Guidance on the economic evaluation of influenza vaccination
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1. INTRODUCTION

Influenza is responsible for substantial morbidity and mortality across the globe, with a large share of the total disease burden occurring in low- and middle-income countries (LMICs) [1]. To understand how best to prevent this burden, there is a need to rigorously assess the impact and value for money offered by influenza vaccination strategies in LMICs. Economic evaluation can help decision-makers evaluate the costs and benefits of potential influenza vaccination strategies in their setting. Assessing the value for money is important because the allocation of resources to a vaccination programme presents an opportunity cost in terms of the other benefits that could have been achieved with these funds [2, 3].

The cost-effectiveness of seasonal influenza vaccination has been widely assessed in high-income countries [4, 5]. The influenza vaccination strategies evaluated have typically been targeted at specific age groups (e.g. children, adults, or the elderly) and/or risk groups (e.g. pregnant women, healthcare workers, those with specific underlying conditions). Influenza vaccination programmes have generally been estimated to be cost-effective in high-income settings [4]. The results of studies evaluating influenza vaccination programmes targeted at children [6], the elderly [7] and those at high risk of infection and/or severe complications [8] have been most favourable. However, the cost-effectiveness evidence has been less consistent for influenza vaccination programmes targeted at lower-risk groups, such as healthy adults [9].

In LMICs there have been relatively few economic evaluations assessing the value of seasonal influenza vaccination [10]. A recent literature review on the topic found nine economic evaluations, all of which were conducted in middle-income countries, with no evaluations identified from low-income countries [10]. The review identified important methodological limitations in several of these studies and called for greater standardization of methods for economic evaluation of influenza vaccines. Key recommendations were that future studies should provide more transparent information about the methods and assumptions used and that further research should be commissioned to provide better estimates of influenza-attributable morbidity and mortality for LMICs [10]. Similarly, a systematic review looking at the availability of economic burden analyses found a lack of data, particularly in sub-Saharan country contexts, and also a lack of evidence focusing on pregnant women – the risk group with the highest priority for influenza immunization [11].

The review by Ott et al. also made a distinction between solely model-based economic evaluations and those which had been conducted alongside clinical trials [10]. The model-based studies generally found positive cost-effectiveness results in high-risk groups and the elderly, whereas those based directly on trial data demonstrated less consistent results [10]. While there can be potential limitations with both approaches, economic evaluation alongside clinical trials that run over a single year or a small number of years can be particularly problematic for the assessment of influenza vaccination due to year-to-year variation in influenza virus transmissibility, virulence, prior immunity and vaccine match [6]. The limitations of model-based approaches typically relate to the assumptions that need to be made (see Chapter 6 and Chapter 8).
Introduction

Purpose of the guidance document (for LMIC)

The purpose of this document is to outline the key theoretical concepts and best practice in methodologies, and to provide guidance on the economic evaluation of influenza vaccination in LMICs. The guidance is aimed at those seeking to conduct, commission or critically appraise economic evaluations of influenza vaccination in LMICs. The document is not intended to be a step-by-step manual for producing an economic evaluation but aims to offer high-level guidance on influenza vaccination assessment which can be adapted to the setting of interest. As we will outline, there are important issues that arise when evaluating influenza vaccination strategies that merit particular attention and consideration. The guide is written for a technically literate audience with a basic knowledge of economic evaluation. The document may be particularly useful for those who have never undertaken or commissioned an evaluation of influenza vaccination but have previous relevant experience in evaluating other interventions.

The influenza-specific guidance should be viewed in conjunction with existing WHO documents on the addition of a vaccine to an immunization schedule. A list of guidance and tools that may be useful when considering the introduction of a new vaccine can be found in Principles and considerations for adding a vaccine to a national immunization programmes [12]. Table 1 presents some of the key WHO documents and tools that may be helpful for economic evaluations of influenza vaccination. One such document, the WHO guide for standardization of economic evaluations of immunization programmes [13, 14], has helped inform the methodological approach that has been applied to provide influenza-specific advice. The other key related documents are WHO's A manual for estimating disease burden associated with seasonal influenza [15] and the WHO Manual for estimating the economic burden of seasonal influenza.

Table 1. WHO documents and tools that may be relevant to the different sub-sections of an economic evaluation of influenza vaccination

