WHO guide for standardization of economic evaluations of immunization programmes

Immunization, Vaccines and Biologicals

World Health Organization

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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.

Abbreviations
and Acronyms

ACER	average cost-effectiveness ratio
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHOICE	CHOosing Interventions that are Cost-Effective
CMA	cost-minimization analysis
CMH	Commission on Macroeconomics and Health
cMYP	comprehensive multi-year plan
CUA	cost-utility analysis
DALY	disability-adjusted life-year
DCPP	Disease Control Priorities Project
DCP2	Disease Control Priorities in Developing Countries, Second Edition
DTP	diphtheria-tetanus-pertussis (vaccine)
EPI	Expanded Programme on Immunization
FSP	financial sustainability plan
GAVI	Global Alliance for Vaccines and Immunization
GDP	gross domestic product
GIVS	Global Immunization Vision and Strategy
GNI	gross national income
HAV	hepatitis a virus
HBV	hepatitis b virus
HCV	hepatitis c virus
Hib	*Haemophilus influenzae* type b
HIC	high-income country
HIV	human immunodeficiency virus
HPV	human papilloma virus

I$	international dollar
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IPV	inactivated polio vaccine
IVB	Immunization, Vaccines and Biologicals
IVR	Initiative for Vaccine Research
LCU	local currency unit
LMIC	low- or middle-income country
MCER	marginal cost-effectiveness ratio
MYP	multi-year plan
OPD	outpatient department
OPV	oral polio vaccine
PPP	purchasing power parity
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomized controlled trial
SA	statistical analysis
SARS	severe acute respiratory syndrome
STI	sexually transmitted infection
TB	tuberculosis
UNICEF	United Nations Children's Fund
VE	vaccine efficacy
VHW	village health worker
VPD	vaccine-preventable disease
WHO	World Health Organization

Acknowledgements

Executive Summary

The traditional Expanded Programme on Immunization (EPI) vaccines are considered to be among the most efficient uses of scarce health care resources. Today, there are many under-used and new vaccines available and many more in the pipeline that in the short- to medium-term will not cost the few cents per dose that the traditional vaccines do, but will be 'multi-dollar' vaccines. Decision-makers will require information on, among other things, their relative cost-effectiveness. A number of reviews have indicated that there is scope for improving the transparency, completeness and comparability of economic evaluations of immunization programmes. Adherence to general guidelines on economic evaluations would increase the quality, interpretability and transferability of future analyses; however, there is reason to believe that more specific advice might be needed in relation to vaccination programmes.

Chapter 2 briefly explains what economic evaluation is, describes the different types of economic evaluation and summarizes the role of economic evaluation, highlighting the distinction between economic evaluation and budget impact analysis/financing of programme implementation. **Chapter 3** considers the various ways of framing an evaluation. As decisions made when framing the evaluation will directly determine which costs and outcomes are considered relevant and should be included in the analysis, choices made at this stage will have an impact on the final results of an analysis. **Chapter 4** describes the various costs that could be included in an assessment and provides guidance on how to identify, measure and value resources in order to estimate the costs associated with an immunization programme. In **Chapter 5,** guidance is given on vaccine efficacy, vaccine effectiveness, vaccine delivery and uptake, including possible adverse events of vaccines and lastly the strengths and weaknesses of different outcome measures. **Chapter 6** begins by describing the parameters that are of particular importance when modelling a vaccine-preventable disease, before considering the impact of vaccines. This chapter then goes on to describe the basic types of infectious disease models and introduces a flow chart to help analysts decide when a dynamic or static model is to be preferred, based on the type of vaccine-preventable disease. The chapter concludes by focusing on approaches to the validation of models. **Chapter 7** discusses the choice of discount rate, as discounting can have considerable influence on the estimated efficiency of vaccination programmes with long-term effects. **Chapter 8** considers the summary measures used to report economic evaluations and how they can be used to inform decision-making. The chapter describes the sources of uncertainty inherent in any economic evaluation and describes some of the methods available for presenting such uncertainty. This chapter also looks at more sophisticated types of sensitivity analysis and explains how they might help with the interpretation and communication of cost-effectiveness data. **Chapter 9** takes a broader view of the decision-making process, presenting the evidence about the use of economic evaluation in practice and policy, and making the case that the use of cost-effectiveness data will not be optimised without decision-making bodies. The various other criteria relevant

for priority-setting in health are then described, with particular attention to equity. Finally, recent literature is reviewed that suggests that conventional economic evaluations of immunization programmes are too reductionist in their consideration of benefits. **Chapter 10** provides a summary of the recommendations and presents them in the form of a checklist intended to be helpful to analysts and reviewers alike.

In conclusion, this guide does not propose any alteration to 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.

Chapter 1:
Introduction

Traditional EPI vaccines are considered to be among the most efficient uses of scarce health care resources (1). Today, many under-used and new vaccines are available, e.g. against yellow fever, hepatitis b virus (HBV), *Haemophilus influenzae* type b (Hib), rotavirus, *Streptococcus pneumoniae*, human papilloma virus (HPV) and Japanese encephalitis, with many more in the pipeline, e.g. against enterotoxigenic *Escherichia coli*, shigellosis, dengue, hookworm, schistosomiasis, herpes simplex virus 2, human immunodeficiency virus (HIV), malaria and tuberculosis (TB). In the short- to medium-term, these vaccines will not cost the few cents per dose the traditional vaccines do, but will be 'multi-dollar' vaccines. Decision-makers will need information on, among other things, their relative cost-effectiveness.

1.1   Evidence-based decision-making

In November 2005 the World Health Organization (WHO) published a document entitled *Vaccine Introduction Guidelines. Adding a Vaccine to a National Immunization Programme: Decision and Implementation* (2). These guidelines present programme managers and policy-makers at the national level with a systematic approach to decision-making when facing the opportunities and challenges inherent in adding a new vaccine product to their national immunization programmes (see Figure 1). More specifically, the approach outlined the key issues to be considered before deciding to introduce a vaccine. A first set of issues, referred to as policy issues, leads high-level decision-makers to agree on whether the introduction of a particular vaccine is acceptable from an immunization policy perspective. The second set of issues, referred to as programmatic issues, addresses the technical feasibility of the vaccine introduction.

Figure 1: Evidence-based decision-making

Source: WHO (2)
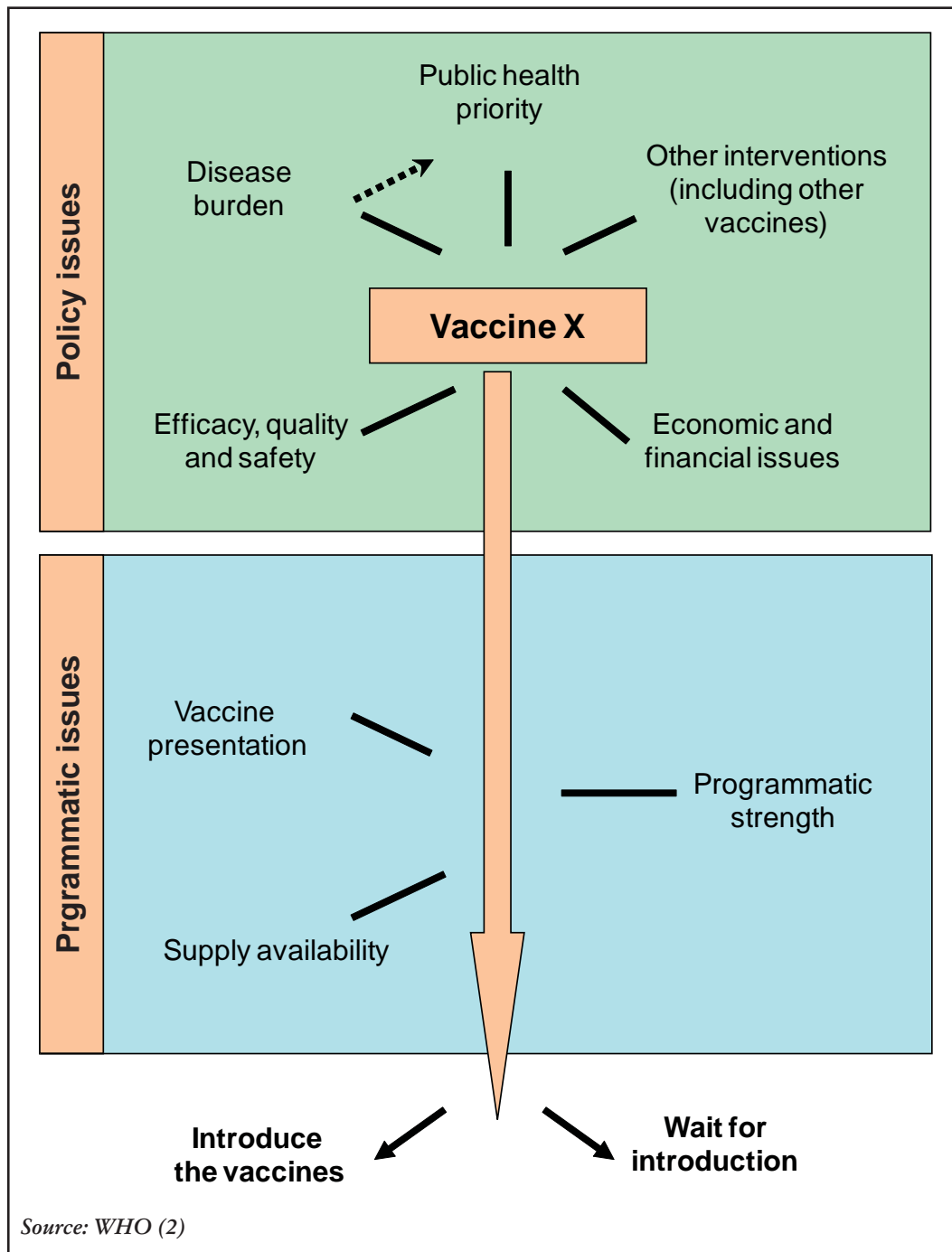
Under the broader heading of 'policy issues', the *Vaccine Introduction Guidelines* identify 'Economic and Financial Issues', which include cost-effectiveness, fiscal impact and financial sustainability. The present Guide provides detailed guidance as to how to evaluate the cost-effectiveness of vaccines.

1.2   Existing guidance on 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'.

There is a growing body of general (3-6) and disease- and intervention-specific (7-9) guidelines on economic evaluation in health care. There are also an increasing number of country-specific guidelines (mainly for developed countries); these are often influenced by the authoritative National Institute for Health and Clinical Excellence guidelines from the United Kingdom (10), but show differences in analytical choices (11).

1.3   What is different about this guide?

A number of reviews have indicated that there is scope for improving the transparency, completeness and comparability of economic evaluations of vaccination programmes (12-24). Thus, there is a need to improve the quality of economic evaluations of vaccination programmes. Adherence to the general guidelines would increase the quality, interpretability and transferability of future analyses (25). However, there is reason to believe that there might also be a need for more specific advice in relation to vaccination programmes. For example, there are inconsistencies in the methods used to estimate the future benefits of vaccination programmes and the relative efficiency of these programmes can be sensitive to some of the more controversial aspects of the general guidelines, such as the inclusion of indirect costs and the discounting of health outcomes.

Cost-effectiveness guidelines have been published that focusi on vaccines against viral hepatitis (26) and there is also guidance on how to evaluate the programmatic costs associated with the introduction of a vaccine (27;28). However, the field of health economic evaluation in general has progressed since those guidelines were published, such as in relation to quantifying and presenting uncertainty. Moreover, more expensive vaccines have become available, increasing the need to make balanced budgetary trade-offs on the basis of cost-effectiveness data. Joint analyses of all antigens in combination vaccines, groups of vaccines or a regional immunization or preventive public health programme could therefore become more relevant.

