and interventions under study induce most decision uncertainty?

The EVPI and EVSI discussed in section 8.5.2.5 can be obtained for single or groups of uncertain input parameters (‘expected value of partially perfect information (EVPPI)’ and ‘Expected value of partially sample information (EVPSI)’). As such, they can inform for which particular uncertain aspects of the disease and intervention under study, obtaining more evidence may be (most) valuable.

Fig. 14 below shows the estimated EVPPI for each uncertain input parameter of a health economic evaluation of three different vaccination strategies. For each uncertain input parameter (i.e. each coloured line in the plot), EVPPI was estimated for a range of willingness-to-pay values. If a decision maker is willing-to-pay US$ 125 per DALY averted, there is a lot of uncertainty about which strategy yields the highest net benefit (high EVPPI values). This uncertainty is caused mainly by the uncertainty around the probability to die if hospitalized for typhoid fever (solid light-blue line in Fig. 14). If the decision maker is willing-to-pay US$ 500 per DALY averted, there is less decision uncertainty, and it is caused solely by the uncertainty around the probability to die if hospitalized for typhoid fever (the EVPPI for all other uncertain input parameters is US$ 0).

8.7 General approach and presenting results to decision makers

We recommend beginning with understanding the impact of individual variables/models by conducting one-way sensitivity analyses, and/or by obtaining variable importance measures and/or value of information measures for individual uncertain parameters. This helps to understand your own model, but the results of this should not necessarily be presented to decision makers. However, analysts should present an analysis of extremes to assess the robustness of the findings to changes in the value of multiple parameters/models at the same time, i.e. analysts should show the complete range of uncertainty in their results. Where a best or worst case scenario changes the conclusions, analysts should perform a probabilistic sensitivity analysis and identify the most optimal strategy for a given willingness-to-pay value as the strategy with the highest expected net benefit. To direct future research, value of information analysis can be performed. We also recommend that analysts place their findings in a broader context by comparing them to other economic evaluations that have been undertaken in the same or similar countries (after relevant adjustments have been made, e.g. purchasing power and/or inflation).
8.8 Recommendations

- Analysts should give a detailed overview of the uncertainties (not) accounted for in their analysis, including for each potential source of uncertainty a rationale for the extent of uncertainty incorporated or a justification why uncertainty was not incorporated.

- Methodological uncertainty should be accounted for with scenario analysis while model- and parameter uncertainty should preferably be accounted for in a probabilistic way. If it makes more sense to account for particular model- or parameter uncertainties in a scenario analysis, this should be justified.

- Analysts should present the full range of potential cost-effectiveness results, at a minimum as a best/worst case scenario analysis, but preferably by showing the results of a probabilistic sensitivity analysis, that is inclusive of all parameters.

- The most cost-effective strategy for a given willingness-to-pay value should be the strategy resulting in the highest expected (or average) net benefit.

- Analysts should present cost-effectiveness results for a range of willingness-to-pay values, reflecting local preferences.

- As a minimum, analysts should assess sensitivity of the results to the following variables: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant), case fatality risks and vaccine price.

- Analysts should also place their findings in broader context by comparing their findings to other economic evaluations that have been undertaken in the same or similar countries after adjustment for inflation and purchasing power.
Chapter 9:
Economic evaluation and the decision-making process

This chapter takes a broader view of the decision-making process. First, it considers the evidence about the use of economic evaluation in practice and policy. Then it describes the range of other criteria relevant for priority setting in health, paying particular attention to equity. Lastly, it summarises literature suggesting conventional economic evaluations of vaccines are too reductionist in their consideration of benefits.

9.1 The use of economic evaluation in policy and practice

There is no doubt that economic evaluation is increasingly being used to guide decisions in health care. Though originally legislated in a few HICs, the acceptance and inclusion of economic evaluation as a required and influential element in the process of policy making has been expanding. Although much of the influence of economic evaluation remains undocumented in the scientific literature, some examples exist for vaccination, both where a positive (Welte et al. (169)) and a negative recommendation (Bos et al. (225)) was influential for policy (see Box 4). Many Health Technology Assessment agencies now keep track of the relationship between their recommendations and the eventual decision that was made (226).

Nonetheless there are still instances where policy has been and remains less inclined to follow evidence provided by economic evaluation.

As there is continuous advancement in methods and tools to perform economic evaluations and to present their results, it is important to align these with the knowledge-base of decision-makers and their advisors. Therefore there should be capacity and opportunity for these policy advisors for regular training in methods for, and in the interpretation of results from, economic evaluation. It should be clear that decision-making procedures will need to be modified to accommodate evidence-based approaches, such as economic evaluation, where this has not yet been the case. Otherwise, economic evaluations (including of immunization programmes) risk being regarded by decision-makers as little more than academic exercises.
Welte et al. (169) estimated the cost-effectiveness of one-time vaccination of all persons aged 14 months to 18 years (catch-up programme) and of routine childhood immunization at either ages 2 + 3 + 4 months, 5 + 6 months, or 14 months with a meningococcal C conjugate vaccine from a societal and a health care payer perspective. The results showed that all vaccination options yield a substantial health gain and that the catch-up programme and routine vaccination at 14 months render favorable cost-effectiveness ratios. In comparison to vaccination at 14 months, routine childhood vaccination during the first year of life was shown to be much less cost-effective. These results played a major role in the decision to add meningococcal C vaccination to the routine childhood immunization schedule at 14 months and to implement a catch-up vaccination programme in The Netherlands in 2002.

Bos et al. (225) estimated the cost-effectiveness of universal infant vaccination with a 7-valent conjugate pneumococcal vaccine. In the Netherlands, a cost-effectiveness ratio of less than €20 000 per LYG or QALY was at that time considered as the threshold willingness to pay value. Their model found a cost-effectiveness ratio of €82 700 per LYG or €71 250 per QALY, both of which are above this suggested threshold. Partly based on these results, the Dutch Health Council decided that although pneumococcal vaccination of infants ideally ought to be incorporated into the routine vaccination schedule in the Netherlands, the unfavorable cost-effectiveness profile and the high budget impact impedes introduction at the moment.

9.2 Decision-making bodies

While a rising number of countries have separate National Immunization Technical Advisory Groups (NITAGs), which use evidence on cost-effectiveness of vaccination strategies and exert great influence on policy, e.g. the United Kingdom’s Joint Committee on Vaccination and Immunisation and the United States’ Advisory Committee on Immunization Practices20, many do not – or else their financial backing is only sufficient to sustain advice on the basis of the literature and ad hoc expert opinion. Most GAVI-eligible countries, however, have little or limited access to formal advisory bodies to review immunization data and provide independent advice to their respective governments.