<table>
<thead>
<tr>
<th>Category</th>
<th>Publication</th>
<th>What it provides</th>
</tr>
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<tbody>
<tr>
<td>Burden of disease</td>
<td>A manual for estimating disease burden associated with seasonal influenza</td>
<td>A standardized tool to estimate the respiratory burden of influenza</td>
</tr>
<tr>
<td>Economic burden</td>
<td>Manual for estimating the economic burden of seasonal influenza</td>
<td>A step-by-step guide and costing tool to estimate the cost of influenza</td>
</tr>
<tr>
<td>Programme cost</td>
<td>Maternal seasonal influenza vaccination programme planning and costing tool</td>
<td>Specific steps and tools to cost maternal influenza vaccination delivery programmes</td>
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<td></td>
<td>Guidelines for estimating costs of introducing new vaccines into the national immunization system</td>
<td>A stepped approach to estimating incremental vaccination programme costs</td>
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<td></td>
<td>WHO-UNICEF guidelines for developing a comprehensive multi-year plan (cMYP)</td>
<td>Steps to develop a cMYP including planning and costing tools</td>
</tr>
<tr>
<td>Economic evaluation</td>
<td>Guidance on the economic evaluation of influenza vaccination (current document)</td>
<td>Specific guidance for the economic evaluation of influenza vaccination</td>
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<tr>
<td></td>
<td>Guide for standardization of economic evaluations of immunization programmes</td>
<td>General guidance on the economic evaluation of vaccination programmes</td>
</tr>
<tr>
<td>Strategic health planning</td>
<td>WHO OneHealth tool</td>
<td>Supporting sector-wide integrated strategic health planning, costing and health impact analysis</td>
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2. ESTIMATING THE DISEASE BURDEN AND ASSOCIATED HEALTH-CARE USE

It can be challenging to estimate the disease burden from influenza using routinely-collected data (i.e. data that is regularly collected but not specifically for the purpose of assessing the burden of influenza). This is the case even in high-income countries that have comprehensive surveillance networks and national electronic health-care records (e.g. for hospitalization episodes). One major reason for this is that laboratory confirmation is not routinely requested in suspected influenza cases. While there are recognized clinical definitions of influenza-like illness (ILI), the positive predictive value of these clinical diagnoses is limited because of the non-specific symptoms of influenza infection [16]. Estimation of disease burden is further complicated because patients may present with secondary complications from infection which may have been triggered by influenza but for which influenza may not be apparent as the cause upon presentation (e.g. acute myocardial infarction) [17].

These issues have led many high-income countries to use statistical modelling techniques to estimate the influenza-attributable disease burden. These methods involve time series analyses of non-specific disease outcomes, such as pneumonia or respiratory hospitalizations or deaths, to estimate a non-influenza baseline burden above which any excess disease may be considered attributable to influenza [18–20]. While these methods are a useful way to estimate influenza-attributable morbidity and mortality, they have specific data requirements (e.g. complete and accurate data on hospitalizations or deaths for the non-specific disease outcomes) and can involve relatively complex technical analysis. Although the use of these statistical methods to estimate influenza-attributable burden are well accepted they involve underlying assumptions which should be acknowledged [21, 22]. These time series methods may be more difficult to apply in (sub)tropical regions where influenza does not always show a clear seasonal pattern of circulation.

Another important factor to consider when estimating influenza disease is the year-to-year variation in the disease burden. This variation is a result of changes in the circulating virus over time and in the way this impacts on transmissibility, virulence and the level of prior immunity in the population [6]. For this reason it is suggested that (ideally) at least five years of data should be used to estimate the existing influenza disease burden [15]. However, data from a shorter period (a minimum of a single calendar year) can serve as a starting point provided that appropriate caution is taken when interpreting the results [15]. In all cases, but particularly when dealing with imperfect data, care should be taken to conduct an appropriate sensitivity analysis across a range of plausible values that extends beyond uncertainty due to sampling (see Chapter 8).

WHO's A manual for estimating disease burden associated with seasonal influenza [15] outlines various methods that can be applied in LMICs to evaluate the disease burden attributable to influenza. Using the definitions set out in A manual for estimating disease burden associated with seasonal influenza [15], the disease burden estimated is divided into two main categories:

1. influenza-associated ILI, which represents an estimate of the outpatient/primary care clinic visits due to influenza illness,
2. influenza-associated severe acute respiratory infections (SARI) which represents an estimate of the hospitalization visits due to influenza illness.
In each of these categories, laboratory confirmation is used (on at least a subset of cases) to estimate the proportion of suspected events that are due to influenza. Mortality in SARI cases can also be evaluated to estimate the case fatality rate in hospitalized influenza-positive cases.

The data collection approach set out in *A manual for estimating disease burden associated with seasonal influenza* [15] has the capacity to provide key information on the influenza disease burden. However, other sources of data will be required to estimate the full range of influenza disease burden (see Figure 1). Applying the methods in the manual [15], it may be possible to estimate the incidence rate of influenza-associated SARI. However, the approach set out requires an estimate of the catchment area (denominator) for collection sites. This information is unlikely to be available for ILI sentinel sites, which would restrict the ability to estimate the incidence of influenza-associated ILI [15]. Likewise, while the manual outlines methods to estimate the case fatality rate in influenza-associated SARI cases, the approach does not capture influenza deaths that do not occur in hospital [15]. Another important estimate that cannot be informed by the manual [15] is the non-medically attended influenza burden (e.g. cases in the community that do not have any interaction with a health-care provider).