1.4   Aim and target audience of this guide

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 LMICs a preference has emerged for the use of disability-adjusted life years (DALYs), whereas in HICs, quality-adjusted life years (QALYs) are the outcome measure of choice (29).

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.

The primary target audience for this guide is economists and health service researchers in the public and private sector 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 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 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.

The guide supports WHO's *Vaccine Introduction Guidelines* (2005) and priority-setting in the health sector at the population level in accordance with the WHO-CHOICE guidelines (6).

1.5 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. Chapters 5 and 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. Chapter 9 takes a broader look at the decision-making process and examines some other considerations in addition to cost-effectiveness. 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' (4). 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[1] 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 of childhood diarrhoea using zinc. *Cost-utility analysis* values outcomes using measures of utility that

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[1]   The terms outcomes, consequences, effects and benefits are used interchangeably in this text.

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].

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. 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.

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 CEA has emerged over other types of analysis as the method of choice for evaluating health care programmes in both developed and developing countries (30;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).

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

Table 1: Summary of the different types of economic evaluation

	Outcomes	Technical efficiency?	Allocative efficiency?
CMA	Not applicable	Yes	No
CEA	Natural Units	Yes	No[3]
CUA	QALYs, DALYs	Yes	Yes, with health care
CBA	$	Yes	Yes

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;33). 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 purposes, but the resources within those budgets are often fixed or semi-fixed (34). 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.

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[4] 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:

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[3]   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.

[4]   A draft is available on www.who.int/immunization_financing/tools/cmyp/

- 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[5], and would require significant efforts to mobilize resources to expand the fiscal space[6] for immunization and sustain the new vaccine in the following years.

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[5] 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).

[6] 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 target audience will depend on the scope and level of analysis. For example, the GAVI Alliance investment cases[7] prepared for the global community will present estimates that are more aggregated and are targeted at international financing agencies, aid agencies, international development agencies, non-governmental organizations and private health care providers. If the scope of the analysis is limited to a single country or a small cluster of countries, then the target audience should include the ministries of health and finance and policy-makers in other branches of government in those countries.

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

- for which new vaccine(s) should the GAVI Alliance open a window of funding?

- should an under-used or new vaccine be introduced, e.g. Hib or rotavirus?

- which strategy should be used to increase vaccination coverage, e.g. fixed sites, mobile teams or campaigns?

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[7]   In May 2004, the GAVI Alliance issued guidelines for preparing proposals for GAVI/Vaccine Fund investment. The guidelines are to "…assist preparation of proposals for activities to save lives and improve health through increasing access to vaccines". The first part should present the project proposed for GAVI/Vaccine Fund investment, the second part should provide the rationale for the investment, and the third part should outline how the project's implementation will be monitored and evaluated (36).

- is targeted or universal vaccination more efficient, e.g. consider vaccines against HIV or other sexually transmitted infections (STIs)?

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

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

- what would be the cost-effectiveness of introducing a new vaccine alone versus in combination with other existing preventive health interventions, e.g. HPV vaccine alone or in combination with cancer screening, or future malaria vaccines alone or in combination with malaria bed-nets?

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. While the type of evaluation chosen will be influenced by the study question, CUA, in which the outcomes are expressed in a combined measure of morbidity and mortality (e.g. QALYs or DALYs), is the preferred option as this will facilitate comparisons both among vaccines and among health-care interventions more generally. This does not of course mean that CEAs or CBAs should not be conducted. Indeed, presentation of a range of outcome measures is encouraged as this will increase the potential utility of the analysis. Furthermore, a CUA will typically use the natural units presented in a CEA to generate measures of utility.

3.4   Target population

The target population is the group intended to receive the intervention. It can vary by, for example, age, sex, occupation and geography (see Box 1), and has a major impact on cost-effectiveness. 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 one age group may have a higher risk profile for a particular disease, e.g. injecting drug users and HIV.

Box 1: Examples of target populations

• Neonates	• Primary school children	• High-risk groups, e.g. commercial sex workers, injecting drug users
• Infants	• Secondary school children	
• Children	• Tertiary school children	
• Adolescents	• Males	• Different socio-economic groups
• Young people	• Females	• Certain geographical areas
• Older people	• Pregnant women	
	• Women of childbearing age	

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 (37). There should therefore be a clear description of the comparators under evaluation. Table 2 summarizes the main comparator options.

Table 2: Potential options against which to compare vaccines

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

Source: Adapted from Cantor and Ganiats (37).

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 intervention(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.

A second issue to consider is that current practice may itself be inefficient (5;6) 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.

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.

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

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. (4) suggest that analysts need to ask (and answer): who, does what, to whom, where and how often (see Box 3 for an example).

Box 3: Example of a description of alternatives for evaluation

	Option 1 (new strategy, e.g. childhood vaccination against HBV with a birth dose)	Option 2 (comparator, e.g. childhood vaccination against HBV without a birth dose)
Who?	Village health workers (VHWs) & nurses	Nurses
To whom?	Newborns and infants	Infants
Where?	At facilities or homes (after birth) and vaccination sites	Vaccination sites
How often?	Once within 48 hours of birth and three subsequent times	Three times

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 person(s) or institution(s) sponsoring the study (the *audience*) might want the analysis to reflect their own *perspective* (Note that it is important that the person(s) or institution(s) sponsoring the study should be clearly stated.). In this case, the choice of the study *perspective* must be consistent with the *audience* choice. Ideally, however, analyses should adopt the perspective of society, and include all effects and all related costs, regardless of who benefits

from or pays for them. 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 GAVI-eligible countries that may be required to co-finance the cost of vaccines[8]. 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. (38) 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. Analysts should therefore be cognizant that whilst a broader perspective that includes productivity losses (gains) will improve cost-effectiveness, it can also be used to justify higher vaccine prices, as it increases the break-even price per dose, i.e. the price at which the cost of the vaccination programme is exactly off-set by the savings due to vaccination.

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. The analytic horizon may often be short (i.e. one year or less), e.g. vaccination campaigns, particularly if herd immunity can be ignored (see Chapter 6 below) and only one (birth) cohort is modelled. However, when using a dynamic model, and if the indirect effects change non-linearly with the number of (birth) cohorts vaccinated, the analytic horizon should be long enough for the modelled infection to attain a new endemic equilibrium, as the current epidemiology is altered after the start or change in the vaccination programme.

The cost-effectiveness ratio for vaccination programmes generally takes 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 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 model-based evaluations should be determined *during* and not *prior* to the analysis.

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[8]   Since 2000, the GAVI Alliance has helped support the purchase of vaccines in many of the poorest countries through GAVI phase 1 funding. The second phase of funding began in 2006. Countries will be expected to co-finance purchases of new or under-used vaccine, with the exception of measles second dose, which will be provided free of charge. Countries may cover their co-payments either through national funding, or in some cases, partners. Minimum co-payments have been set by GAVI, and will be periodically reviewed.

3.8 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 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 alternatives into the analysis, such as a best available alternative, a viable low-cost alternative or a do-nothing option;

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

- Ideally analyses 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 so far as possible in order to allow judgments to be made from the perspectives of the various decision-makers;

- The person(s) or institution(s) sponsoring the study 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.

Chapter 4:
Assessing the Cost of a Vaccination Programme

This chapter provides guidance on how to identify, measure and value resources in order to estimate the costs associated with a vaccination programme. 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 (39) 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.

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 (28) and incremental[9] (27) 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.

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[9]   Sometimes referred to as marginal costing (4).

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 general 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.

Work undertaken by the WHO's Global Programme on Evidence for Health Policy, known as WHO-CHOICE, which began in 1998 with the development of standard tools and methods, represents the first systematic attempt to estimate unit costs at both the patient and programme level for health interventions in all countries and regions of the world. This makes it possible not only to generate unit costs that are consistent across interventions within one country, but also allows comparisons across countries with similar determinants such as background epidemiology and socio-economic factors, as well as estimates of the cost of scaling-up interventions to different coverage levels by varying capacity utilization. One key finding from this work is that 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 (40). 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[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.

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[10] Although with globalization labour has become increasingly tradable.

In nearly all economies, domestic market price levels are higher than international market price levels (41). 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. 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 3). 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.

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' (42) 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 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.

Table 3: Example calculation of vaccination programme costs in the presence of import tariffs in a hypothetical district[11]

Type of good	Quantity	Imported	Tariff	International prices		Domestic prices	
				Price level	Total costs	Price level	Total costs
Vaccines	1,000	Yes	25%	$0.10	$100	$0.125	$125
Syringes	1,000	No	NA	$0.08	$8	$0.01	$10
Refrigerators	1	Yes	25%	$500	$500	$625	$625
Nurses (FTE)	2	No	NA	$400	$800	$500	$1,000
Total					$1,408		$1,760

Source: Adapted from Hutton and Baltussen (41).

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[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)).

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, e.g. whether it is to inform a decision by a local policy-maker, e.g. should a new vaccine be introduced into a country X's national immunization programme? Or for a series of GAVI investment cases. In the case of the first example, 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 considerations 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.

In the case of the second example, 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.

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.

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 (treatment cost savings).

Guidance on how to estimate total vaccination programme costs can be obtained from a recent ingredients-based approach to estimating the costs (43), or from the guidelines for producing immunization multi-year plans[12]. 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* (27). 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 is simpler to introduce than a 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 4 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.

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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: www.who.int/immunization_financing/tools/cmyp/

Table 4: Inputs to be assessed according to vaccine presentation

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

Source: Adapted from Kou (27)

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 a hospital stay/visit (including medical staff time), diagnostic tests and pharmaceuticals. These costs might be borne by the health sector and / or by patients and their families.

4.2.2 Costs for patients and their families, including lost productivity

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.

4.2.3 Future costs

There is not yet professional consensus on the issue of how to properly account for costs that are not costs of 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 in the future because life is extended (see for example Meltzer (44)). The Disease Control Priorities Project (DCPP) guidelines recommend that such 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." The present guide endorses that recommendation. However, it should be noted that the exclusion of unrelated future costs might create a favourable bias towards interventions aimed at persons at an increased risk of unrelated illnesses over interventions for healthy persons (e.g. most general prevention programmes, including many vaccines).

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* (27) 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 (45). 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 may be 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 Drug Price Indicator Guide (http://erc.msh.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 (www.unicef.org/supply/ and www.ops-oms.org/).

In this guide, we define hospital costs per bed-day[13] 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:

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/en).

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.

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 (40).

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[13] 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.

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, or accessing vaccination services, is the human capital approach, which values lost time using an individual's gross earnings. 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. As a consequence, this approach produces lower estimates of production lost/gained. Although this approach appears conceptually superior, 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 a question over whether production gains should be taken into account. 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. 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 ever 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 – 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 on how vaccination programme costs change as coverage changes is, despite its importance for policy decisions, lacking.

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 (46). 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 (47) 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 (48).

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 under-nourished 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 (49). 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 very 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 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;

- 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 (50-52):

- 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 (50-53):

- 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). 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 vaccinee'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 impact of health interventions (basically RCTs, case-control studies and cohort studies, for a succinct review of these see Grimes and Schulz (54)). 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

$$VE = 1 - \frac{C_V/N_V}{C_U/N_U}$$

endpoints 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, etc. 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:

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. This 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 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. Figure 2 illustrates the processes at work in persons vaccinated against an infectious pathogen, which circulates in their environment.