There is a need to support the establishment of national or regional processes to enhance evidence-based decision-making in immunization, and health more generally, in

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20 By way of example, the Advisory Committee on Immunization Practices is comprised of 12–15 experts in immunization practices, public health, use of vaccines in clinical practice, assessment of vaccine safety and efficacy, consumer perspective and/or social and community aspects of immunization (one consumer representative). There are also eight non-voting ex-officio members from the Food and Drug Administration, National Vaccine Program Office and a number of non-voting liaison members from approximately 20 organizations (e.g. American Medical Association, industry groups, the United Kingdom’s Department of Health, and equivalent groups from Mexico and Canada).
order to routinely and formally address the range of questions described in Chapter 3, such as whether, when and how a new vaccine should be introduced. In order to make informed decisions, countries need to have both the necessary evidence and clear processes. Much work has been done (for example see Jauregui et al. (227) for Latin America and Wilkinson et al. (8) for iDSI) to develop the evidence base countries need for making informed decisions, but less effort has thus far been expended to ensure that countries have processes in place to evaluate and use this information. In this context, it is important to create an enabling environment for NITAGs to consider the evidence (including model-based and economic evidence) independently to formulate vaccine policy recommendations in an interactive process with Ministries of Health. While there has been a gradual evolution to establish and strengthen NITAGs in LMICs, the consideration of cost-effectiveness evidence in these processes remains limited in most places up to now (228).

Using cost-effectiveness information in priority setting and decision making is challenging, but necessary in order to increase efficiency of health system spending whilst working toward Universal Health Coverage (UHC). However cost-effectiveness alone is not sufficient to make reimbursement decisions. Countries should consider establishing context-specific processes for decision making that are supported by legislation, have stakeholder buy-in and are transparent, consistent and fair. Cost-effectiveness ratios are undoubtedly informative in assessing value for money. However, they need to be considered alongside other quantitative measures such as feasibility and budget impact, as well as value-based considerations such as fairness (202).

9.3 Equity-related criteria

The emphasis of this guide is on value for money – that is, whether a vaccination strategy is worth investing in – and not on who pays for it. If the objective is to decide how to spend public funds, economic evaluation is only one of at least nine criteria relevant for priority-setting in health (229). Cost alone matters, as do the capacities of potential beneficiaries to pay for an intervention. The other criteria that may affect priorities include horizontal equity (equal treatment for people in equal circumstances); vertical equity (priority for people with worse problems); adequacy of demand; and public attitudes and wants. Two criteria – whether an intervention is a public good and whether it yields substantial externalities – are classic justifications for public intervention, because private markets could not supply them efficiently.

Equity, poverty, and risk of impoverishment from ill health may also influence priorities; so do the budgets available, and the decisions of how much to make available for buying interventions. Finally, the effectiveness of an intervention and, therefore, the degree to which it deserves priority depend on how far it is culturally appropriate or acceptable for the population it is intended to benefit. An identical intervention, technically speaking, may lead to different degrees of use or compliance in different population groups, and information and incentives may be needed to achieve the full potential outcomes.

Sometimes two criteria will be incompatible, forcing difficult choices to be made, particularly when the choice is between efficiency and equity. While it might be more efficient to introduce a new vaccine rather than vaccinate more people with the same
vaccines, the inequitable clustering of interventions at the level of the child raises the possibility that the introduction of new vaccines might primarily benefit children who are already covered by existing interventions (230). Furthermore, in general, the population likely to be vaccinated with a new vaccine will differ in some important features from the population likely to be unvaccinated that is at risk from the same disease; it will be richer, or more urban, or may differ in education, religion or whatever other characteristics affect the likelihood of coverage. Whenever the currently unprotected population is at equal or greater risk than those already covered, and in addition suffers some equity-related disadvantage such as poverty, any move in the direction of universal coverage is likely to be equity-enhancing whether it improves or worsens cost-effectiveness. Therefore, analysts are urged to consider the distributional impacts of the vaccine(s) analysed and to note how far its introduction would affect equity.

When equity is considered to be an objective inherent to social welfare, policy makers may aim to achieve social justice, understood in terms of a broader commitment to secure a sufficient level of health for all and to narrow unjust inequalities. In this case, policy makers could benefit from separate analyses on equity alone or equity and efficiency side-by-side to support deliberation. The latter can be provided by so-called Extended cost effectiveness analysis (ECEA). Equity can also be considered a constraint on the goal to maximize welfare across the population and therefore an overarching analytical framework to quantify trade-offs between efficiency and equity in the whole population may be adopted. This can be done, using distributional cost effectiveness analysis (DCEA), which is a relatively recent development in health economics.

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9.4 Potential “broader” benefits of vaccines

Vaccines can be considered a special group of drugs, as they are often implemented on a large scale, and often act against infectious diseases that are highly prevalent in infancy and childhood. Infections can have short and long term health and non-health consequences. For these reasons the scope of the different impacts of vaccination may be broader than that of other health technology (149). The benefits we discuss briefly in this section have often been ignored in economic evaluations, and have been termed “broader” benefits of vaccinations, to underline that such benefits fall outside the scope of traditional health economic analyses (25, 51, 52, 234).
In traditional health economic evaluation it is a given that at least averted direct health care costs, as well as health gains in vaccine recipients are included. Chapter 3 discussed different perspectives, indicating that the aversion of indirect costs of lost (productive) time arising to patients and their caregivers should also be included when adopting a societal perspective. This principle is well-established in economic theory, but most countries prefer to adopt a narrower perspective, where only costs arising to the health care budget holder are considered relevant for policy. Inclusion of illness and care-related productivity gains from interventions is not an issue specific to vaccines, and is the subject of debate in the wider health economic literature (235, 236). As explained in Chapter 3, this guide advocates a societal perspective, but also advises analysts to apply the perspective mandated by the decision makers for whom the analysis is meant, in order to make a timely analysis for policy. Showing results from both the societal and the mandatory narrower perspective is considered best practice in those circumstances. Chapter 3 also explicitly recommends considering whether incorporating broader economic impacts of a vaccination can be included, and whether this would be consistent with the policy context.

As explained in Chapter 5 and Chapter 6, the potential impact of vaccines on the transmission dynamics of pathogens, calls for a careful consideration of their health consequences at the population level, in both vaccinated and unvaccinated persons. These indirect transmission-dependent effects include altered exposure risks, with modifications in risk of infection by age, in risk of clinical disease and associated resource use (e.g. hospitalisations), in probability of natural boosting and in use of antimicrobials (and therefore in contributions to antimicrobial resistance). Despite the fact that these direct and indirect effects, have been generally acknowledged vaccine attributable phenomena for a long time, it was not until the 21st century that part of these indirect effects – herd immunity effects – were frequently quantified as part of economic evaluations of vaccines. Still, since they usually require stronger assumptions than models without herd effects, the quantification of some of these other indirect effects, such as the contributions of specific vaccines to reduced antimicrobial resistance, remain to date largely unexplored. While diagnostic tools may also stimulate more appropriate antibiotic prescribing and reduce AMR, the scope for this from potentially widespread childhood vaccinations, such as pneumococcal conjugate and influenza vaccination, is undeniable. Yet it remains rare in health economic evaluation that the impact on AMR is included as an attributable benefit from widespread use of a specific vaccine, because it is difficult to estimate and may be difficult to justify, although there is no question that it is a benefit from vaccination (see for instance (237)).