**Figure 1. Elements of the influenza disease burden that may/may not be estimated using WHO’s *A manual for estimating disease burden associated with seasonal influenza* [15]**

- **Non-medically attended influenza burden**: These data will not be available from the manual. Estimations of incidence may need to be based on population influenza attack rates (excluding medically attended cases).

- **Outpatient (primary care) influenza burden**: Potential to use "influenza-associated ILI". However, estimation of incidence is possible only if denominator data are available. Data on the catchment area are often unavailable.

- **Inpatient (hospitalized) influenza burden**: Potential to use "influenza-associated SARI". It is often possible to estimate the catchment area for hospitals which can then be used to help estimate incidence.

- **Influenza mortality burden**: Potential to estimate a case fatality rate for hospitalized cases identified. However, the available data may be incomplete and will not capture deaths in the community.

Non-medically attended influenza cases have been found to be influential in many economic evaluations of influenza vaccination in high-income settings [4], particularly when examining strategies targeted at those with a lower risk of influenza mortality (e.g. healthy adults) [9]. While the costs and consequences attached to each non-medically attended case may be relatively small, the large number of cases can mean that they have an important impact on cost-effectiveness. In
Estimating the disease burden and associated health-care use

LMICs, as a result of cost and health access issues faced by some individuals within the society, the burden not captured in the formal health-care system may be more likely to extend beyond those with mild influenza disease. These individuals may seek no care, may self-medicate or may seek informal care. However, these cases may still result in indirect (productivity) costs and/or other direct health-care costs (e.g. out-of-pocket medication costs). The events may also result in (often short-term) quality-of-life deficits and/or disability due to the acute illness caused by the influenza infection.

Unless specific estimates already exist for the target population, options to estimate the non-medically attended influenza burden are limited without the commission of potentially expensive empirical data collection or complex modelling studies. Nevertheless, plausible estimates should ideally be included, at least in sensitivity analysis, to allow for an understanding of their impact on evaluation results. The overall symptomatic attack rate for influenza comprises the medically attended influenza-associated ILI [15] and the non-medically attended symptomatic influenza burden. As a consequence, non-medically attended symptomatic disease can be calculated from estimates of the total symptomatic attack rate after excluding the medically attended influenza-associated ILI rate [15].

Estimates of the symptomatic attack rate will vary substantially from year to year and, as with all estimates of the influenza disease burden, age will be a critical factor that must be considered, with age-specific rates used whenever possible. For example, in children a 25-year longitudinal study in the USA estimated a symptomatic influenza attack rate for those aged 0–4 years ranging between 1% and 19% with an average of 9.5% [23]. In another example, estimates from Turner et al., who reviewed symptomatic influenza attack rate data in adults from those allocated to placebo arms in influenza vaccine or antiviral trials found values in the range 0–20% with a base-case estimate of 6.5% [24]. Infection rates in subgroups who have increased exposure to influenza may be elevated. For example, a meta-analysis estimated a symptomatic attack rate of 7.5% in unvaccinated health-care workers (over 7 seasons), with this group having a significantly higher infection rate compared to other working adults [25]. Setting-specific (geographical) factors will have an impact on such estimates; however, there may be relatively less variation than for some other estimates of disease burden, where health-seeking behaviour will further hinder the transferability of study results.

A mortality estimate from only hospitalized influenza cases [15] is likely to be a conservative estimate of influenza mortality as some deaths from influenza infection do not occur in a hospital setting. The extent to which such an estimate under-reports influenza deaths will depend on several factors which should be considered when applying a mortality estimate based only on hospitalized cases. For example, the propensity to seek hospitalization for influenza illness may vary in between settings dependent on access to health care, geographical location, and out-of-pocket health-care costs faced by patients and/or their family. Age may be another important factor, with the potential for different health-seeking behaviour and/or variation in the rapidity of death after the onset of severe influenza-related symptoms, and therefore the chance to reach a hospital before death.
Alongside reporting results in natural units (e.g. cost per death prevented), it can be informative to calculate the results of cost-effectiveness analyses using an outcome measure that incorporates changes in both morbidity and mortality. In LMICs the outcome measure of choice has often been DALYs averted [14]. This contrasts with high-income (and increasingly middle-income) countries where QALYs have frequently been chosen as the “gold standard” outcome measure. In either case (for DALYs or QALYs) a major advantage of these utility measures is that they are able to incorporate changes in both morbidity and mortality as a result of different health-care interventions. This enables the results of economic evaluations that use these outcomes (i.e. cost-utility analyses) to be compared with evaluations of other health programmes that also calculate their results using this approach. This can allow a decision-maker to better understand which health-care intervention strategy has a lower cost per DALY averted (or QALY gained) and consequently provides better value for money (all else being equal). In this way the use of the approach can help to facilitate a form of allocative efficiency within the health sector [14].