Figure 2: What happens when an individual is vaccinated?
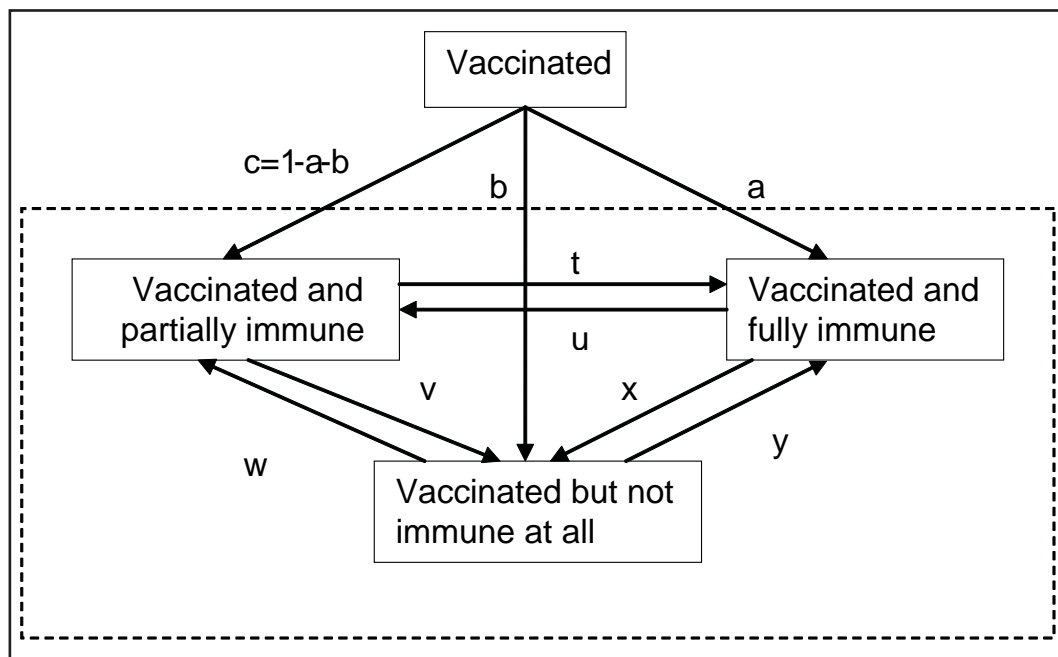
Vaccinated persons end up in the dashed rectangle after receiving vaccination in one of three compartments with probabilities a, b or c (note that for some vaccines some of these probabilities may be zero).

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 Figure 2. Both the "partially immune" and the "not immune at all" compartments will 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 and effectiveness from vaccine trials (52;55-65).

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 environmental 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 less or not at all oncogenic. In this instance, 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.

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 (www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). When a systematic review is not available, analysts should strive to derive estimates on vaccine efficacy from trial data using formal meta-analytic techniques (66-69). 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 (eg, unpublished data from industry sponsored trials) regarding vaccine efficacy and subject them to sensitivity analyses (see below).

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. Thus, effectiveness is dependent on the impact that widespread vaccination has on the occurrence of infections and disease episodes both in vaccinated (including unprotected, partially and fully protected vaccinated persons) and unvaccinated persons. Given a number of conditions, many aspects of the indirect impact, such as herd immunity or impact on 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, and provide guidance on how to choose an appropriate model, and on taking account of necessary influences while 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.[14]

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[14]   www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html

5.2.2 Adverse events from immunization

Adverse events from vaccination 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 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. For instance, the use of whole cell pertussis vaccination is known to be associated with side effects, which may in some circumstances justify a switch to acellular pertussis vaccines (70). Furthermore the choice of switching from OPV to IPV in many developed countries 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 (71).

At the time of licensure not all (rare) side effects may have been documented. 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 (72).

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.

5.3 Choosing and valuing outcomes

The strengths and weaknesses of different outcome measures are described in Table 5. 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 of this, and because the DALY is the only summary measure for which consistent estimates are available across all parts of the world, this guide recommends using DALYs[15], especially if suitable QALY weights are not readily available. Their use will also inform allocative efficiency decisions. Authors should first present estimates of burden in natural units—cases, deaths, years of life lost (YLL) and years lived with disability (YLD) or impaired quality of life, before these units are converted to DALYs (or QALYs if QALY weights are available). The burden of disease using DALYs should be estimated both with and without age weighting.

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[15] For details on how to estimate DALYs, refer to Fox-Rushby and Hanson (73). For a comparison of QALYs and DALYs, refer to Sassi (74).

Table 5: The strengths and weaknesses of different outcome measures

Outcome measure	Strengths	Weaknesses
Process outcomes, e.g. number of children (fully) vaccinated	• Ease of collection; these measures are part of routine monitoring • Reflects technical efficiency of programme • Can identify most efficient method of delivery	• Routine statistics may be unreliable, incomplete or biased • No measure of impact on disease transmission
Intermediate outcomes, e.g. number of children immunized	• Relative ease of measurement and interpretation • May give some indication of impact, even though final health status unknown • Reflects technical efficiency of programme • Can identify most efficient method of delivery	• Require studies to measure serological status • No measure of impact on disease transmission • Gain achieved may not reflect real change in impact
Disease-specific outcomes, e.g. measles cases averted	• Comparisons across different prevention strategies are possible • DALYs can be derived with adequate information on mortality and life expectancy	• Unable to compare across health interventions • May not include indirect consequences of intervention
Quality-adjusted life years (QALY) gained	• Cross-vaccine and cross-sector comparisons are possible • Ability to assess impact of combined clinical management and prevention strategies • Quantity and quality effects combined in one measure	• Quality of life (QoL) 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
Disability adjusted life years (DALY) averted	• Cross-vaccine and cross-sector comparisons are possible. • Ability to assess impact of combined clinical management and prevention strategies • Morbidity (years of life lived with a disability – YLDs) and mortality (years of life lost – YLLs) effects combined in one measure	• Based on subjective measures of disability (i.e. expert opnion) • Possible over-simplification • Debate over their validity • Not widely recognized outside the health sector
Socio-economic measures, e.g. bed-days, OPD visits	• Indicate to what extent resource savings will offset intervention costs • Indicate those interventions which increase national income	• Difficult to measure and value gain in labour time • Information on the saved costs of treatment and gains in production are usually not routinely available • Indicators used do not reflect the primary aim of health interventions, namely health improvement

5.4　Recommendations

- Estimates of vaccine efficacy should be based upon systematic reviews of available 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 effectiveness of vaccines should be calculated by multiplying routine 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.

- 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.

- Authors should first present estimates of burden in natural units—cases, deaths, years of life lost (YLL) and years lived with disability (YLD) (or years lived with impaired quality of life, if such data are readily available. These units should be converted to DALYs (or QALYs if QALY weights are available).

- The burden of disease based on DALYs should be estimated both with and without age weighting.

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 (or analysis) for which a dynamic model is 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 (49;75;76).

6.1.1 The reproduction number

The effective reproduction number R_t 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:

Probability of transmission following exposure, p
Average number of new contacts made by an individual host per unit of time, c
Duration of infectiousness, D
Host population size, N
Number of susceptible hosts at time t, X_t
Proportion of susceptible hosts at time t, x_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 susceptible 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):

$$R_t = R_0 x_t$$

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 (77). 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.

If A is low, e.g. measles infection in developing countries, it would be more accurate to take the period of protection from maternal antibodies (M) into account:

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

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 (78;79). 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 (eg, assumptions regarding mixing, survival and heterogeneity) and specifying the defining equations.

6.1.2 Incidence and the force of infection

The force of infection (λ) is defined as the probability per unit of time that a susceptible person becomes infected (80). 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 are typically based on the assumptions that λ is constant and 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 (81). 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 more sense to use case notification data – if the transmission of infection is likely to have changed over time for instance, e.g. the improvements in hygiene have altered the transmission of hepatitis a virus (HAV) in many populations. 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 traditionally becomes 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 substantially less reliably diagnosed in most European countries than 30 years ago, when measles was still a common childhood infection (82;83). Furthermore for diseases with subclinical infection at the time infection occurs, this approach links only some (or none) of the infections to the correct time and age at infection, e.g. HBV, hepatitis c (HCV), 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 (81;84;85) and nonparametric approaches (86;87) have been proposed.

In calculating the force of infection λ 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, e.g. measles in sub-Saharan Africa, or when background mortality interferes significantly, e.g. HBV and HCV in Russia occurs primarily in risk groups where background mortality is very high due to other sexually transmitted and blood borne infections, such as HIV. 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_t), 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 epidemic threshold, implying that the incidence will decrease. So if vaccination reduces the proportion of immunes to less than $1-x^*$, 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 6 shows the epidemiological parameters for a number of childhood infections 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 not perfect (take and degree are less than 100%) and it is not always injected at birth or immediately after maternal immunity has waned (as implicitly assumed).

Table 6: Illustration of the relationship between important epidemiological parameters (for certain childhood infections)

Infection	Average age at infection (A)	Basic reproduction number (R0)	Critical proportion (pc)
Measles	5.0-8.0*	9.3-15.6	89-94%
Pertussis	4.5-6.5§	10-17.5	90-94%
Mumps	5.7-9.9	7.4-14.4	86-93%
Diphtheria	10.4	6.1	84%
Polio	10-14	5-7	80-86%
Rubella	10.2-10.8	7.2-7.3	86%

* 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 (1948-68) the overall average age at infection was 5 years.

§ In rural areas in the USA (1908-17), 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 1944-78 (4.5 years).

Sources: (49;75)

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 (88):

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

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 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 generation 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 Rt new cases and the slower the epidemic rises. The greater the average age at infection, the lower the birth rate (for a particular R0) and the slower the pool of susceptibles is replenished. Vaccination will decrease λ, which implies that the generation time increases, which in combination with a higher age at infection lengthens the inter-epidemic period.

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 (89). 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) (90).

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 evaluation 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 (91-93). There are however some specific issues related to mathematical models for infectious diseases as an integral part of model-based economic evaluation (26;94). These specific issues will be further highlighted in this section.

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 (95). 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, serology 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 recalculating the force of infection from the proportion of susceptible and infectious people 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).

Static and dynamic models can be either **deterministic** or **stochastic**. In the context of infectious diseases, we define a model 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 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 as a system of inter-acting individuals. In the latter case, in an **individual-based** model (or micro-simulation) the individuals that make up a population 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 interpret as the main drivers of the outcomes in such models are harder to identify. A recent example of this type of model (without economic analysis) is provided in relation to pandemic influenza (96;97). Examples of this type of model in applications integrated with economic evaluation are not to our knowledge currently available.

One of the most popular types of model in health economics in general is a static cohort model, in which events are simulated on an aggregate basis in a single **closed** cohort, ageing over time – typically from birth until death – but without interacting with other cohorts. It is also possible to model the entire population (as a sum of cohorts, which are in practice often assumed to be equal in size over the average life-expectancy) 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, whereas in dynamic systems this inflow is often assumed to equal the outflow of deaths.

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 only on the generally most influential choice of model attribute for the estimated cost-effectiveness ratio of vaccination: choosing between static and dynamic models. However, as transparency is key in model-based economic analysis, analysts should report on all the above modelling attributes, not just on the static/dynamic choice. Therefore, economists should be aware of different model attributes for specific infections and interventions, and 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 (98) for an explanation of inference robustness analysis as a way of dealing with this problem.

6.3.2 Choosing between static and dynamic models

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, such as by solving sets of difference equations, or sets of differential equations, 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).

Static models are a priori suited for evaluation of the impact of vaccination if herd immunity does not play an important role – i.e. when the additional effectiveness per additional vaccinee is constant. One particular 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. Immunizing such groups will not cause nonlinear differences in transmission to the groups in question or in the population as a whole, provided that the number of vaccinees remains relatively small compared with the total population size. Examples of the sort of vaccination programmes that fall into this category are HAV vaccination of travellers from low to high endemic areas, influenza and pneumococcal vaccination programmes targeted at the elderly or varicella-zoster virus vaccination of (susceptible) pre-adolescents or healthcare workers. Another example is where vaccination against an infection will not induce herd immunity, simply because the transmission of the infectious agent does not depend on the presence of infectious humans, e.g. tetanus and rabies.

Figure 3 and Table 7 indicate the types of infection 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.