Similarly, the macroeconomic impact of potentially disruptive events – public health emergencies of international concern – like a pandemic with a high case-fatality ratio, have rarely been quantified, and are almost never considered as part of health economic evaluations of funding decisions, even if these would contribute to controlling or preventing such major disruptive events (46, 238). In Chapter 3, macroeconomic analysis was also listed as an exceptional possibility to help guide policy in this respect.

Furthermore other benefits due to vaccination include non-use value, arising from the piece of mind derived from knowing that one lives in a society where receiving an effective and safe vaccine is possible, or subsidized, and the safety net generated by herd immunity is maintained for those who cannot be protected by vaccination (e.g. im-
munocompromised persons). Further there is also the routinely excluded use value, or positive utility, through the peace of mind from having received a vaccination against a potentially lethal disease (42, 146). Although the risk of disease prevented by a licensed vaccine should on average outweigh by far the risk of adverse effects from this vaccine, this peace of mind would be partially counterbalanced by a disutility from anxiety caused by not knowing with certainty whether a vaccine will be 100% effective and 100% safe for the specific person receiving it.

Setting up and maintaining a vaccination programme is a complex undertaking, which can bring opportunities to achieve economies of scale and scope, by facilitating the addition of different preventive, curative or social interventions on the infrastructure needed to deliver vaccines, including subsequent vaccine introductions. Such structural benefits are rarely attributed to the value of introducing a specific vaccination programme, when it is subject to health economic evaluation, even if its costs are included (as discussed in Chapter 4) (239, 240).

When it comes to valuing the consequences of health gains from vaccination – be it directly obtained in vaccinated persons, or indirectly in unvaccinated persons through herd immunity – it has been argued that these can be different from many other interventions, because such gains arise often as a result of primary prevention, in many people simultaneously and often early in life. These health gains are argued to generate additional benefits, as healthier people are more likely to lead lives that are more productive at the individual, the household and the community level. The underlying mechanisms can be made clear through the following examples, which are discussed along with other examples in reviews by Jit et al. (241) and Deogaonkar et al. (242):

- Healthier children are better able to attend school and learn more effectively while in class.
- Healthier workers are less absent from work, and more productive at work, because they are better equipped, both physically and mentally. When the whole community enjoys better health, then this is reinforced as workers would have to interrupt their normal activities less frequently to take care of others.
- Better health prospects influence household choices related to fertility, and consumption and investment per child, leading to improved female labour participation and dependency ratios.
- Better health prospects create greater incentives to save for retirement, and this can take place over a longer period if longevity increases, providing better conditions for investments and employment.

The relevance of these effects is borne out by work demonstrating the link from improved health to economic growth (243). This research has demonstrated the importance of health interventions for achieving growth. The production of wealth through health improvements is a cyclical process where health generates wealth and well-being, leading to more health, which in turn stimulates productivity. Vaccination is likely one of the main instigators setting this process in motion in low income countries, and maintaining its momentum as communities and countries continue to grow and create wealth, but this process is also subject to the law of diminishing marginal returns. In sum, economic evaluations, as currently conducted, are likely to underesti-
mate the economy-wide benefits of any intervention aimed at preventing infectious diseases, and particularly so in low and lower middle income countries (25). It is also in these countries that the redistributive consequences of vaccination, which improve health equity, would also in turn lead to better average population health (see also previous section).

Since many of these hard-to-quantify broader impacts seem undeniable, it is important that policy makers are aware that these are not reckoned with in traditional economic evaluation. Further research into estimating such broader impacts (see for instance (244, 245)), to which extent they arise for different interventions (ie, what is unique about vaccines/infectious disease prevention versus other interventions), and further efforts to raise awareness for them should lead to broader acceptance of these benefits in policy making, even if they are not (yet) fully quantifiable as part of state-of-the-science applied economic evaluation.

9.5 Budget-impact and multi-product analyses

One of the biggest hurdles for policy makers to adopt new health care technologies is the impact it would have on the payer’s budget, and in particular the health care budget, especially in the short run.

This guide focuses on economic evaluation, and has not attempted to develop specific guidance for budget-impact analysis, mainly because this type of analysis is unlikely to be different for vaccines, as opposed to other health care technology (34, 36). However, there are at least two areas of special interest:

1) A noteworthy difficulty may arise when governments are offered a “package deal”, for instance in terms of simultaneously purchasing different products (including vaccines) from the same company, which would require countries to perform joint (multi-product) economic evaluation and make trade-offs between different product and price combinations assuming a fixed constraint, most commonly a fixed health care budget (see also the 2018 ISPOR guide on economic analyses for vaccines, which advocates such constrained optimization analysis (10)). Full multi-product analysis is rarely performed in practice, but as models become more sophisticated and data availability becomes more detailed and expansive, simultaneous modelling of multiple pathogens – and thence joint economic evaluation and budget-impact analysis – becomes more feasible for researchers and more acceptable and useful for policy makers.

2) The expected price evolution of new vaccines (as with most new and innovative health care technology) is somewhat unpredictable as it depends on the evolutions of competition (determined by the longevity of patent protections, and/or the advent of more innovative products), of the disease burden (e.g. serotype replacement) and of world wide demand (for the product and its substitutes and complements). These price evolutions could have a substantial impact on the cost-effectiveness and budget-impact over time, especially over longer time spans (>5 years).
9.6 Assessing models made by third parties

When model-based economic evaluations are presented to policy makers, they will have to make sure that these submitted models are fully transparent in their assumptions, how they were validated and how they deal with uncertainty. Some models may have used different approaches, hence it is important to understand these differences, and to which extent these approaches are in line with the normative guidelines for the perspective of the decision maker. This guide advises to design local guidelines (at the decision maker’s level, e.g. the level of a country or an autonomous region), in which normative choices are made to enable consistent policy making across interventions in society, or in health care. These choices should minimally include a prescribed perspective and its scope in relation to its costs and benefits, as well as discounting. I.e. it should describe which costs and benefits should be taken into account, and which should not, and how the policy makers will make comparisons across interventions and over time. If different models reach different conclusions, then the policy maker needs to understand why that is, by going for each model through the checklists provided in Chapter 10. Is it due to the assumed vaccine price, the effectiveness, the choice of comparator, etc? Policy makers should be aware of any biases or conflicts of interest of the modellers when appraising the results. Biased results can be produced by having overly optimistic assumptions on for instance delivery costs, duration of effectiveness, QALY or DALY impact, the low value of current practice (as a comparator). The way the model is structured and uncertainty is handled is therefore of ever-increasing importance in HTA: ideally all parameters should be defined by data, and where data are absent, parameter distributions should reflect high uncertainty. A potentially useful guide for formal model comparisons can also be consulted in this context (192).