For these reasons it is generally recommended that a cost-utility approach be used for economic evaluations [14]. In some cases DALYs may be a more appropriate outcome measure than QALYs, as estimates are consistently available across all countries [14]. However, careful thought must be given to whether DALYs or QALYs are the more appropriate measure to apply to (uncomplicated) acute influenza illness. The availability and/or transferability of quality-of-life weights to the setting under evaluation and local guidelines should help inform these decisions. All of the cost-utility analyses identified in LMICs to date have used a QALY framework [10]. In either case, model results should first be presented in terms of natural outcome measures (e.g. cases, deaths, life-years saved) [14].
3. ESTIMATING THE ECONOMIC BURDEN ASSOCIATED WITH INFECTION

As recommended by the WHO guide for standardization of economic evaluations of immunization programmes [13, 14], evaluations should ideally adopt a societal perspective, including all relevant costs and consequences irrespective of who incurs them. However, as different decision-makers or audiences may have different viewpoints, costs borne by different entities (e.g. local governments, donors) should be reported separately (where possible) within economic evaluations [14].

Detailed advice on how to calculate the cost of influenza disease can be found in the WHO Manual for estimating economic burden of seasonal influenza. This manual offers a step-by-step guide to help analysts estimate the economic burden of influenza in their setting. As a complement to this costing manual, this chapter focuses more on the methodological issues that arise when considering the use of such estimates in economic evaluations. In economic evaluation, unit costs are typically attached to model states. Model states may represent health states (e.g. influenza deaths) or health-care events (e.g. hospitalization for influenza-associated SARI). The model can then be used to calculate total costs (e.g. by multiplying the number of events in each strategy by the unit costs attached to these events in order to obtain the total health-care costs under each strategy).

The WHO Manual for estimating economic burden of seasonal influenza separates influenza-associated costs into direct medical, direct non-medical and indirect costs. The unit costs calculated as part of this manual may be useful to apply to model health states in economic evaluations of influenza vaccination. However, care must be taken to ensure that they are appropriate for the group(s) that are being considered for vaccination, as different age and risk groups may have different resource use and associated costs from influenza disease. In evaluations conducted for high-income countries, indirect productivity costs have been found to be influential in determining cost-effectiveness [4, 6, 8, 9]. These indirect costs may result from time off work due to influenza illness or while caring for those ill (e.g. children). In LMICs the costs attached to each day off work may be substantially lower than in high-income countries but should still be considered if they fit within the perspective being adopted (i.e. a societal perspective).

It should be noted that there is also debate between health economists about how and if productivity costs should be included in economic evaluations [26]. The decision about the inclusion of productivity costs will be driven by the perspective adopted in the analysis. There remains an active debate about how to value any lost time, with some arguing that due to compensatory behaviour a human capital approach may overestimate the true benefit of prevented illness [2]. For these reasons, if indirect costs are to be used, it is recommended that they are reported separately from other costs and that cost-effectiveness results are presented with and without the inclusion of productivity costs [14].

Another concern about the use of indirect costs involves a desire to avoid “double counting”. For instance, when considering the value of preventing an influenza death in a cost-effectiveness or cost-utility framework, one would usually value this event in the denominator side of the cost-effectiveness equation (e.g. as lost life-years) [3]. If this event is also valued by the lost lifetime
earnings of this individual in the numerator side of a cost-effectiveness ratio, some health econo-
mists have argued that this may indicate it is being counted twice [3]. Productivity costs may also
be incurred when receiving vaccination, seeking health care for influenza-related illness and/or
taking time off work due to influenza morbidity. In some of these cases there may be less concern
with double counting, provided that any outcome attached to the event (e.g. a utility weight) does
not already incorporate the disutility of lost income.
4. ESTIMATING THE COSTS ASSOCIATED WITH THE VACCINATION PROGRAMME

This chapter outlines issues to be considered when costing an influenza vaccination programme for an economic evaluation. In the case of influenza vaccination there may be a cost difference between the type of vaccine being evaluated – such as between live-attenuated vaccines (LAIV) and trivalent inactivated vaccines (TIV), and when considering the use of adjuvanted and/or quadrivalent vaccines (where available). However, several WHO documents give costing guidance for immunization programmes that should be applied as appropriate.

These documents provide detailed information on how to evaluate resource use and associated costs involved in vaccination programmes, including vaccine purchase, transportation, wastage and other important factors. The most suitable document to use under specific circumstances will depend on whether one seeks to cost the total vaccination programme or take an incremental approach, estimating only the additional cost of adding it to the schedule [14]. For example, the WHO-UNICEF guidelines for developing a comprehensive multi-year plan (cMYP) for producing multi-year planning is a useful reference for estimation of the total costs, whereas the incremental costs may be estimated using the stepped approach in the Guidelines for estimating costs of introducing new vaccines into the national immunization system [14]. The WHO Maternal seasonal influenza vaccination programme planning and costing tool is a useful resource when evaluating the vaccination of pregnant women.