Figure 3: Flow chart to help determine when dynamic or static models are appropriate


```
                            ┌─────────────────────────┐
                            │  Vaccination in humans  │
                            └─────────────────────────┘
                   ┌──────────────────────┐          ┌──────────────────────────────┐
                   │ Infectious disease   │          │ Non-infectious disease       │
                   │ (at equilibrium)     │          │ (e.g. leukaemia, breast      │
                   └──────────────────────┘          │ cancer)                      │
                                                      └──────────────────────────────┘
                                                                    │
                                                      ┌──────────────────────┐
                                                      │ Static model         │
                                                      │ (1)                  │
                                                      └──────────────────────┘
```

Human to human transmission non-existent or exceptional (e.g. rabies, tetanus, Q fever, Japanese encephalitis)

Human to human transmission common (including via a vector; e.g. malaria)

Vaccine does not reduce susceptibility to infection or infective transmission potential *

Vaccine reduces susceptibility to infection and/or infective transmission potential (e.g. measles, varicella-zoster, hepatitis B)

Static model (2)

One of the eligible target groups is or includes an epidemiologically influential subgroup (e.g. children for airborne infections, intravenous drug users for parenteral infections, young adults and sex workers for STIs)

The eligible target groups are not or do not include an epidemiologically influential subgroup (e.g. the elderly for influenza or pneumococcus, travellers from low to high endemic areas for HAV)

There are no negative externalities from vaccination, or these are very likely to be smaller than positive externalities

There are negative externalities from vaccination, which potentially exceed positive externalities

Static model (3)

Dynamic model (8)

Static model (4)

Static model shows unfavourable or borderline favourable** result for vaccination

Static model shows favourable** results for vaccination

Dynamic model (7)

Dynamic model (9)

Static model including observations on externalities from a comparable setting acceptable (5)

Static model acceptable (6)

* Note that this box of the flow chart represents an unlikely outcome, as there are to our knowledge currently no other vaccine examples that perfectly match the description given here. For instance, for current rotavirus vaccines, it is generally understood that these protect against disease (i.e. reduce the severity of disease), without preventing infection. In the absence of vaccination, children are regularly reinfected with rotavirus, showing less severe symptoms with each new infection, but without establishing immunity against infection (99). However, infectivity of vaccinated persons to susceptible persons may be reduced (as the severity of their diarrhoea episodes is reduced through rotavirus vaccination) to such an extent that, given a particular type of social contact, the probability of transmission of the infection (termed the "infective transmission potential" here) is reduced as well. With rotavirus vaccines (as with oral polio vaccine), there may also be an indirect vaccination effect, if vaccinated persons get an opportunity to shed and transmit vaccine viral load through their stool to others in their vicinity who are not vaccinated. In summary, at the current state of knowledge, it is not clear whether rotavirus vaccines would fit in this box in the flowchart, but at the time of drafting this guide most researchers assume that it would.

** By favourable it is meant here that the results (e.g., expressed as incremental cost-effectiveness ratios), compare favourably with some locally defined cut-off expressing willingness to pay for a QALY gained or a DALY averted (e.g., GDP per capita). 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. The analyst can make the results more conclusive by progressing further down the flow chart (preferably following a solid line, less preferably a dashed line). 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.

The general philosophy behind the preferred and acceptable options depicted in Figure 3 is "to make everything as simple as possible, but not simpler", with the aim of minimizing the risk of doing harm. Hence the use of static models is supported 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.

In other applications, ignoring herd immunity will have some effect on the estimated cost-effectiveness of the programme. 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 underestimate the benefits of vaccination – i.e. there will be positive externalities. Indeed, 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 and Hib vaccination.

When the evaluation of such vaccination programmes yields favourable results with sufficient certainty, the analyst can assume that it will be even more favourable in reality. Hence, the associated simplification from using a static model will not have changed the recommended decision. If however, allowing for uncertainty, the results are borderline favourable or moderately unfavourable, the information provided by the analysis will only be of limited value to the decision-maker.

Table 7: The acceptability of static versus dynamic models depending on pathogen (and epidemic situation), target group and vaccine effectiveness

Flow chart model choice number	Confidence in decision if based on a static model strong/weak/ unacceptable	Examples of vaccination programmes in this part of the flow chart (non-exhaustive)	References to studies with corresponding "good" model choice (d)
1	Strong: non-infectious disease	Therapeutic vaccines against cancer (under development)	
	Strong: absence of evidence of herd immunity and other indirect effects (e.g. environmental pathogens like tetanus)	Rabies, tetanus, Q fever, Japanese encephalitis, (current) rotavirus vaccines (see Note to Fig. 3)	(100-103)
3	Strong: target group not influential for transmission	Hepatitis A vaccination of health care workers, pneumococcala and influenza vaccination of the elderly and working adults, varicella-zoster vaccination for adolescents and adults	(104;105) (106-108)
4	Weak: depends on the results (leading to 5 and 6), dynamic model would be preferable	Pneumococcal, pertussis and Haemophilus influenzae type b vaccination for children, adolescents and adults, human papilloma virus vaccination for girls	
5	Weak: depends on transferability of results between comparable settings (e.g. applying real world observations from US to Europe and Asia), dynamic model would be preferable	Pneumococcal conjugate vaccination for children, influenza vaccination for children	(109;110)
6	Strong: cost-effectiveness is attractive and known to be underestimated, dynamic model would remain preferable to allow an incremental analysis of all potential options of vaccination	HPV vaccination of a single cohort of girls; influenza vaccination for children, hepatitis B vaccination for adults in low endemic areas	(111;112)
7	Unacceptable: negative indirect effects could outweigh positive indirect effects, dynamic model is required	Childhood varicella-zoster, measles, mumps, rubella vaccination	(111) (113)
8, 9	There is preference for using dynamic models, especially if both targeted and universal strategies are feasible options requiring comparisonc	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 HBV vaccination versus injecting intravenous drug user vaccination in low endemic countries	(114-116)

[a] Population group of adults currently targeted with pneumococcal polysaccharide vaccines, which do not protect against nasopharyngeal carriage and hence do not induce herd immunity.

[b] Population group of children <2y currently targeted with pneumococcal conjugate vaccines, which protect against nasopharyngeal carriage and hence induce herd immunity.

[c] 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.

[d] the references given here are to indicate that these papers made a choice about their model that corresponds to the given choice number. This does not necessarily imply that this guide endorses these studies in their entirety.

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 (117). 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. New vaccination programmes that are most likely to meet this requirement are those that are introduced immediately as an extra antigen in a combined vaccine, so that no additional injections are required and the coverage of other important vaccination programmes is not endangered, e.g. the addition of varicella to the measles-mumps-rubella vaccine. At high vaccination coverage, the shift in the average age at infection 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 that can only be estimated by dynamic transmission models that simulate interactions between the age cohorts that make up the entire population, and not just a single closed cohort in isolation, as is customary in static models.

The informative value of the analysis based on a static model would be very limited if the results produced turned out to be moderately favourable (or unfavourable) as it could potentially lead to wrong or even harmful policy decisions. In such situations, a dynamic model is preferable. Sometimes observations from a similar setting are available and can be used as a ready estimate in a static population model (this has been the case for pneumococcal conjugate vaccination in the United States of America for instance). Dynamic models are also necessary to analyse programmes targeted at epidemiologically influential groups of an infection. Immunizing such groups would have complex non-proportional effects on the propagation of the pathogen in the population. Targeted vaccination could then have a substantial impact on the epidemiology of infection, which cannot be projected by static models. Examples of such interventions include vaccination against blood-borne and sexually transmitted diseases targeted in intravenous drug users and people with high sexual partner change where the main routes of transmission are needle sharing and sexual intercourse, such as HIV or HBV. Cohort models are likely to be most accurate for the first cohort to be vaccinated and become less and less so for further cohorts. This implies that, even more than for dynamic models, repeated economic evaluations are required as the epidemiological (and economic) parameters change after a programme is implemented. Too little attention is currently being paid to this kind of analysis, as the tendency is to take a decision and not look back at cost-effectiveness empirically.

Table 8: Practical differences of static versus dynamic models for economic evaluation

	Static	Dynamic
Typical population in which costs and effects are monitored	A single ageing cohort (with removal of deaths from all causes through time)	The entire population (with introductions of births and removal of deaths from all causes through time)
Development complexity	Easy to develop, embedded in traditional health economic methods	Not part of the traditional toolbox of epidemiologists and health economists
Ready to use software[a]	Spreadsheets, e.g. MS ExcelTM (www.microsoft.com) @RiskTM (www.palisade.com) TreeAge ProTM (www.treeage.com), Crystal BallTM (www.crystalball.com)	Berkeley MadonnaTM (www.berkeleymadonna.com) Model MakerTM (www.modelkinetix.com) StellaTM (www.iseesystems.com) VensimTM (www.vensim.com)
Required data	Requires (usually age-specific) data on epidemiology, demography, course of illness, vaccine efficacy, costs	Same as with static models + average duration of infectiousness + information on relevant[b] mixing patterns between infectious and susceptible people

[a]   note that both static and dynamic models can also be programmed directly in basic programming languages or more generic software (e.g. C++, Visual basics, S-plus), including freeware (e.g. R, WinBUGS).

[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 patterns could be estimated partially from prevalence data, but not completely without making some simplifying assumptions (75;118-122).

There are many challenges to modelling infections beyond herd immunity effects for a single pathogen, which is the situation we have implicitly emphasized here. The consideration of various expressions (e.g. serogroup, serotype, genotype) of pathogens, which may or may not be competing 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 convincing 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. Clearly, this would further increase 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).

6.4   Model validation

In principle, there is no difference between model validation for vaccination programmes and for other interventions that inform policy. Analysts should strive, as much as possible, to explore the various facets of validation outlined in this section (123).

6.4.1 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 (12). 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 (see flow chart). Results of validity analysis (before interventions are introduced into the model) should be presented in an appendix.

Calibration implies checking the results of the model versus unrelated observations (unrelated in the sense that they were not used as parameters in the model). Furthermore, uncertain parameters in the model can be changed to obtain the best fit for the model results to unrelated observations. An example of such fitting for Meningococcal C vaccination is provided in Trotter et al (124). Unrelated observations could for instance come from vital statistics or health care utilization data, e.g. cancer registry data to fit models for HPV (125).

6.4.2 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 some examples of dynamic models reaching substantially different results to static models (12;21). 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. In fact, in the absence of herd immunity, the multi-cohort static model result should theoretically be identical to the dynamic model result.

6.4.3 Face and predictive 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.

Predictive validity is often problematic to show as circumstances change. Vaccine prices, for instance, have been known to fluctuate significantly and many other factors are subject to future 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.

6.5   Recommendations

The mathematical model should be:

- Transparent in that the structure and implicit or explicit assumptions are all clearly described.

- Static, if vaccination is unlikely to change the force of infection in susceptibles or as a means to make a conservative estimate when externalities from herd-immunity 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

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 most vaccination programmes is highly sensitive to discounting. This chapter examines why vaccination programmes tend to be sensitive to the choice of discount rate.

7.1   Using constant discount rates

The choice of discount rate is particularly critical as discounting can greatly influence the estimated efficiency of vaccination programmes with long-term effects. The prevailing opinion in the health economics community is that health effects should be discounted at the same rate as costs. However, some health economists argue that health effects should be discounted at a lower rate than costs (126-128). Most general guidelines reflect these different opinions by recommending that health effects be presented as both discounted and undiscounted values (129). It should be noted that a zero discount rate for health effects could lead to undesirable implications such as infinite benefits arising from successful eradication programmes, e.g. polio, measles. Therefore, a non-zero discount rate for health effects, lower than the rate for costs, could be considered when presenting results.

This guide recommends initially using the rate used in the country in question, but also, in order to be consistent with earlier recommendations made by WHO-CHOICE and the Second Edition of Disease Control Priorities in Developing Countries (DCP2), a 3% discount rate. Authors should conduct sensitivity analysis using discount rates of 0%, near-zero, 5% and 10% for evaluations undertaken in developing countries in order to reflect the (probably) higher real risk-free cost of capital in developing countries[16].