9.7 Recommendations

- Other important factors for the decision under consideration should be discussed when results are communicated to policy makers. Besides technical study limitations, these other factors typically include equity-related aspects, broader economic benefits, and budget-impact.
Chapter 10: Conclusions and summary of recommendations

Decision-making for vaccines is getting more complex, as vaccines get more expensive, along with other, competing new health technologies. With the advent of new more expensive products, countries face a significant decision-making challenge. Data regarding the relative cost-effectiveness of these products is an important criterion for decision-makers to consider. This guide does not propose any alteration of the general guidelines for economic evaluations, but merely offers a specific interpretation of them with respect to vaccination and advocates a more rigorous application of them in general, including paying special attention to special epidemiological and economic features of vaccine-preventable diseases such as transmissibility.

Economic evaluations in the field of vaccine-preventable diseases, which are often complicated by many parameters and assumptions, should first of all be explicit and transparent. All assumptions should be clearly stated and justified. Sections dealing with methods and assumptions should clearly and explicitly describe all weaknesses of the analysis.

Table 17 summarizes the full list of recommendations made in each chapter. It has also formulated the recommendations as questions, in order to help analysts improve the quality of their evaluations and also to provide a structure for critical appraisal of evaluations by the consumers of economic evaluations. Table 18 provides an example of how to apply the Checklist to a published economic evaluation of an immunization programme.
Table 17. A Checklist for appraising the quality of economic evaluations of immunization programmes