Influenza vaccine administration may differ in some important ways from the introduction of an infant vaccine to a pre-existing vaccination schedule. Firstly, influenza vaccination can be targeted at a variety of different age and risk groups, depending on the specific strategies being evaluated. This choice of target may have an impact on the uptake (coverage) of the programme, as well as on the resources used and the associated costs of administration to these persons. For example, in programmes targeted at adults, influenza vaccination is more likely to be given at a health-care visit where no other vaccines are administered. Furthermore, the timing of administration of influenza vaccine within a given year is important in order to try to ensure that those vaccinated are protected before the peak of seasonal influenza transmission. The nature of this timing may differ in (sub)tropical regions where influenza transmission is more constant; however, important seasonal variation in transmission may still occur even in these settings. The timing of influenza vaccination programmes may have an impact on the effectiveness of the intervention (see Chapter 5).

The level of uptake for influenza programmes can be hard to predict in advance. Unlike the addition of a new vaccine to an infant schedule, where estimates of the uptake of existing vaccines in the setting may provide a template to predict demand, current influenza vaccines require annual revaccination and may be targeted at age or risk groups in whom vaccination is not routine. As a consequence, the uptake obtained in influenza vaccination programmes may be lower than that obtained from traditional infant-schedule vaccines in the same country. The uptake may be influenced by risk and benefit perceptions about influenza infection and influenza vaccination in both the vaccinee and those providing the vaccination. The method of delivery can also have an impact
on the level of uptake obtained in the target group – such as school-based delivery, vaccination at the workplace and retail sites.

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization identified risk groups for influenza, including those at increased risk of exposure to influenza virus (health-care workers) and those at particular risk of developing severe disease (“pregnant women, children aged < 5 years, the elderly, and individuals with underlying health conditions such as HIV/AIDS, asthma, and chronic heart or lung diseases”) [27]. Pregnant women, children aged 6 months to 2 years, and health-care workers were highlighted as those who may require relatively fewer resources in an influenza vaccination programme [27, 28]. These groups are likely to be present in the health system already for unrelated reasons and may be able to be given influenza vaccine in an opportunistic manner at a relatively low incremental administration cost. This ease of access may also be advantageous to vaccination uptake in these groups. However, factors such as perceptions of risk from influenza and misconceptions about influenza vaccination may remain important barriers to high uptake. For example, these factors have been longstanding barriers to obtaining high influenza vaccination uptake among health-care workers, where it is not mandated [29]. It should also be noted that eligible children aged under 9 years being vaccinated for the first time may be recommended to receive two doses of vaccine ≥ 4 weeks apart to help ensure a protective immune response [28] (see applicable current recommendations). This may present an additional challenge when seeking to vaccinate young children.

Influenza vaccination strategies targeting those with specific underlying conditions may be hindered by difficulties in identifying those to be vaccinated. In high-income countries, such risk-based strategies have often resulted in relatively low uptake [30] and this may be exacerbated in LMICs where information on chronic conditions in potential vaccinees may not be easily accessible. Strategies that seek to obtain a high uptake in such groups may need to consider any additional costs for identifying (e.g. screening) those suitable for vaccination. Other groups that are recommended as priorities by the SAGE Working Group, such as the elderly and children aged 2-5 years, are more easily identified but may not always be present in the health-care system on a routine basis for opportunistic vaccination [28]. As such, any ongoing resources required to target these groups effectively need to be carefully considered when costing such programmes. In order to scale up the uptake of vaccine use among different target groups, additional efforts would be needed in terms of information, education and communication and social mobilization. Estimating cost consequences of these activities will be crucial in economic evaluations of influenza vaccine. Lessons can be learned from HPV vaccine introductions.

The mode of delivery has been found to be influential in determining the cost-effectiveness of influenza vaccination strategies [10]. Several important distinctions can be made between different delivery methods; these include non-medical versus medical administration, and opportunistic vaccination versus vaccination at a separate health-care visit. These choices may have a substantial impact on the resources and associated costs required for the programme. As discussed above, a method of delivery with a relatively low incremental cost may be opportunistic vaccination. This typically involves administration where an individual is already in the health-care setting for another purpose – e.g. where influenza vaccination can be added into existing childhood vaccination platforms or at other incidental non-vaccination health contacts [28]. However, additional complexities around the seasonal timing of influenza vaccination and the potential requirement for two doses in unvaccinated children [28] must be considered when evaluating “add-on” administration strategies.
Administration in a medical setting can involve higher incremental costs than non-medical administration because the costs associated with a physician's visit/time for influenza vaccination are likely to be higher than administration by non-medical personnel. However, the cost of vaccine administration in a medical setting may be reduced if opportunistic vaccination is possible or vaccination can be given by those with a lower wage (time cost), such as nurses or other qualified staff. Potential non-medical sites for influenza vaccination may include retail (pharmacy) sites, workplace vaccination or school-based vaccination programmes. Outreach vaccination strategies may also play an important role in some regions – such as when trying to vaccinate those in remote or hard-to-reach locations where outreach staff may be required actively to seek out those to be offered influenza vaccine.