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[16]   There is still controversy and less than full professional consensus on these choices, particularly as to their application to poorer countries (130).

7.2 When a non-constant discount rate should be considered

There are two circumstances in which constant discounting may appear to under-value the future (131). The first is when the consequences of what happens today may endure a long time into the future; any constant rate much above zero will then give almost no weight to distant consequences. This consideration may apply to estimates of the burden of disease, for deaths at early ages that imply the loss of many decades of life (e.g. rotavirus), or early incidence of permanent disability that lasts for the rest of life and does not hasten death (e.g. polio). Similarly, it applies to economic evaluation for all interventions that avert death or chronic disability at very early ages. To the extent that an intervention protects future generations, the effect may last even beyond the lifetime of the initial beneficiary.

The second circumstance is when an intervention today begins to take effect only after a long interval, during which discounting will reduce the importance of the time after which the effect occurs. Immunization in infancy against HBV in order to reduce the risk of liver cancer after age 40 or 50 is an example of this; it is quite different in this respect from immunization against polio or measles (but similar to HPV vaccination).

For the few interventions where the costs and benefits are likely to be observed over time horizons of 100 years or more, or where there is a lag of several decades between the costs of the intervention and the beginning of the benefit stream, analysts are encouraged to check the sensitivity of their results to the application of a non-constant discount rate (declining or "slow", compared to exponential discounting, i.e. discounting at a constant rate) (131).

7.3 Recommendations

- Discount costs and effects initially using the rate in the country in question (for studies to inform local decision-makers) and then using a 3% discount rate (consistent with WHO-CHOICE and DCP2);

- Conduct sensitivity analysis using discount rates of 0%, near-zero, 5% and 10% to reflect the (probably) higher real risk-free cost of capital in developing countries;

- A non-constant (declining or 'slow') discounting procedure may be applied where the effects begin only long after the intervention, e.g. vaccination against HBV or HPV, or last for an exceptionally long time, e.g. polio eradication.

Chapter 8:
Estimating, Presenting and Interpreting Cost-effectiveness Data

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 some of the methods available for presenting such 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.

8.1   Linking costs and effects

Having assessed the costs (Chapter 4) and effects (Chapters 5 and 6) of a vaccination programme, the next step in an economic evaluation is to bring together these results, in the form of a ratio, to provide an overall indication of cost-effectiveness in a way that will inform decision-making. 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 programme 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).

$$ACER = \frac{C_{Intervention\ A}}{E_{Intervention\ A}}$$

- 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.

$$MCER = \frac{C_{Intervention\ A+1} - C_{Intervention\ A}}{E_{Intervention\ A+1} - E_{Intervention\ A}}$$

- 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 productivity losses depending on the choice of perspective. Similarly, the ICER denominator is the difference in health outcomes[17].

$$ICER = \frac{C_{Intervention\ A} - C_{Intervention\ B}}{E_{Intervention\ A} - E_{Intervention\ B}}$$

8.1.1 Comparing 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[18]. 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 (see below on interpreting cost-effectiveness data). 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.

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[17] 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.

[18] When usual practice is no vaccination, e.g. screening, it is rare for this to be more effective than vaccination but it might be less costly. This is obviously the case when only the programme costs are considered but may also be the case when treatment costs and productivity losses are considered. However, 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. Indeed, depending on the cost of targeting, universal vaccination may also be less costly.

8.1.2 Comparing multiple interventions

In studies that compare multiple mutually exclusive vaccine strategies, i.e. if a child receives one of the strategies they will not receive the other, 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 or vice versa. The analyst should then apply the principle of extended dominance (sometimes called 'weak dominance'). The list of interventions, trimmed of strongly dominated alternatives, is ordered by 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. The decision-maker prefers the more effective intervention with a lower ICER. Approving the more effective interventions allows DALYs averted to be purchased more efficiently.[19] It is important to note that while this approach is technically correct, 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 introduce a less cost-effective, or even dominated, vaccine.

Table 9 and Figure 4 illustrate how the three measures of cost-effectiveness differ, and the principles of strong and weak (or extended) dominance, using a hypothetical example of three different ways to deliver immunization.

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 E2 (measured as coverage or as disease reduction, e.g. DALYs averted) at a total cost C2. The ratio C2 to E2 is the ACER, shown by the slope of the line O-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 C2 to C3, yields only a small increment E3-E2 in effect. The slope of the line X-X1 represents the MCER of that expansion, which would raise the ACER to line O-X1. A reduction in coverage from X to X2 would improve the average cost-effectiveness (to C1/E1) because marginal costs are rising steeply near point X. The MCER of the reduction in coverage is the ratio of C2-C1 to E2-E1. In Figure 4 MCERs are indicated as red arrows.

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[19] Dominance principles can be also applied by ranking interventions in the order of their cost; the same finding will result. Dominance principles can be applied when outcomes are measured in units other than DALYs.

Figure 4: Average, marginal and incremental cost-effectiveness and intervention choices – comparison of three ways to deliver vaccination
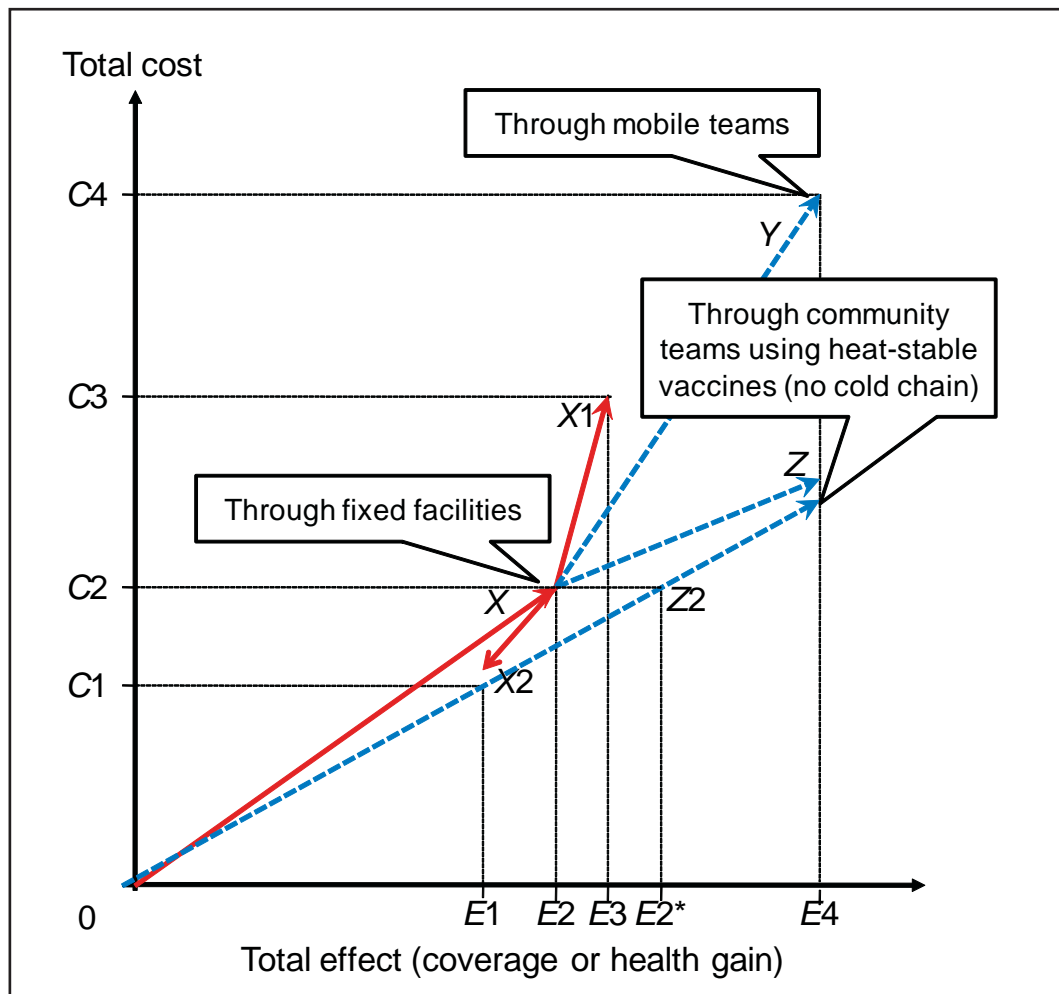
Source: Musgrove & Fox-Rushby (132)

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 E4 at a total cost of C4. 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 O-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 9: Average, marginal and incremental cost-effectiveness
and intervention choices – comparison of three ways to deliver vaccination
(Note: numbers are for illustration purposes)**

Intervention	Total costs	Total effects	ACER	MCER	ICER
X	100	10	=10 (100/10)	-	-
X1	180	12	=15 (180/12)	=40 compared to X, i.e. (180-100)/(12-10)	-
X2	63	7	=9 (63/7)	=12.3 compared to X1, i.e. (100-63)/(10-7)	-
Y	250	20	=12.5 (250/20)	-	=15 compared to X, i.e. (250-100)/(20-10)
Z	125	20	=6.25 (125/25)	-	=2.5 compared to X, i.e. (125-100)/(20/10)
Z2	100	16	=6.24 (100/16)	=6.25 compared to Z (assumes that intervention Z is perfectly divisible and exhibits constant returns to scale	Z2 weakly dominates X because it is the same cost but more effective

If intervention Z is divisible (meaning that it can be operated at any desired scale, such as Z2), then it is preferable to X at a cost of C2 because of the additional effect E2*-E2. 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, or threshold, value for the ICER is determined, then any intervention that falls below it would be acceptable, and those that fall above it would not be (see sections 8.3 and 8.4 below). 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.

8.2 Sources of and methods of representing uncertainty

Uncertainties pervade all economic evaluations. Good evaluation involves assessing the impact of the uncertainties in the parameter values used and in the relationships that determine how model outputs depend on model inputs.

Manning et al. (133) distinguished two types of uncertainty: parameter and modelling. Parameter uncertainty is "…uncertainty about the true numerical values of the parameters used as inputs". They argue it arises for several reasons. For example:

- The size of key inputs (either their quantity or value of the quantity) in the economic evaluation is unknown or not observable, e.g. the price of future vaccines.
- There is not consensus about what value an input parameter should take, e.g. the discount rate.

- There is uncertainty about the process behind variables, e.g. factors explaining utilization of services or aspects of the epidemiology of disease.

- There is sampling variability of parameters, e.g. estimates of the response to vaccination or treatment.

- It is unclear how estimates relate to different populations, e.g. extrapolating costs or effects to a random, rather than convenience, sample.

Modelling uncertainty is broken down into 'model structure uncertainty' and 'modelling process uncertainty' (133). Model structure uncertainty concerns doubts about the correct method for combining the parameters of the costs, consequences and/or combinations of costs and consequences. This could include debates about whether particular types of costs or effects should be included, e.g. productivity costs or decisions to include/exclude particular types of adverse reactions, and about the functional form associated with effectiveness, e.g. the impact on disease of coverage of a population by a vaccine, or cost, e.g. the impact of scale of production on the various inputs costed, or the relationship between costs and effects. In all instances, questions of whether the parameters assume multiplicative or additive forms can influence the results. Modelling process uncertainty is the uncertainty introduced by the combination of decisions made by the analyst. The analyst retains the most influence over choosing what variable to include and how. For example, Busulwa et al. (134) showed that the training and working pattern of economic evaluation students affects both the variables selected for analysis as well as the results.