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Attributes of good practice</th>
<th>Questions for critical appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framing the analysis (Chapter 3)</td>
<td>The study question should be well-defined, stated in an answerable form and relevant to the decision the target audience is facing.</td>
<td>Is there a clear statement of the study question?</td>
</tr>
<tr>
<td></td>
<td>The comparators under study should be clearly described. The most relevant comparison for new vaccines is usually current practice. If existing practice itself appears to be cost-ineffective compared to other available options, the analyst should include other relevant options into the analysis, such as a best available alternative, a viable low-cost alternative or a do-nothing option. Non-vaccine interventions against the same disease should be considered where appropriate and should be captured by the current or alternative practice comparators.</td>
<td>Have the comparators been clearly described?</td>
</tr>
<tr>
<td></td>
<td>The type of economic evaluation should be clearly stated and justified. Cost-utility analysis is the preferred type of evaluation (with DALYs or QALYs as outcome measures), although a cost-effectiveness analysis, which presents outcomes using natural units as outcome measures specific to the vaccine(s) in question, is also encouraged.</td>
<td>Has a cost-utility analysis been performed? If not, has that decision been justified appropriately?</td>
</tr>
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<td></td>
<td>The perspective of the analysis should reflect national guidelines if the audience is the national decision maker. Where absent they should adopt the societal perspective, and include all related effects and costs regardless of who benefits from or pays for them. However, the costs borne by providers (e.g. donors and governments), patients and their families and others should be disaggregated as much as possible in order to allow judgments to be made from the perspectives of the various decision-makers.</td>
<td>Is the perspective of the analysis clearly stated? If a societal or multiple perspectives have been adopted, have the costs and outcomes been disaggregated to allow judgments to be made from different perspectives? Are the costs and outcomes reported consistent with the perspective reported?</td>
</tr>
<tr>
<td></td>
<td>The institution(s) sponsoring the study and individual authors should be clearly stated.</td>
<td>Is/are the institution(s) sponsoring the study and the individual authors clearly stated?</td>
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<td></td>
<td>The time frame and analytic horizon should be clearly stated. Their respective durations are contingent on the type of vaccine, the intervention and target population, and thus the type of model developed.</td>
<td>Are the time frame and analytic horizon clearly stated and justified?</td>
</tr>
<tr>
<td></td>
<td>Broader economic benefits besides improved health, reduced health care expenditure and short-term productivity gains can be incorporated if consistent with the way vaccines are funded and the decision-maker(s)’ objectives.</td>
<td>Are broader economic benefits besides improved health, reduced health care expenditure and short-term productivity gains incorporated? If yes, is this consistent with the way vaccines are funded and the decision-maker(s)’ objectives?</td>
</tr>
<tr>
<td>Aspect</td>
<td>Attributes of good practice</td>
<td>Questions for critical appraisal</td>
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<tr>
<td>Costs (Chapter 4)</td>
<td>The methods used for the estimation of costs should be clearly stated.</td>
<td>Have the methods used for the estimation of costs been clearly stated?</td>
</tr>
<tr>
<td></td>
<td>A summary should be provided of the expected resource use and unit costs for each alternative. This should include specifying the assumptions behind the calculations of costs, e.g. amounts and types of health service use with and without the alternative, given a specific coverage of the alternative and indicating actual and potential ranges of each estimate.</td>
<td>Has a summary been provided of the expected resource use and unit costs for each alternative, including a specification of the assumptions behind the cost calculations?</td>
</tr>
<tr>
<td></td>
<td>A full costing study should only be considered if precise estimates are needed and it is considered worth the additional effort involved. Otherwise, it is recommended that standardized WHO-CHOICE estimates be used or existing country-specific cost data if available.</td>
<td>Have the data sources used to estimate costs been clearly stated?</td>
</tr>
<tr>
<td></td>
<td>Costs for patients and their families, including lost productivity if considered, should be reported separately. This guide recognizes that several methods exist for valuing lost productivity; analysts should therefore make clear and justify why a particular method was chosen and set out its pros and cons.</td>
<td>If productivity losses were estimated, have they been reported separately? Has their relevance been discussed? Have the methods used to estimate them been described and justified?</td>
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<td></td>
<td>Future unrelated costs should not be included, both because of the practical difficulties of estimation and because their inclusion involves conceptual and ethical issues concerning differences in incomes, unless it is a requirement of the reference case for the local policy maker, for whom the analysis is meant. In that case, we recommend presenting the results with and without including these costs.</td>
<td>Have future unrelated costs been included? If yes, was this a requirement of the reference case for the local policy maker, for whom the analysis was meant and have the results been presented with and without including these future costs?</td>
</tr>
<tr>
<td></td>
<td>Costs should be reported in local currency units, ideally using the most recent year as the base-year, converted to US$ using official exchange rates for the base-year in question or also converted to $ using purchasing power parity (PPP) exchange rates for the purposes of regional or global comparison.</td>
<td>Is the currency stated? If so, is the date of the currency and prices used in the model stated, with details of any adjustments or conversions provided?</td>
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<td>Aspect</td>
<td>Attributes of good practice</td>
<td>Questions for critical appraisal</td>
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<tr>
<td><strong>Effects</strong> <em>(Chapter 5)</em></td>
<td>Estimates of vaccine efficacy should be based upon systematic reviews of the literature where available, taking account of the biological characteristics of the pathogen in question and how its infectious nature may have influenced the efficacy estimates derived from trials.</td>
<td>Was the evidence on vaccine efficacy identified systematically, and was taken account of the biological characteristics of the pathogen in question and how its infectious nature may have influenced the efficacy estimates derived from trials?</td>
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<td></td>
<td>The effective coverage of vaccines should be calculated by multiplying vaccination coverage (based on relevant resources depending on the type of programme) adjusted for non-compliance, by vaccine efficacy adjusted for loss of potency due to heat and freeze exposure, where such data are available.</td>
<td>Was the effective coverage of vaccines calculated by multiplying vaccination coverage adjusted for non-compliance, by vaccine efficacy adjusted for loss of potency due to heat and freeze exposure, where such data were available?</td>
</tr>
<tr>
<td></td>
<td>The population effectiveness (or “impact”) of vaccines should be calculated using empirical information on both the direct and indirect effects of the vaccination program, where this is available, and requires integrating this information in a mathematical model (see also Chapter 6).</td>
<td>Was the population effectiveness (or “impact”) of vaccines calculated using empirical information on both the direct and indirect effects of the vaccination program, and was this information integrated in a mathematical model?</td>
</tr>
<tr>
<td></td>
<td>If adverse events from immunization are likely to have a substantial impact on the results of the analysis, they should be included on both the costs and effects sides of the analysis. The significance of the impact depends on both their likelihood of occurring as a consequence of vaccination and their severity.</td>
<td>Are adverse events from immunization impacts likely to have a substantial impact on the results of the analysis? If so, have they been included on both the costs and effects sides of the analysis?</td>
</tr>
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<td>Since the estimation of the duration of efficacy, inferred from clinical trials, is influential for the effectiveness and cost-effectiveness of vaccination programs, the duration of protection over time should be as much as possible data driven, made completely transparent and subjected to thorough uncertainty analysis, in line with recommendations in Chapter 8.</td>
<td>Was the estimated duration of vaccine protection over time data driven, completely transparent, and subjected to thorough uncertainty analysis?</td>
</tr>
<tr>
<td></td>
<td>Estimates of burden should be presented in natural units—cases, deaths, years of life lost (YLL). Also years lived with disability (YLD), or years lived with impaired health-related quality of life are informative, and necessary to estimate either DALYs or QALYs lost as recommended final outcome of burden of disease.</td>
<td>Have estimates of burden been presented in natural units – cases, deaths, years of life lost (YLL)? Have estimates of DALYs or QALYs lost been presented as final outcome of burden of disease?</td>
</tr>
<tr>
<td></td>
<td>If suitable QALY weights are not readily available, it is recommended to use DALYs for cost-utility analyses.</td>
<td>If suitable QALY weights were not readily available, have DALYs been used for cost-utility analysis?</td>
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<td></td>
<td>When DALYs are used in cost-utility analysis, like QALYs they should not be subjected to social weighting, such as age weighting, unless explicitly desired by the policy maker the analysis is meant to advise.</td>
<td>When DALYs have been used in cost-utility analysis, were they subjected to social weighting, such as age weighting? If yes, was this explicitly desired by the policy maker the analysis was meant to advise?</td>
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<tr>
<td>Aspect</td>
<td>Attributes of good practice</td>
<td>Questions for critical appraisal</td>
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<tr>
<td><strong>Modelling</strong></td>
<td>The model should be transparent in that the structure and implicit or explicit assumptions are all clearly described and motivated.</td>
<td>Are the model structure and implicit or explicit assumptions clearly described and motivated?</td>
</tr>
<tr>
<td>(Chapter 6)</td>
<td>The model should be static if vaccination is unlikely to change the force of infection in susceptibles or as a means to make a conservative estimate when indirect transmission-dependent effects cannot on the whole be adverse. The model should be dynamic if vaccination is likely to change the force of infection in susceptibles, and a static model would not yield a conservative estimate, or if the conservative estimate from a static model does not lead to an outcome which would be considered favourable by decision makers. The model should be stochastic if chance plays an important role in the transmission process of the pathogen.</td>
<td>Is the model type (static, dynamic or stochastic) clearly stated and justified in the light of likely changes to the force of infection and the role of chance in the transmission process? Have the model’s strengths and weaknesses been discussed?</td>
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<td></td>
<td>The model should be validated, in as many facets of validation (verification, face validity, predictive validity) as possible, but at least verified.</td>
<td>Has the model been validated? If so, has it been validated in as many facets of validation as possible?</td>
</tr>
<tr>
<td><strong>Discounting</strong></td>
<td>Discount costs and effects initially using the rate in the country in question (for studies to inform local decision-makers) and also using WHO recommend schemes of (i) 3% and 0% discounting for consumption and health respectively in the base case, (ii) 3% discounting for both health and consumption.</td>
<td>Is the discount rate clearly stated and justified? Have WHO recommended schemes of (i) 3% and 0% discounting for consumption and health respectively in the base case, and (ii) 3% discounting for both health and consumption been used?</td>
</tr>
<tr>
<td>(Chapter 7)</td>
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</tr>
<tr>
<td><strong>Uncertainty</strong></td>
<td>Analysts should give a detailed overview of the uncertainties (not) accounted for in their analysis, including for each of them a rationale for the extent of uncertainty incorporated or a justification why uncertainty was not incorporated.</td>
<td>Are all known sources of uncertainties not accounted for justified to the extent possible?</td>
</tr>
<tr>
<td>(Chapter 8)</td>
<td>Methodological uncertainty should be accounted for with scenario analysis while model- and parameter uncertainty should preferably be accounted for in a probabilistic way. If it makes more sense to account for particular model- or parameter uncertainties in a scenario analysis, this should be justified.</td>
<td>Have methodological uncertainties been accounted for with scenario analysis and model and parameter uncertainties with probabilistic sensitivity analysis?</td>