If appropriate to the perspective taken (Chapter 3), patient indirect productivity costs and direct (non-medical) transportation costs may also be considered when evaluating the cost of a vaccination strategy. The inclusion of productivity costs, in terms of lost time to patients or caregivers to allow receipt of influenza vaccination, will increase the costs attributable to the programme. The inclusion of transportation costs paid by individuals to attend for vaccination will also add to the total societal costs of the influenza vaccination strategy. However, these costs will vary widely according to the method of administration (as outlined above) and in some cases the incremental cost to individuals may be insignificant and may not warrant inclusion (e.g. for opportunistic influenza vaccination at an existing health-care visit).

**Adverse events due to vaccination**

An adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. Severe adverse events following immunization for influenza vaccination are very rare and mild adverse events usually resolve after a short period of time and pose little danger to the vaccine recipient [31–34]. For injectable vaccines, pain and infection site reactions are relatively frequent vaccine reactions [31–33]. Due to the relatively minor consequences from these events, economic evaluations have not always included adverse events from influenza vaccination and, where they have been included, they have generally not been found to be influential in determining cost-effectiveness [6]. However, where possible, estimates of AEFI should be included in economic evaluations of influenza vaccination. This is particularly important when evaluating programmes targeted at vulnerable populations such as pregnant women [35, 36], younger children or those with certain underlying conditions [28, 34].
Estimates of influenza vaccine efficacy should generally be obtained from randomized clinical trial evidence. Ideally these would be from meta-analyses that appropriately synthesize all the relevant available data rather than from a single vaccine trial [4]. As with disease burden estimates, it is important that estimates of efficacy should incorporate multiple influenza seasons because of the year-to-year variation in vaccine match as well as in transmissibility and prior immunity in the population [6]. Likewise, efficacy estimates may differ depending on the population group being targeted, with age and underlying medical conditions being known factors that may have an impact on vaccine efficacy [31–33]. Distinctions should also be made between the different types of influenza vaccines (e.g. between LAIV and TIV, and adjuvanted and quadrivalent vaccines (where available).

Estimates of influenza vaccine efficacy have been calculated against a range of clinical outcomes. These include laboratory-confirmed influenza disease as well as non-specific endpoints such as ILI, pneumonia hospitalization and all-cause mortality [31–33]. If these non-specific outcomes are to be used in economic evaluation models, it is important that there is consistency between the definitions used to inform disease rates in the model and the vaccine efficacy estimate that is applied to reduce these estimates of disease burden [6]. In model-based approaches, estimates of efficacy and disease burden will often be from different sources. This can create problems even if the definitions are the same, because the proportion of the non-specific outcome (e.g. ILI) caused by influenza may vary between sources [6]. If efficacy estimates for non-specific outcomes are based on the reduction of events only within the influenza season (e.g. reduction in pneumonia hospitalization over x weeks) these should not be inadvertently applied to disease estimates based on annual rates.

Although efficacy estimates against non-specific outcomes have sometimes been used in economic evaluations of influenza vaccination programmes [4, 6], the most straightforward estimate to use is an efficacy against confirmed influenza disease. In the case of influenza disease estimates, such as those calculated using A manual for estimating disease burden associated with seasonal influenza [15], it is reasonable to apply a vaccine efficacy calculated against confirmed influenza disease to all estimates of influenza-specific outcomes, including influenza hospitalizations and influenza deaths. Efficacy estimates specifically against severe influenza outcomes cannot easily be measured in clinical trials because of the large sample sizes that would be required to detect adequate numbers of events [37]. As a consequence, a simplifying assumption can be made that the prevention of influenza infection will prevent all subsequent disease outcomes from this infection.

The probability of vaccine match to the circulating strains must be accounted for when evaluating the cost-effectiveness of influenza vaccination strategies. While the vaccine may match in any given year, over the longer term the match to the predominate strain/s will not always be successful [38]. This is because the strains included in the vaccine have to be selected in advance. The probability of match in a given context is influenced by several factors – including the hemisphere of the target population and the vaccine chosen (i.e. trivalent or quadrivalent). The vaccine
match is important as it has been shown that a poor match will reduce the efficacy of the vaccine to prevent influenza illness [31–33]. Economic evaluations can apply a vaccine efficacy estimate from a meta-analysis that already incorporates both matched and poorly-matched seasons (e.g. they may apply a single estimate of vaccine efficacy derived from trials run over multiple years). In many cases this method may be a reasonable approach; however, it can be problematic when using modelling techniques that seek to estimate herd protection effects [22, 39].

An additional complexity is introduced when evaluating the impact of influenza vaccination in regions where influenza activity is less seasonal. In these regions, a significant proportion of the annual influenza burden may occur before influenza vaccine can be administered. In (sub)tropical regions where this is a factor, it is important that economic evaluations take this into account and make appropriate model assumptions to ensure that the predictions of vaccination impact are realistic.