The principal methods for handling uncertainty are (135):

- One-way 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 level at which the results change, e.g. the price per dose at which the cost per DALY averted reaches the GNI per capita of the country where the intervention is being evaluated – this would determine the threshold, sometimes referred to as the switching price. 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 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 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 (highest) and the best (lowest) cost-effectiveness ratios are combined. The second is the use of an agreed 'reference case' of methods by analysts. The best known reference case is described by Gold et al. (5)[20], 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. (136) 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 economics evaluation of immunization programmes;

- Probabilistic sensitivity analysis: another kind of sensitivity analysis that is becoming widely used in model-based economic evaluations. In this type of analysis, probability distributions are applied to specified ranges for the key parameters and samples are drawn at random from these distributions to generate an empirical distribution of the cost-effectiveness ratio (4);

- Sensitivity analysis varying structure (for model structure uncertainty);

- Examination of analyses by multiple analysts (for model process uncertainty).

We recommend beginning with one-way analyses as a route to understanding the impact of individual variables/models, before moving to multivariate analyses. As a minimum, analysts should conduct one-way sensitivity analyses of the following variables: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant) and vaccine price. Analysts should also conduct an analysis of extremes to assess the robustness of the findings to changes in the value of multiple parameters at the same time. Where a best or worst case scenario changes the conclusions, analysts should perform a probabilistic sensitivity analysis and use a CEAC to represent the uncertainty (see below).

8.3   Interpreting results

Faced with a fixed health budget and the goal of minimizing population ill health, as measured by an index such as the DALY, the best approach is to rank all independent health interventions in descending order of efficiency determined by the cost per DALY averted and then fund interventions running down the list until the money runs out. At that point, the last intervention funded would have a threshold ICER that reflected the willingness to pay for an extra DALY averted for a given budget. When, as in low-income countries, budgets are small, the threshold ICER will be much lower than in high-income countries. Note that although there is often said to be a tension between the cost-effectiveness of an intervention and its affordability, if a vaccine is cost-effective it should also be affordable, so long as the cost-effectiveness threshold has been set appropriately.

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[20]   See their Appendix A and applications of the reference case given in Appendices B and C in Gold et al. (5).

There are a number of technical problems in using an ICER threshold decision rule for priority-setting. Accurate ranking of interventions would need perfect information on the costs and outcomes of all current and potential interventions in all relevant populations. Only then could we say with confidence that a new vaccine with, for example, an ICER of $500 per DALY averted will represent 'value for money' because it will displace spending on other interventions that cost more than $500 per DALY averted. Such complete data will never be available, and so we need a second best heuristic for our imperfect world. The pragmatic approach is comparing an ICER with a notional threshold, adjusting for the budgetary impact and considering other relevant factors.

In economic evaluations of health care interventions to date, many analysts have avoided the issue, and have simply presented results without interpretation or recommendation; definitions of the threshold, or ceiling ratio, have been left largely to the discretion of the analyst. The ceiling ratio represents a decision maker's valuation of a unit of health gain and is a particularly crucial and politically sensitive element of economic evaluation, as it is the relative value against which the acceptability of ICERs are judged. If the value of an ICER is below the ceiling ratio, an intervention is deemed acceptable on grounds of cost-effectiveness. However, the value of the ceiling ratio that is appropriate may be heavily contingent upon several factors (see Chapter 9), and is likely to vary across time and space.

Based on the recommendation of the Commission on Macroeconomics and Health (CMH)(137), WHO classifies interventions as 'highly cost-effective' for a given country if results show that they avert a DALY for less than the per capita national GNI or GDP. Such reference case estimates for ceiling ratios are often useful. Consider, for example, the following four reasons:

- With no standard value for the ceiling ratio, analysts may be tempted to promote interventions based on comparison with studies that evaluate interventions with unattractive ICERs.

- Decision-makers may wish to be consistent with other decision-making bodies or their own former decisions, and an explicit and transparent normative definition may reduce the risk of them being held culpable for unpopular decisions.

- Across sectors, economic evaluation in the health sector makes the extra-welfarist assumption that society wants to maximize health from their investment, and estimates of the ceiling ratio allow decision-makers to convert outcomes to a metric that can be compared across different economic sectors, as in the Copenhagen Consensus.

- Technically, a reference case estimate for the ceiling ratio is necessary for new developments in decision analysis, such as expected value of perfect information analysis, or cost-effectiveness probability planes that test robustness of results according to uncertainty in several dimensions.

Several countries have their own thresholds. For example, $50,000 per QALY gained (1982 US$) is commonly used as the threshold in the USA (138;139); if this threshold is inflated to 2005, it becomes $99,805/QALY. Likewise, in Canada the range of values proposed is CAN$20,000-$120,000 (1990 CAN$) (140), which is equivalent to US$18,796-$93,720 (2005 US$). In the UK, £30,000/QALY is commonly used in economic evaluation as the ceiling ratio (141;142). Recently, the Council of Public Health and Health Care in the Netherlands announced a threshold of £80,000/QALY (143) while the commonly used ceiling ratio would be €20,000/QALY (144). These thresholds all apply to decision-making at the national level; however, decisions may be made at the international, sub-national, or individual hospital levels and decision-makers may wish to define thresholds according to their own contexts.

We also recommend that analysts place their findings in broader context by comparing them to other economic evaluations that have been undertaken in the same or neighbouring countries after adjustments have been made for inflation.

8.4   Reporting uncertainty to decision-makers

Although calculations are often reported to several significant digits, such precision is not really feasible given the uncertainties in the original data: Morgenstern cites the remark of Norbert Wiener that "…economics is a one or two digit science" (145). Therefore, given the nature of the uncertainties, it is not possible to recommend that a vaccine shown to cost $50 per DALY averted is more efficient than one costing $60. However, we can place much greater confidence in the difference between $50 per DALY averted and $500 per DALY averted.

Cost-effectiveness acceptability curves (CEACs) have been developed as a technical approach that absolves analysts from committing to a fixed value for the ceiling ratio (146-149). CEACs summarize results by plotting the probability that an intervention is cost-effective according to a range of ceiling ratios (Figure 5). The CEAC presented here is a 'textbook' example. However, this familiar 'ogive' shape represents just one of the possible shapes that CEACs can take. This typical example, illustrates the scenario where the entire joint density of incremental costs and effects is contained within the northeast quadrant of the cost-effectiveness plane, where the intervention is both more costly and more effective[21].

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[21]   See Fenwick et al. (147). For a recent critique of the limitations of CEACs for presenting uncertainty to decision-makers, see Groot.-Koerkamp et al. (150).

Figure 5: Cost-effectiveness acceptability curve
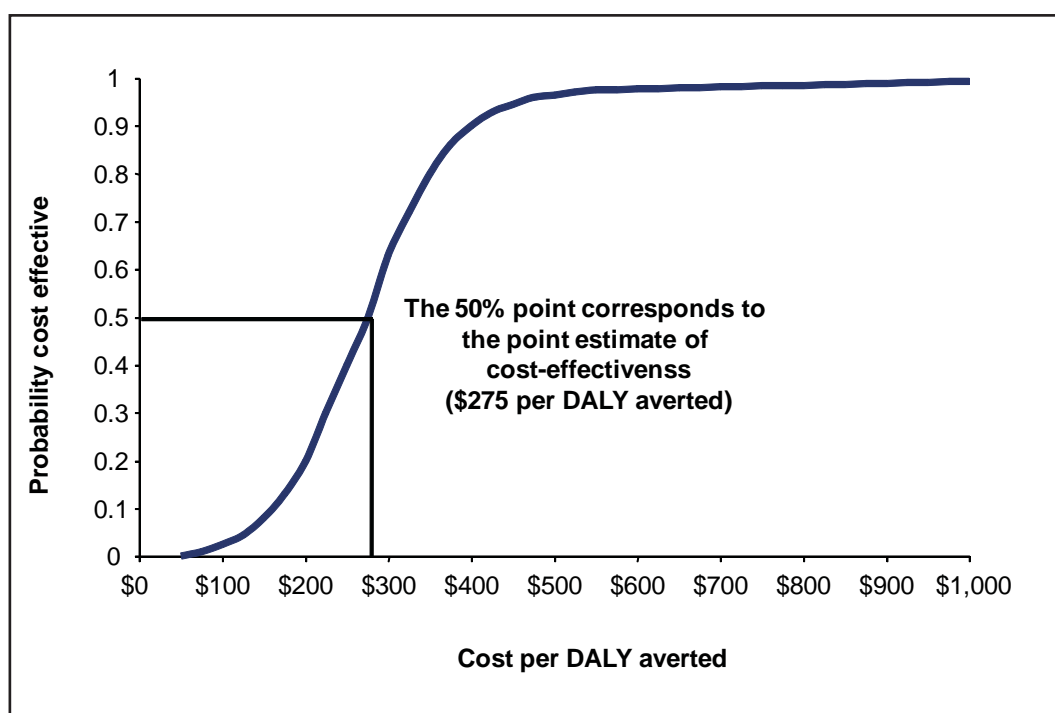
The presentation of the results of uncertainty analysis in CEA in the literature has been relatively academic, with little attention paid to the question of how decision-makers should interpret the information, particularly when confidence intervals overlap. Hutubessy et al. (151) introduced the concept of stochastic league tables to inform decision-makers about the probability that a specific intervention would be included in the optimal mix of interventions for various levels of resource availability, taking into account the uncertainty surrounding costs and effectiveness. This information helps decision-makers decide on the relative attractiveness of different intervention mixes, and also on the implications of trading gains in efficiency for gains in respect of other goals such as reducing health inequalities or increasing health system responsiveness.

8.5 Recommendations

- Analysts should begin by excluding those interventions that are dominated, i.e. both more costly and less effective than alternative options;

- As a minimum, analysts should conduct one-way sensitivity analyses of the following variables: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant), case fatality rates and vaccine price;

- The classification of cost-effective and cost-ineffective interventions should not be made on the basis of point estimates of cost-effectiveness because of uncertainty about the estimates of cost, effects and hence cost-effectiveness;

- Analysts should use the recommendation of the CMH that has been endorsed by WHO and classify the results of their evaluation according to the per capita national GDP of the country in question: less than one classifies a vaccine as 'highly cost-effective'; between 1 and 3 times classifies an intervention as 'cost-effective'; and more than 3 times classifies an intervention as 'cost ineffective';

- 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.

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 reviews recent 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

Although more than 200 economic evaluations of vaccination programmes have been published (the *supply* of economic evidence) (94), there are unfortunately few examples of evidence about their use at global, regional, national or local levels (the *demand* for economic evidence). The analyses by Welte et al. (152) and Bos et al. (153) are rare documented examples in the literature of studies that have informed the decision-making process. Interestingly, the study by Welte et al. (152) supported the Dutch government's decision to implement a new vaccination programme, while the study by Bos et al. (153) supported the Dutch government's decision not to implement a different vaccination strategy (Box 4).

Box 4: The use of economic evaluation in policy and practice – examples from The Netherlands

Welte et al. (152) 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. (153) 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 is considered the ceiling ratio. 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.

Indeed, it is difficult to gauge the usefulness of economic evaluations for the decision-making process. Brinsmead et al. (16) looked at the published economic evaluations regarding Hib vaccines. Hib vaccines have been implemented in all of the industrialized, and a number of the developing, countries where published economic evaluations have been set (and in many countries where no economic evaluations have been undertaken). For some of these settings the decision-making process could be partially characterized based on the published literature. In addition, Brinsmead et al. (16) contacted some of the authors of the studies for their views on the role their studies had played in the local decision to introduce Hib vaccine. Overall it was clear that a published economic evaluation is neither necessary nor sufficient to a decision to implement Hib vaccination. In one setting for example, CBA was able to influence decision-making only after the intercession of "luck" brought Hib to the attention of treasury personnel. That economic evaluation alone was not sufficient is not surprising – indeed, as we will see below, there are many other criteria that should be borne in mind when making decisions – but that it was unnecessary is of concern.

Vaccine decision-makers operate at levels ranging from the national (ministry of health) to the global (e.g. GAVI, WHO). Although the process at the global level is increasingly systematized, e.g. through templates such as GAVI's Financial Sustainability Plan, which have been replaced by cMYPs, the decision process at the national level appears to be variable and poorly understood. The optimal role of economic evaluation (the "moments" in decision-making when it might be most influential) remains undefined.