</tr>
<tr>
<td></td>
<td>Analysts should present the full range of potential cost-effectiveness results, at a minimum as a best/worst case scenario analysis, and/or preferably by showing the results of a probabilistic sensitivity analysis.</td>
<td>Has the full range of potential cost-effectiveness results been presented, preferably in a probabilistic way, but at a minimum by presenting a best and worst case scenario?</td>
</tr>
<tr>
<td></td>
<td>The most cost-effective strategy for a given willingness-to-pay value should be the strategy resulting in highest average net benefit.</td>
<td>Has the intervention identified as being the most cost-effective, the highest average net benefit?</td>
</tr>
<tr>
<td>Aspect</td>
<td>Attributes of good practice</td>
<td>Questions for critical appraisal</td>
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<td>Analysts should present cost-effectiveness results for a range of willingness-to-pay values.</td>
<td>Have the results been presented for a range of willingness-to-pay values?</td>
</tr>
<tr>
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<td>As a minimum, analysts should assess sensitivity of the results to the following variables: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant), case fatality risks and vaccine price.</td>
<td>Has the sensitivity of the results to the following variables been assessed: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant), case fatality risks and vaccine price?</td>
</tr>
<tr>
<td></td>
<td>Analysts should also place their findings in broader context by comparing their findings to other economic evaluations that have been undertaken in the same or neighbouring countries after adjustment for inflation and purchasing power.</td>
<td>Have the findings been compared to other economic evaluations undertaken in the same or neighbouring countries?</td>
</tr>
<tr>
<td>Other Factors (Chapter 9)</td>
<td>Other important factors for the decision under consideration should be discussed when results are communicated to policy makers. Besides technical study limitations, these other factors could include equity-related aspects, broader economic benefits, and budget-impact.</td>
<td>Is there a discussion of other important factors for the decision under consideration?</td>
</tr>
<tr>
<td>Conclusions</td>
<td>&quot;An answer to the study question should be given. The conclusions should follow from the data reported. The conclusions should be accompanied by the appropriate caveats.</td>
<td>Is an answer given to the study question? Do the conclusions follow from the data reported? Are the conclusions accompanied by the appropriate caveats?</td>
</tr>
<tr>
<td>Aspect</td>
<td>Questions for critical appraisal</td>
<td>Answers</td>
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<tr>
<td>Framing the analysis (Chapter 3)</td>
<td>Is there a clear statement of the study question?</td>
<td>Yes, the study questions is to evaluate the cost-effectiveness of five TCV delivery strategies in three urban areas (Delhi and Kolkata, India and Nairobi, Kenya) and two rural settings (Lwak, Kenya and Dong Thap, Vietnam) with varying incidence (p. 3506–7).</td>
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<td></td>
<td>Have the comparators being compared been clearly described?</td>
<td>Yes, (I) routine vaccination at 9 months of age; and routine vaccination at 9 months plus a one-time catch-up campaign among individuals, (II) 9 months to 5 years old, (III) 9 months to 15 years old, (IV) 9 months to 25 years old, (V) all ages &gt; 9 months (p. 3507).</td>
</tr>
<tr>
<td></td>
<td>Has a cost-utility analysis been performed? If not, has that decision been justified appropriately?</td>
<td>Yes, DALY’s are used as health outcome, but CUA not explicitly stated</td>
</tr>
<tr>
<td></td>
<td>Is the perspective of the analysis clearly stated? If a societal or multiple perspectives have been adopted, have the costs and outcomes been disaggregated to allow judgements to be made from different perspectives? Are the costs and outcomes reported consistent with the perspective reported?</td>
<td>Yes, healthcare payer perspective and therefore considering only the DALYs lost by care-seeking individuals and the direct treatment and vaccination costs accrued by the healthcare system (p. 3507).</td>
</tr>
<tr>
<td></td>
<td>Is/are the institution(s) sponsoring the study and the individual authors clearly stated?</td>
<td>Yes, section 2.5 ‘Role of the funding source’ and p.3513.</td>
</tr>
<tr>
<td></td>
<td>Are the time frame and analytic horizon clearly stated and justified?</td>
<td>Yes, 10-year time horizon but not justified (p. 3507).</td>
</tr>
<tr>
<td></td>
<td>Are broader economic benefits besides improved health, reduced health care expenditure and short-term productivity gains incorporated? If yes, is this consistent with the way vaccines are funded and the decision-maker(s)’ objectives?</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Costs (Chapter 4)</td>
<td>Have the methods used for the estimation of costs been clearly stated?</td>
<td>Yes, Appendix 6</td>
</tr>
<tr>
<td></td>
<td>Has a summary of the expected resource use and unit costs for each alternative been provided, including a specification of the assumptions behind calculations of the costs?</td>
<td>Yes, based on secondary data from existing studies (p. 3508, 3510, Appendix 6).</td>
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<tr>
<td>Aspect</td>
<td>Questions for critical appraisal</td>
<td>Answers</td>
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<td>Have the data sources used to estimate costs been clearly stated?</td>
<td>Yes, existing country-specific cost data have been used when available, otherwise WHO-CHOICE estimates for unit costs of hospital stay and outpatient visit have been used, costs have been extrapolated to other countries or assumptions have been made (p. 3508, 3510, Appendix 6).</td>
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<td>If productivity losses were estimated have they been reported separately? Has their relevance been discussed? Have the methods used to estimate productivity losses been described and justified?</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Have future costs been included? If yes, was this a requirement of the reference case for the local policy maker, for whom the analysis was meant and have the results been presented with and without including these future costs?</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Is the currency stated? If so, is the date of the currency and prices used in the model stated, with details of any adjustments or conversions provided?</td>
<td>Yes, 2015 international dollars (p. 3507) with details provided in Appendix 6.</td>
</tr>
<tr>
<td>Effects (Chapter 5)</td>
<td>Was the evidence on vaccine efficacy identified systematically, and was taken account of the biological characteristics of the pathogen in question and how its infectious nature may have influenced the efficacy estimates derived from trials?</td>
<td>Partial, Appendix 4 describes the available efficacy studies for typhoid vaccines</td>
</tr>
<tr>
<td></td>
<td>Was the effective coverage of vaccines calculated by multiplying vaccination coverage adjusted for non-compliance, by vaccine efficacy adjusted for loss of potency due to heat and freeze exposure, where such data were available?</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Was the population effectiveness (or &quot;impact&quot;) of vaccines calculated using empirical information on both the direct and indirect effects of the vaccination program, and was this information integrated in a mathematical model?</td>
<td>Partial, vaccine efficacy parameters were estimated by fitting a mathematical model to available data (Appendix 4); direct and indirect effects of the vaccination program were accounted for in a mathematical disease transmission model.</td>
</tr>
<tr>
<td></td>
<td>Are adverse events from immunization impacts likely to have a substantial impact on the results of the analysis? If so, have they been included on both the costs and effects sides of the analysis?</td>
<td>No, evidence to date suggests that there are no serious adverse events caused by any of the modern typhoid vaccines (p. 3513).</td>
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<tr>
<td>Aspect</td>
<td>Questions for critical appraisal</td>
<td>Answers</td>
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<td>Was the estimated duration of vaccine protection over time data driven, completely transparent, and subjected to thorough uncertainty analysis?</td>
<td>Partial, a mathematical model was fitted to vaccine efficacy data over time to estimate duration of protection; this was described transparently in Appendix 4; uncertainty around waning rate was accounted for in PSA but not further explored in scenario analysis.</td>
</tr>
<tr>
<td></td>
<td>Have estimates of burden been presented in natural units – cases, deaths, years of life lost (YLL)? Have estimates of DALYs or QALYs lost been presented as final outcome of burden of disease?</td>
<td>Yes, cases, hospitalizations, deaths, years of life lost, years lived with disability and DALYs have been presented (Table 2).</td>
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<tr>
<td></td>
<td>If suitable QALY weights were not readily available, have DALYs been used for cost-utility analysis?</td>
<td>Yes, DALYs have been used for cost-utility analysis.</td>
</tr>
<tr>
<td></td>
<td>When DALYs have been used in cost-utility analysis, were they subjected to social weighting, such as age weighting? If yes, was this explicitly desired by the policy maker the analysis was meant to advise?</td>
<td>No, DALYs were not subjected to social weighting.</td>
</tr>
<tr>
<td>Modelling</td>
<td>Are the model structure and implicit or explicit assumptions clearly described?</td>
<td>Yes, Appendix 1</td>
</tr>
<tr>
<td>(Chapter 6)</td>
<td>Is the model type (static, dynamic or stochastic) clearly stated and justified in light of likely changes to the force of infection and the role of chance in the transmission process? Have the model’s strengths and weaknesses been discussed?</td>
<td>Yes, an age-stratified compartmental model of typhoid transmission was used to fully account for the decreased risk of infection that vaccination may confer on the population (herd immunity) (p. 3507, 3511). Strengths and weaknesses are discussed (p. 3511, 3513).</td>
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<td></td>
<td>Has the model been validated? If so, has it been validated in as many facets of validation as possible?</td>
<td>Partially, the model provided a good fit with the observed incidence of typhoid fever in the 5 settings (p. 3509).</td>
</tr>
<tr>
<td>Discounting</td>
<td>Is the discount rate clearly stated and justified?</td>
<td>Yes, costs and DALYs are averted at 3% per year as per the Gates Reference Case (p. 3508, Appendix 6).</td>
</tr>
<tr>
<td>(Chapter 7)</td>
<td>Have WHO recommended schemes of (i) 3% and 0% discounting for consumption and health respectively in the base case, and (ii) 3% discounting for both health and consumption been used?</td>
<td>No</td>
</tr>
<tr>
<td>Aspect</td>
<td>Questions for critical appraisal</td>
<td>Answers</td>
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<tr>
<td>Uncertainty (Chapter 8)</td>
<td>Are all known sources of uncertainties not accounted for justified to the extent possible?</td>
<td>Partial, e.g. uncertainty around improved sanitation or enhanced capacity to treat or isolate cases to decrease typhoid incidence over the time horizon of the analysis has not been accounted for, but has been discussed (p. 3513).</td>
</tr>
<tr>
<td></td>
<td>Have methodological uncertainties been accounted for with scenario analysis and model and parameter uncertainties with probabilistic sensitivity analysis?</td>
<td>Partial, parameter uncertainty has been accounted for with PSA (p. 3507), but methodological and model uncertainties have not been accounted for.</td>
</tr>
<tr>
<td></td>
<td>Has the full range of potential cost-effectiveness results been presented, preferably in a probabilistic way, but at a minimum by presenting a best and worst case scenario?</td>
<td>Yes (p. 3510–11)</td>
</tr>
<tr>
<td></td>
<td>Has the intervention identified as being the most cost-effective, the highest average net benefit?</td>
<td>Yes (p. 3509)</td>
</tr>
<tr>
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<td>Have the results been presented for a range of willingness-to-pay values?</td>
<td>Yes (p. 3509, Figure 3)</td>
</tr>
<tr>
<td></td>
<td>Has the sensitivity of the results to the following variables been assessed: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant), case fatality risks and vaccine price?</td>
<td>Yes, except for discount rate</td>
</tr>
<tr>
<td></td>
<td>Have the findings been compared to other economic evaluations undertaken in the same or neighbouring countries?</td>
<td>Yes, but for different vaccines not including infants under 2 years of age in Delhi and Kolkata (p. 3511).</td>
</tr>
<tr>
<td>Other Factors (Chapter 9)</td>
<td>Is there a discussion of other important factors for the decision under consideration?</td>
<td>Partly, three technical factors that were not taken into account were discussed as these could raise the WTP of these interventions: only urban slum areas with high incidence were involved; incidence of typhoid varies over time; the assumption that there are no side-effects of TCV (p. 3513).</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Is an answer given to the study question?</td>
<td>Yes (p. 3511)</td>
</tr>
<tr>
<td></td>
<td>Do the conclusions follow from the data reported?</td>
<td>Yes (p. 3511)</td>
</tr>
<tr>
<td></td>
<td>Are the conclusions accompanied by the appropriate caveats?</td>
<td>Yes, considerable uncertainty around some parameters (BoD, effects, costs of treatment etc) but did not have strong influence (p. 3511–13)</td>
</tr>
</tbody>
</table>
References


118) Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Analysis of varicella vaccine breakthrough rates: implications for the effectiveness of immunisation pro-


202) Bertram MY, Stenberg K, Brindley C, Li J, Serje J, Watts R et al. Disease control programme support costs: an update of WHO-CHOICE methodology,


236) Sevilla JP, Bloom DE, Cadarette D, Jit M, Lipsitch M. Toward economic evaluation of the value of vaccines and other health technologies in addressing AMR.


Appendix 1: Sources of data
(all sites as at October 2019)

<table>
<thead>
<tr>
<th>CORE HEALTH INDICATORS, E.G. POPULATION SIZE, LIFE EXPECTANCY AT BIRTH, MORTALITY RATES, ETC.</th>
</tr>
</thead>
</table>
| World Health Organization  
[🔗](https://www.who.int/gho/)  
[🔗](https://www.who.int/healthinfo/) |
| United Nations Population Division  

<table>
<thead>
<tr>
<th>VACCINE EFFICACY</th>
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<tbody>
<tr>
<td><a href="https://www.cochranelibrary.com">🔗</a></td>
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<table>
<thead>
<tr>
<th>COVERAGE DATA</th>
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</table>
| World Health Organization/United Nations Children’s Fund  
[🔗](https://www.who.int/immunization/monitoring_surveillance/) |

<table>
<thead>
<tr>
<th>DISABILITY WEIGHTS</th>
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</thead>
</table>
| WHO Burden of Disease Project  
[🔗](https://www.who.int/healthinfo/paper54.pdf) (see Annex Tables 1 and 5a) |

<table>
<thead>
<tr>
<th>IMMUNIZATION EXPENDITURES AND FINANCING DATA (COUNTRY LEVEL)</th>
</tr>
</thead>
</table>
| World Health Organization  
[🔗](https://www.who.int/immunization/programmes_systems/financing/) |

<table>
<thead>
<tr>
<th>UNIT COST DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRICES FOR VACCINES</td>
</tr>
</tbody>
</table>
| Global Alliance for Vaccines and Immunization/The United Nation's Children's Fund:  
[🔗](https://www.unicef.org/supply/index_57476.html) |
Pan American Health Organization Revolving Fund
https://www.paho.org/hq/index.php?option=com_topics&view=article&id=396&Itemid=42192

Unit costs for patient services:
https://www.who.int/choice/costs/unit_regions/

Prices for local (non-traded) goods
https://www.who.int/choice/costs/prog_costs/

Prices for traded goods
https://www.who.int/choice/costs/traded_items/

Management Sciences for Health International Drug Price Indicator Guide
https://www.msh.org/resources/international-medical-products-price-guide

FINANCIAL DATA

International Monetary Fund

World Bank
https://datacatalog.worldbank.org

GNI PER CAPITA

World Bank

PURCHASING POWER PARITY EXCHANGE RATES

World Bank

OFFICIAL EXCHANGE RATES

OANDA
https://www1.oanda.com
Appendix 2:
List of useful websites

Please note that this list is not intended to be exhaustive.