**Potential for herd protection effects**

In addition to the direct protection conferred on vaccinated individuals, influenza immunization programmes have the capacity to help protect the population through reduced transmission in the community and within households [40, 41]. The effects of herd protection are not usually measured in clinical trials which, for reasons of practicality and cost, usually randomize individuals rather than communities [4]. However, the inclusion of herd immunity effects can be influential in determining the cost-effectiveness of influenza vaccination programmes [39]. These herd effects will be larger when programmes target a substantial proportion of those responsible for influenza transmission, e.g. universal (all age) programmes or those targeted at all eligible children [40, 41]. Conversely, the impact of herd protection will be smaller when programmes are focused on relatively small subgroups within the population (e.g. those with underlying risk conditions) or at those groups that may contribute less to community transmission, such as the elderly [42].

Herd protection effects can be estimated and incorporated into economic evaluations of influenza vaccination through the use of dynamic transmission models (see Chapter 6). However, these models can be complex to construct and sometimes a proxy form of herd protection has been included in influenza economic evaluation models [6]. This approach may involve the application of a “static” (fixed) reduction in disease, based on empirical trial evidence, to contacts of persons vaccinated. For instance, in strategies targeted at children, an indirect protection effect might be applied to household contacts. This method can be conservative as it assumes only a limited form of herd protection for close contacts rather than protection for all who are in contact with the vaccinated individual [6]. However, it may be potentially misleading if the estimate of indirect protection is being transferred to a setting which differs in important ways from the trial (e.g. those in the original trial may have different contact patterns from those in the setting of interest) [6]. If proxy estimates are used, this form of uncertainty needs to be considered, and it may be more appropriate to apply estimates of proxy herd protection only in sensitivity or scenario analysis (Chapter 8). Similar complexities arise when attempting to capture indirect benefits to patients as a result of vaccinating health-care workers against influenza.
Assessing the impact of vaccination efforts

Uptake (or coverage) of influenza vaccination

Another important factor that has an impact on the population protection from influenza vaccination is the uptake (or coverage) of the programme in the targeted groups. The level of uptake obtained from a programme has an impact on the total direct protection and may also (depending on those targeted) have a substantial impact on any indirect protection of the community through herd protection. In evaluations that do not incorporate herd protection, uptake will have an impact on the absolute benefits of vaccination and the total cost of the programme but the impact on the cost-effectiveness ratio may not be as substantial. This is because the costs of the vaccination programme and the health benefits that accrue through the programme may both increase (approximately) proportionally with uptake [14]. However, if there are substantial fixed programme costs that are unchanged by vaccination uptake or there is potential for economies of scale (e.g. when purchasing large orders), then obtaining higher coverage may improve the cost-effectiveness of the programme. When herd protection is modelled, the impact of vaccination uptake can become more influential in determining cost-effectiveness because the herd benefit from each additional vaccinated individual may be nonlinear [43] (see Chapter 6).
6. ALTERNATIVE MODELLING APPROACHES

Static models (not directly incorporating herd protection effects)

The simplest approach to evaluating the cost-effectiveness of influenza vaccination is to apply a “decision tree” model (Table 2). In these models each pathway through the “tree” represents a sequence of events, and is associated with costs and consequences [2]. Decision trees are often used when the costs and consequences of an intervention occur over a short period of time, as is the case for influenza vaccination. This is because decision tree models cannot explicitly account for time. However, as is discussed in Chapter 7, this may not be essential in influenza models since the impact of long-term consequences from mortality can be incorporated through a discounted pay-off attached to specific endpoints where required. Nevertheless, there are some situations where there may be a need to account for time explicitly by modelling inter-year changes in costs or consequences. For instance, in the case of vaccination programmes targeted at eligible children under 9 years of age, two doses of influenza vaccination may be required for unvaccinated children who then may require only one dose in subsequent years [28].

In most circumstances, “Markov” state-transition models with a static (fixed) force of infection irrespective of the proportion of the population that is infectious have limited advantages over decision tree models in the context of influenza evaluations. This type of state-transition model allows for time- or age-dependent transition probabilities to be specified and is therefore often appropriate when costs and consequences occur over an extended period (e.g. as in chronic diseases) [2]. However, the duration of influenza vaccine protection is typically modelled as lasting only for a single season because of strain changes that occur from season to season. Furthermore, the consequences from influenza infection (with the exception of mortality) are usually short-lived, lasting only for a number of days or weeks. One advantage of state-transition models with short cycles (e.g. weeks) is that they can be used to explore alternative options for the timing of vaccination, where vaccination uptake can be modelled as a gradual process over several months.