Common sense suggests two potential solutions to suboptimal use of economic models in decisions: adopting methodologies and presentation formats that decision-makers understand; and/or training and supporting decision-makers in the use of existing models. The choice between these approaches has been debated elsewhere in health care decision-making (154). However, without a full understanding of the decision-making process, it is not clear which solution is required. Thus, there is a need for better understanding of the relevant decision process. Attention to these aspects of

usefulness will ensure the role of future economic evaluations as important decision tools in the implementation of new vaccines. It is apparent –and this applies to developing and, albeit to a lesser extent, to developed countries – that decision-making procedures will need to be modified to accommodate evidence-based approaches, such as economic evaluation. Otherwise, economic evaluations of immunization programmes risk being regarded by decision-makers as little more than academic exercises.

9.2   Decision-making bodies

While some countries have a separate advisory group on vaccination, which uses evidence on cost-effectiveness and exerts great influence on policy, e.g. the United Kingdom's Joint Committee on Vaccination and Immunisation and the United States' Advisory Committee on Immunization Practices[22], most 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 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 and is underway (for example see Andrus et al (155) for Latin America) to develop the evidence base countries need for making informed decisions; little effort has thus far been expended to ensure that countries have processes in place to evaluate and use this information.

9.3   Other criteria to consider when making decisions

While the emphasis of this guide is on value for money – that is, whether a vaccine is worth buying – and not who pays for it, if the object is to decide how to spend public funds, economic evaluation is only one of at least nine criteria relevant for priority-setting in health (156). 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[23]; 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, just as in other sectors.

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[22] 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).

[23] See Yeung and Smith (2005) for a review of contingent valuation, or willingness to pay, studies (157).

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.

Polio vaccination is an example of where other elements in the decision-making process have 'trumped' the 'logic of cost-effectiveness'. Polio is eliminated from most of the developed world. This makes the risk of acquiring paralytic polio from the live OPV unacceptable. However, the risk-free IPV is far more expensive, and would be judged unacceptable if value for money were the only criterion considered. Nevertheless, until polio is eradicated globally, the risk of outbreaks remains very real. Therefore, concerns over the public's perception about the risks associated with OPV led to its replacement by IPV in most developed countries. Interestingly, however, one must assume that value for money has thus far been an important part of the rationale to continue using OPV in developing countries.

9.4 The trade-off between efficiency and equity

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 (158) raises the possibility that the introduction of new vaccines might primarily benefit children who are already covered by existing interventions. 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 (see section 4.5). Therefore, analysts are urged to consider the distributional impacts of the vaccine(s) analysed and to note how far its introduction would affect equity (159).

9.5 Including the broader benefits of vaccines

To date, guidelines for economic evaluations have not advocated taking full account of the broader economic impacts of measures to control vaccine-preventable diseases, particularly those targeted at infants and children. Examples of broader economic impacts are that (160):

- Healthy children are better able to attend school and learn effectively while in class.

- Healthier workers, like schoolchildren, have better attendance rates and are more energetic and mentally robust. Moreover, workers living in healthy communities need to take less time off to care for sick relatives.

- Healthier people expect to live longer, and thus have greater incentive to save for retirement. They are also able to work productively for longer, giving them more time to save. Workers and entrepreneurs therefore have a larger capital base to draw on for investment, leading to greater job creation and higher incomes.

These impacts stem from the fact that many interventions not only treat, or protect individuals against getting, a disease per se, but also protect against the long-term effects of that disease on their physical, emotional, and cognitive development. For example, by stunting physical growth, childhood diseases can curtail opportunities for undertaking manual labour during adulthood. In developing countries, where manual work is frequently the only option, physical handicaps are particularly damaging. Cognitive development may also be affected by vaccine-preventable disease. Measles, for example, can cause brain damage or impair learning abilities, with severe impacts on a child's life prospects.

The importance of these effects is borne out by recent work demonstrating the link from improved health to economic growth (137). This research has made clear the importance of health interventions for achieving growth and suggests that economic evaluations, as currently conducted, are likely to underestimate the benefits of any interventions aimed at vaccine-preventable diseases.

Chapter 10: Conclusions and Summary of Recommendations

Decision-making for vaccines is getting tougher. Over the next decade, a number of new vaccine products will become available. With the advent of new more expensive products ("product pile-up"), countries will face a significant decision-making challenge. Data regarding the relative cost-effectiveness of these products will be 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.

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 10 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 11 provides an example of how to apply the Checklist to a published economic evaluation of an immunization programme.

Table 10: A Checklist for appraising the quality of economic evaluations of immunization programmes

Aspect:	Attributes of good practice	Questions for critical appraisal
Framing the analysis (Chapter 3)	The study question should be well-defined, stated in an answerable form and relevant to the decision facing the target audience.	Is there a clear statement of the study question?
	The alternatives being compared should be clearly stated.	Have the alternatives being compared been clearly stated?
	Cost-utility analysis is the preferred form of economic evaluation.	Has a cost-utility analysis been performed? If not, has that decision been justified appropriately?
	Ideally analyses should adopt the perspective of society, although the costs and outcomes should be disaggregated so far as possible, to allow judgments to be made from the viewpoints of different decision-makers.	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?
	The time frame and analytic horizon should be clearly stated. Their respective durations are contingent on the type of vaccine-preventable disease evaluated and thus the type of model developed.	Are the time frame and analytic horizon clearly stated and justified?
Costs (Chapter 4)	A summary should be provided of the methods used to estimate costs. Ideally, quantities of resources should be reported separately from their unit costs. This should include specifying the assumptions behind the cost calculations.	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?
	Costs for patients and their families, including lost productivity if considered, should be reported separately.	If productivity losses were estimated have they been reported separately? Has their relevance been discussed?
	Where productivity losses have been estimated, the method used should be clearly described and justified.	Have the methods used to estimate them been described and justified?
	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 and also converted to I$ using purchasing power parity (PPP) exchange rates for the purposes of regional or global comparison.	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?

Aspect:	Attributes of good practice	Questions for critical appraisal
Effects (Chapter 5)	Estimates of vaccine efficacy should be based upon systematic reviews of the literature where available.	Was the evidence identified systematically?
	The methods should be described, e.g. if a single study is used, its internal validity should be discussed, if multiple studies are used, the method used to synthesize the results should be discussed.	Were the methods described? If a single study was used, was its internal validity discussed? If multiple studies were used, was the method used to synthesize the results also discussed? Was the external validity of the evidence discussed?
	Evidence regarding vaccine safety should be provided or referenced.	Was appropriate evidence of vaccine safety provided or referenced?
	If applicable, the method of valuation and the source of the values should be described.	If applicable, were the method of valuation and source of the values described?
	If adverse events from immunization impacts 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 their likelihood of occurring as a consequence of vaccination and their severity.	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?
Modelling (Chapter 6)	The model should be transparent in that the structure and implicit or explicit assumptions are all clearly described.	Are the model structure and implicit or explicit assumptions clearly described?
	The model should be static if vaccination is unlikely to change the force of infection in susceptibles or as a means to make a worst-case estimate when externalities from herd-immunity cannot on the whole be adverse.	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?
	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 worst case estimate, or if the worst case estimate from a static model does not lead to a favourable outcome.	
	The model should be stochastic/micro simulation, if chance plays an important role in the transmission process.	
	The model should be validated, in as many facets of validation (verification, calibration, face validity, predictive validity) as possible, but at least verified.	Has the model been validated? If so, has it been validated in as many facets of validation as possible?
Discounting (Chapter 7)	For national analyses, the local rate should be used. However, to improve comparability with other studies, a 3% rate should be used to be consistent with international recommendations such as WHO-CHOICE and DCP2.	Is the discount rate clearly stated and justified?
	Sensitivity analysis should be conducted using discount rates of 0%, near-zero, 5% and 10% to reflect the (probably) higher real risk-free cost of capital in developing countries.	Has sensitivity analysis been conducted to explore the impact of varying the discount rate?
	A non-constant (declining or 'slow') discounting procedure may be applied where the effects start only long after the intervention, e.g. vaccination against HBV or HPV, or last for an exceptionally long time, e.g. polio eradication.	

Aspect:	Attributes of good practice	Questions for critical appraisal
Uncertainty (Chapter 8)	The costs and effects should be presented for all alternatives as well as the incremental costs and effects between alternatives.	Have the costs and effects been presented for all alternatives?
	Those interventions that are dominated, i.e. both more costly and less effective than alternative options, should be excluded first.	Have dominated interventions been identified and excluded?
	As a minimum, one-way sensitivity analyses should be conducted of the following variables: discount rate, vaccination effectiveness (where unknown or uncertain), incidence of disease (including complication rates where relevant), case fatality rates and vaccine price.	Has sensitivity analysis been conducted to assess the robustness of the findings to changes in the value of key parameters? Has the choice of parameters and the ranges over which they have been subjected to sensitivity analysis, been stated and justified?
	Analysis of extremes should be conducted in order to assess the robustness of the findings to changes in the value of multiple parameters at the same time. Where a best or worst case scenario changes the conclusions, a probabilistic sensitivity analysis should be conducted and a CEAC used to represent the uncertainty.	Has analysis of extremes been conducted? Where a best or worst case scenario changes the conclusions, has a probabilistic sensitivity analysis been conducted and a CEAC been used to represent the uncertainty?
	If there is a national CE threshold, analysts should use it. Otherwise, the recommendation made by CMH, and endorsed by WHO, should be used, and the results of their evaluation be classified according to the per capita national GDP of the country in question: less than one classifies a vaccine as 'highly cost-effective'; between 1 and 3 times classifies an intervention as 'cost-effective'; and more than 3 times classifies an intervention as 'cost-ineffective'.	Has the national CE threshold been used, if one exists? If there is no national CE threshold, have the results of the evaluation been classified according to the per capita national GDP of the country in question?
	Findings should be placed in broader context by comparing them to other economic evaluations that have been undertaken in the same or neighbouring countries, after adjusting for inflation.	Have the findings been compared to other economic evaluations undertaken in the same or neighbouring countries?
Other Factors (Chapter 9)	Other important factors in the decision under consideration should be discussed, e.g. distribution of the costs and effects, or relevant ethical issues.	Is there a discussion of other important factors in the decision under consideration?
Conclusions	An answer to the study question should be given. The conclusions should follow from the data reported.	Is an answer given to the study question? Do the conclusions follow from the data reported?
	The conclusions should be accompanied by the appropriate caveats.	Are the conclusions accompanied by the appropriate caveats?

Table 11: A critical appraisal of Akumu et al. (161) using the Checklist (answer either 'yes', 'no', 'partially', 'not clear' or 'not applicable')

Aspect:	Questions for critical appraisal	Answers
Framing the analysis (Chapter 3)	Is there a clear statement of the study question?	Yes - the objective of this study was to estimate the incremental costs per case, death and DALY, averted by delivering Hib vaccine in routine infant immunization services in Kenya.
	Have the alternatives being compared been clearly stated?	Yes – vaccination and no vaccination.
	Has a cost-utility analysis been performed? If not, has that decision been justified appropriately?	Yes – both a CUA and CEA were performed.
	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?	Yes – the analysis was carried out from a public health provider perspective; costs incurred by households were not included.
	Are the time frame and analytic horizon clearly stated and justified?	Yes – a model was developed to follow the 2004 birth cohort until death.
Costs (Chapter 4)	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?	Yes – Table 2 provides details of the quantities of vaccines and their unit costs. Other vaccine delivery costs, such as staff salaries and transport, were not included. These, the authors argue, would not be affected markedly as there is no difference in the number of health service contacts for the two different types of vaccines. Ministry of Health staff members were interviewed in order to assess other costs related to vaccine introduction, such as enhanced surveillance and training activities. GAVI supported the Kenyan Government with US$100,000 to finance training and communication activities. For Hib disease treatment costs, the authors reviewed the hospital records of 31 children admitted in 2001 with proven invasive Hib disease (21 meningitis and 10 non-meningitis invasive disease) and extracted information on diagnostic tests, drugs administered and the length of hospital stay. Because the facility from which they obtained the records is a research setting, certain diagnostic tests and treatment procedures differ from standard Kenyan practices. So as to avoid inflating the national cost estimates the authors substituted Kilifi District Hospital costs for third-generation cephalosporins, not currently recommended as first-line antibiotic therapy in Kenya, with costs for penicillin and chloramphenicol, and excluded blood culture costs. For non-bacteraemic Hib pneumonia, patient-specific data on resource usage were collected from a total of 76 pneumonia patient records at three district hospitals. Unit costs for drugs were collected largely from the Kenya Medical Supplies. Agency. Costs per bed-day and per outpatient visit were taken from the WHO-CHOICE database.
	If productivity losses were estimated have they been reported separately? Has their relevance been discussed?	Not applicable.