<table>
<thead>
<tr>
<th>GENERAL</th>
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</thead>
<tbody>
<tr>
<td>Centers for Disease Control &amp; Prevention (CDC)</td>
</tr>
<tr>
<td><a href="https://www.cdc.gov">https://www.cdc.gov</a></td>
</tr>
<tr>
<td>Cochrane Library</td>
</tr>
<tr>
<td><a href="https://www.cochranelibrary.com">https://www.cochranelibrary.com</a></td>
</tr>
<tr>
<td>Gavi, the Vaccine Alliance</td>
</tr>
<tr>
<td><a href="https://www.gavi.org">https://www.gavi.org</a></td>
</tr>
<tr>
<td>International Vaccine Institute</td>
</tr>
<tr>
<td><a href="https://www.ivi.int">https://www.ivi.int</a></td>
</tr>
<tr>
<td>PATH</td>
</tr>
<tr>
<td><a href="https://www.path.org">https://www.path.org</a></td>
</tr>
<tr>
<td>The United Nations Children’s Fund</td>
</tr>
<tr>
<td><a href="https://www.unicef.org">https://www.unicef.org</a></td>
</tr>
<tr>
<td>World Health Organization, Immunization, Vaccination &amp; Biologicals</td>
</tr>
<tr>
<td><a href="https://www.who.int/immunization/">https://www.who.int/immunization/</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VACCINE INITIATIVES</th>
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</thead>
<tbody>
<tr>
<td>Aeras Global TB Vaccine Foundation</td>
</tr>
<tr>
<td><a href="http://www.aeras.org">http://www.aeras.org</a></td>
</tr>
<tr>
<td>Cholera Vaccine Initiative</td>
</tr>
<tr>
<td><a href="https://www.stopcholera.org">https://www.stopcholera.org</a></td>
</tr>
<tr>
<td>Dengue Vaccine Initiative</td>
</tr>
<tr>
<td><a href="https://www.sabin.org/programs/vaccine-advocacy/dengue-vaccine-initiative">https://www.sabin.org/programs/vaccine-advocacy/dengue-vaccine-initiative</a></td>
</tr>
<tr>
<td>Global Initiative against HPV and cervical cancer</td>
</tr>
<tr>
<td><a href="https://giahc.org">https://giahc.org</a></td>
</tr>
<tr>
<td>Hib Initiative</td>
</tr>
<tr>
<td>Human Hookworm Vaccine Initiative</td>
</tr>
<tr>
<td><a href="https://www.sabin.org/programs/hookworm">https://www.sabin.org/programs/hookworm</a></td>
</tr>
</tbody>
</table>
International AIDS Vaccine Initiative
https://www.iavi.org

Japanese Encephalitis project
https://www.path.org/japanese-encephalitis/

Malaria Vaccine Initiative
https://www.malarivaccine.org

Measles and rubella Initiative
https://measlesrubellainitiative.org

Rotavirus Vaccine support
https://www.gavi.org/support/nvs/rotavirus/

VACCINE SUPPLY & FINANCE

Immunization Financing Website
https://www.who.int/immunization/programmes_systems/financing/

This site is being developed under the auspices of Gavi, the Vaccine Alliance, and is intended to be an online resource for partners, international donors, policy-makers, health planners, immunization programme managers, and researchers who seek and share information about immunization financing in the poorest countries.

- Gavi partners, international donors, researchers and other groups can benefit from country-specific information on immunization financing, and the immunization financing database designed to provide recent data and indicators on immunization expenditures and financing in the poorest countries.

- Policy-makers and health planners can learn more about available options to finance their national immunization programme. The option briefing sheets bring together up-to-date knowledge about the major advantages and drawbacks of available financing options for immunization.

- National immunization programme managers can learn more about the value of strategic planning for immunization through comprehensive multi-year planning (cMYP) or how to develop and implement financial sustainability plans for their programmes, and existing immunization costing and financing guidelines, tools and related resources.

WHO-UNICEF guidelines for developing a comprehensive multi-year plan (cMYP)
https://www.who.int/immunization/programmes_systems/financing/tools/cmyp/

Strategic planning for immunization requires reliable information on the costs and financing of the programme. In order to assess the financial sustainability of immunization programs, fundamental questions need to be answered, such as:

- What amounts of resources are needed to meet the programme objectives?
- What are the funding channels and what quantity of funds are expected over the period of the plan?
- What amount is the funding gap and on which of the immunization programme components does the funding fall short?
- How should activities be prioritizes based on the available funds?
For this reason, estimating the costs and financing of a national immunization programme, is a key step in the developing a comprehensive Multi-Year Plan (cMYP) for immunization.

International Finance Facility for Immunization Company (IFFIm)
https://www.iffim.org

EPIC
http://immunizationeconomics.org/about

VACCINE ECONOMICS

Bulletin of the World Health Organization: special issue on the economics of immunization
https://www.who.int/bulletin/volumes/82/9/

Health Affairs: special issue on the economics of vaccines
https://www.healthaffairs.org/toc/hlthaff/35/2

COST-EFFECTIVENESS/HEALTH ECONOMICS

Commission on Macroeconomics and Health
(Sever discussed discussion papers summarizing evidence on cost-effectiveness of health interventions in low/middle income countries)
https://www.who.int/macrohealth/

Copenhagen Consensus
https://www.copenhagenconsensus.com/?ID=675

Disease Control Priorities Project
http://dcp-3.org

Idsi
https://www.idsihealth.org

International Health Economics Association
https://www.healtheconomics.org/

ISPOR
https://www.ispor.org

DATABASES OF COST-EFFECTIVENESS STUDIES:

Cost-effectiveness Analysis Registry
https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Centre for Reviews and Dissemination
https://www.york.ac.uk/crd/#NHSEED
- Covers also peer-reviewed health technology assessment agency reports that are not offered for publication to journals

Cochrane economic methods group
https://methods.cochrane.org/economics/welcome
MAIN JOURNALS WITHIN THE FIELD OF HEALTH ECONOMICS:

Cost-Effectiveness and Resource Allocation
https://resource-allocation.biomedcentral.com

European Journal of Health Economics
https://link.springer.com/journal/10198

Health Affairs
https://www.healthaffairs.org/topics

Health Economics
https://onlinelibrary.wiley.com/journal/10991050

Journal of Health Economics
https://www.journals.elsevier.com/journal-of-health-economics

Medical Decision Making
https://journals.sagepub.com/home/mdm

Value in Health
https://www.valueinhealthjournal.com
The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB’s mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director’s Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.