Aspect:	Questions for critical appraisal	Answers
	Have the methods used to estimate them been described and justified?	Not applicable.
	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?	The 2004 average exchange rate of 79.49 Kenyan shillings to US$1 was used in all calculations.
Effects (Chapter 5)	Was the evidence identified systematically?	Not applicable – the hospital incidence of Hib invasive disease per 100 000 children aged < 5 years was 66 (95% confidence interval, CI: 49.6–81.6) before the introduction of Hib vaccine (2000/2001) and 7.6 (95% CI: 1.6–22.3) three years after its introduction (2004/2005). See reference: Cowgill et al.. (162).
	Were the methods described? If a single study was used, was its internal validity discussed? If multiple studies were used, was the method used to synthesize the results also discussed? Was the external validity of the evidence discussed?	
	Was appropriate evidence of vaccine safety provided or referenced?	No reference was made to vaccine safety.
	If applicable, were the methods of valuation and source of the values described?	Disability-adjusted life years (DALYs) were estimated using the method recommended in the 1996 global burden of disease study. Age-weighting was included. The disability weight is 0.616 for the acute phase of bacterial meningitis and 0.28 for an episode of non-meningitis invasive Hib disease and non-bacteraemic pneumonia.
	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?	No reference was made to adverse events.
Modelling (Chapter 6)	Are the model structure and implicit or explicit assumptions clearly described?	No – the authors simply state that "A model was developed to follow the 2004 birth cohort until death. Two scenarios were constructed: one with Hib vaccine in routine immunization services and one without. Only immediate costs of care were estimated, excluding the costs of providing long-term care for patients with severe sequelae."
	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?	Unclear but appears to be a static model.
	Has the model been validated? If so, has it been validated in as many facets of validation as possible?	Unclear.
Discounting (Chapter 7)	Is the discount rate clearly stated and justified?	Yes – all future costs and outcomes were discounted at 3%. However, no justification was given.
	Has a sensitivity analysis been conducted to explore the impact of varying the discount rate?	Yes – both discounted and undiscounted results are presented in Table 4.

Aspect:	Questions for critical appraisal	Answers
Uncertainty (Chapter 8)	Have the costs and effects been presented for all alternatives?	Yes – see Table 4.
	Have dominated interventions been identified and excluded?	No applicable – vaccination is both more costly and more effective
	Has sensitivity analysis been conducted to assess the robustness of the findings to changes in the value of key parameters? Has the choice of parameters and the ranges over which they have been subjected to SA, been stated and justified?	Yes – the authors undertook probabilistic sensitivity analysis to assess the impact of uncertainty in parameter values. Prediction intervals around the mean cost-effectiveness ratios were derived from 50,000 Monte Carlo simulations by Crystal Ball software. For the disease burden parameters the authors assumed either triangular or normal distributions with ranges or standard deviations respectively (Table 1). Based on previous patterns and the analysis of patient records, a lognormal distribution was assumed for the treatment cost parameters. One-way sensitivity analyses were undertaken to assess the importance of herd immunity and vaccine price. The authors also calculated the break-even price of the vaccine.
	Has the national CE threshold been used, if one exists? If there is no national CE threshold, have the results of the evaluation been classified according to the per capita national GDP of the country in question?	Yes – the authors used the WHO recommendation that an intervention may be considered very cost-effective if the costs per DALY averted are less than the country's per-capita GDP. The cost per DALY averted ranged between US$26-63; the GDP per capita of Kenya in 2004 was US$481.
	Have the findings been compared to other economic evaluations undertaken in the same or neighbouring countries?	Yes – the authors note that "A cost-effectiveness analysis is relative in the sense that one intervention can only be considered cost-effective in relation to another." However, there is little cost-effectiveness information on other interventions in Kenya for comparison. The cost-effectiveness of Hib vaccine is comparable to preventive interventions against malaria, such as bednets (US$4-85 per DALY averted) and to some tuberculosis control strategies (US$13-496 per DALY averted).
Other Factors (Chapter 9)	Is there a discussion of other important factors in the decision under consideration?	Partially – the authors make reference to affordability.
Conclusions	Is an answer given to the study question?	Yes – Hib vaccination is highly cost-effectiveness.
	Do the conclusions follow from the data reported?	Yes
	Are the conclusions accompanied by the appropriate caveats?	Not applicable – the authors provide a number of reasons, supported by data, why the cost-effectiveness results are likely to be under-estimates.

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Glossary

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 (R_0): 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 results of a **probabilistic sensitivity 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.

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 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 (R_t): 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 indigenously induced 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.

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.

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 sensitivity analysis: a method of analysis that explicitly incorporates parameter 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.

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.

Appendix 1:
Sources of data
(all sites as at September 2007)

Core health indicators, e.g. population size, life expectancy at birth, mortality rates, etc.:

- World Health Organization: www3.who.int/whosis/core/core_select.cfm

- United Nations Population Division: http://esa.un.org/unpp/

Vaccine efficacy:

- Cochrane Library: Swingler G, Fransman D, Hussey G. Conjugate vaccines for preventing Haemophilus influenzae type B infections. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD001729. DOI: 10.1002/14651858. CD001729 (available at: www.mrw.interscience.wiley.com/cochrane/clsysrev/ articles/CD001729/frame.html

Coverage data:

- World Health Organization/United Nations Children's Fund: www.who.int/ immunization_monitoring/en/globalsummary/timeseries/tswucoveragedtp3. htm

Disability weights:

- WHO Burden of Disease Project: www.who.int/healthinfo/paper54.pdf (see Annex Tables 1 and 5a)

Immunization expenditures and financing data (country level):

- World Health Organization: www.who.int/immunization_financing/data

Life tables:

- World Health Organization: www3.who.int/whosis/life/life_tables/life_tables. cfm?path=life_tables

Unit cost data:

- Prices for vaccines: Global Alliance for Vaccines and Immunization/The United Nation's Children's Fund: www.unicef.org/supply/files/UNICEF_-_Procuring_ supplies_for_children_-_GAVI.pdf and Pan American Health Organization Revolving Fund: www.paho.org/English/AD/FCH/IM/sne2801.pdf

- Unit costs for patient services: www.who.int/choice/country/en/index.html

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

- Prices for traded goods: www.who.int/choice/costs/traded_items/en/index.html

- Management Sciences for Health International Drug Price Indicator Guide: http://erc.msh.org/dmpguide/index.cfm?search_cat=yes&display=yes&module=dmp&language=english&year=2005

Financial data:

- International Monetary Fund: www.imf.org/external/pubs/ft/weo/2006/02/data/index.aspx

- World Bank: http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20899413~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html

GNI per capita:

- World Bank: http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf

Purchasing power parity exchange rates:

- World Health Organization: www.who.int/choice/costs/ppp/en/index.html

Official exchange rates

- OANDA : www.oanda.com/

Appendix 2:
List of useful websites

General:

- Centers for Disease Control & Prevention (CDC) (www.cdc.gov)
- Global Alliance for Vaccines and Immunization (www.gavialliance.org)
- International Vaccine Institute (www.ivi.org)
- John Hopkins Bloomberg School of Public Health (www.jhsph.edu)
- London School of Hygiene and Tropical Medicine (www.lshtm.ac.uk)
- PATH (www.path.org)
- The United Nations Children's Fund (www.unicef.org)
- World Health Organization, Immunization, Vaccination & Biologicals (www.who.int/immunization)

Vaccine Initiatives:

- Aeras Global TB Vaccine Foundation (www.aeras.org)
- Cervical Vaccine Project (www.path.org/projects/cervical_cancer_vaccine)
- Cholera Vaccine Initiative (www.ivi.int)
- Hib Initiative (www.hibaction.org)
- Human Hookworm Vaccine Initiative (www.sabin.org/programs/hhvi)
- International AIDS Vaccine Initiative (www.iavi.org)
- Japanese Encephalitis Project (www.path.org/projects/japanese_encephalitis_project)
- Malaria Vaccine Initiative (www.malariavaccine.org)
- Measles Initiative (www.measlesinitiative.org)
- Pediatric Dengue Vaccine Initiative (www.pdvi.org)
- PneumoADIP (www.preventpneumo.org)
- Rotavirus Vaccine Program (www.rotavirusvaccine.org)

Vaccine Supply & Finance:

•   Immunization Financing Website (www.who.int/immunization_financing/en/)

This site is being developed under the auspices of the GAVI 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 Alliance 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) (www.who.int/immunization_financing/tools/cmyp/en/)

In response to global immunization challenges, including the need to protect more people and introduce new vaccines, WHO and UNICEF, in consultation with other partners, have developed the Global Immunization Vision and Strategy (GIVS) for the period 2006-2015. GIVS is a framework that offers policy-makers and stakeholders a unified vision of immunization and a set of strategies from which countries can select those most suited to their specific needs. In conjunction with GIVS, countries are encouraged to develop comprehensive multi-year plans for immunization (cMYP) as a means of implementing GIVS at national level. In late 2005, WHO and UNICEF, together with GAVI Alliance partners, developed guidelines for comprehensive multi-year planning (cMYP) for immunization. This new approach was guided by the need and desire to simplify and harmonize the proliferation of immunization planning activities at national level, which had led to duplication of efforts, high transaction costs to national and partners, planning documents with variable degrees of national ownership, and a lack of alignment with sectoral planning systems. The cMYP process turns current efforts to streamline immunization planning at national level into a single comprehensive and costed plan. It is within this context that these new guidelines build on existing multi-year planning experience, while adding the critical elements of costing and financing that draw heavily upon the financial sustainability plans (FSP). Likewise, the accompanying cMYP costing and financing tool builds on the FSP costing tools and methodologies. The latest versions of the guidelines, the costing and financing tool and user guide are available for download on the cMYP web page.

International Finance Facility for Immunization Company (IFFIm) (www.iff-immunisation.org)

Cost-effectiveness:

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

- Disease Control Priorities Project (www.dcp2.org/main/Home.html)

- Copenhagen Consensus (www.copenhagenconsensus.com/Default.aspx?ID=675)

Databases of cost-effectiveness studies:

- Cost-effectiveness Analysis Registry (www.tufts-nemc.org/cearegistry)

- Centre for Reviews and Dissemination (www.york.ac.uk/inst/crd/crddatabases.htm#NHSEED)

Journals:

- Health Economics www3.interscience.wiley.com/cgi-bin/jhome/5749

- Cost-Effectiveness and Resource Allocation (www.resource-allocation.com)

- Medical Decision Making (www.smdm.org)

Vaccine economics:

- Bulletin of the World Health Organization: special issue on the economics of immunization (www.who.int/bulletin/volumes/82/9/en/index.html)

Cochrane:

- Cochrane Library (www.theCochraneLibrary.com)

- Campbell & Cochrane economic methods group: www.c-cemg.org

Vaccine e-learning sites:

- Advanced Immunization Management (http://aimstaging.path.org/)

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.

Department of Immunization, Vaccines and Biologicals
Family and Community Health