Dynamic models (incorporating herd protection effects)

Dynamic transmission models are able to incorporate herd protection into economic evaluations by having the risk (force) of infection vary (being dynamic rather than static) on the basis of the proportion of the population that is infectious over time [44, 45]. These models are increasingly being applied in economic evaluations of influenza vaccination [6]. However, dynamic models are often more complex, time-consuming and costly to produce than static models and have additional data requirements [22] (e.g. information on contact patterns between individuals). As such, these models may not be the most appropriate choice for evaluations in LMICs in all circumstances. The WHO guide for standardization of economic evaluations of immunization programmes has an informative decision chart that can be used to help decide what type of model may be appropriate in different circumstances [14]. This guide also provides important information on model validation and collaboration [14].
Evaluations alongside clinical trials

In most circumstances a representative clinical trial will not have been completed in the setting under evaluation for the specific influenza vaccination strategies that are to be analysed. However, evaluation alongside clinical trials is of interest for LMICs as several of the published economic evaluations for middle-income countries have used this approach [10]. While this method may be appropriate or even advantageous for some medical interventions, it is likely to be problematic in the case of influenza vaccination [4, 6]. As has been mentioned, year-to-year variation is an important factor for influenza vaccine assessment, and many influenza clinical trials are run over only a small number of seasons. Furthermore, in healthy individuals, even relatively large trials are unlikely to detect representative numbers of relatively rare severe events, such as influenza deaths. This has led some economic evaluations completed alongside trials to disregard these events entirely [6]. However, at a population level, relatively rare events may still be important if the costs or consequences associated with them are substantial.

Table 2. Alternative approaches to the economic evaluation of influenza vaccination

<table>
<thead>
<tr>
<th>Assessment approach</th>
<th>Advantages for influenza vaccination evaluation</th>
<th>Disadvantages for influenza vaccination evaluation</th>
<th>When to consider using this approach</th>
</tr>
</thead>
</table>
| Static decision tree model | • Adequate to assess most influenza strategies  
  • Relatively simple to construct and interpret | • Unable to predict herd protection effects  
  • Unable to explicitly incorporate time | • Vaccinated groups unlikely to change population disease transmission substantially  
  • Dynamic modelling is impractical due to cost etc. |
| Static Markov model | • Relatively simple to construct and interpret  
  • Allows the explicit inclusion of time | • Unable to predict herd protection effects | • See above  
  • Need to model time explicitly (e.g. when dose number varies by previous year’s vaccine status) |
| Dynamic transmission model | • Able to predict herd protection effects | • Increased complexity to build and interpret results  
  • Time-consuming and more costly to construct  
  • Has additional data requirements | • Vaccinated groups likely to change population disease transmission substantially (e.g. children)  
  • Expertise, time and data are available to facilitate dynamic modelling |
| Economic evaluation alongside clinical trial | • Can facilitate collection of resource use and quality-of-life data | • Unable to predict herd protection (non-cluster trials)  
  • Unlikely to capture rare events (e.g. influenza death)  
  • May not capture inter-year variability from influenza | • An economic evaluation can be added (“piggyback”) on to a clinical trial already planned in the setting  
  • Existing data from a clinical trial can be used |
7. DISCOUNTING AND ANALYTICAL HORIZON

Impact of discounting for influenza prevention

The majority of the costs and consequences resulting from influenza vaccination occur within a single year. This makes discounting less influential than for some vaccination programmes where there is a longer delay between the upfront costs of the vaccination programme and the benefits derived from prevented illness. The impact of discounting is often most important in influenza evaluations to account for the long-term consequences that accrue from prevented influenza mortality. While the prevention of deaths occurs in the year of vaccination, the life-years (or DALYs/QALYs) and/or any productivity gains included from prevented mortality accrue over time and should be discounted at the appropriate level indicated in relevant guidelines for the setting under evaluation. To be consistent with current WHO-CHOICE recommendations, in sensitivity analysis (Chapter 8) a discount rate of 3% for both costs and effects (alternative 0%) should also be applied.

Analytical horizon for influenza modelling

The analytical horizon for economic evaluations should be long enough to account for differences in costs and consequences between the various strategies being evaluated [2] (e.g. between “no influenza vaccination in group X” and “influenza vaccination targeted at group X”). As the majority of costs and consequences resulting from influenza vaccination occur in a single year, a one-year time horizon may be appropriate for the economic evaluation. However, it is important that the long-term consequences from prevented influenza mortality that occur outside of this single-year time frame are fully incorporated into model results. The simplest way to do this is to apply a discounted pay-off in the model that incorporates the full benefits of prevented influenza mortality. For instance, in a strategy that prevents an influenza death, rather than attributing the 1 QALY gained for the single year of the model, the total QALYs gained would be calculated on the basis of the discounted life-expectancy of that individual (adjusted for any background utility age-weighting). It should be noted that longer time horizons are often required in more complex modelling approaches (Chapter 6), such as those which follow populations through time to account for the build-up of immunity and the impact of herd protection.
8. ESTIMATING AND PRESENTING RESULTS OF THE ECONOMIC EVALUATION

Presentation of costs and outcomes

Costs and outcomes should be presented in a detailed manner for each strategy being evaluated. This may include a table presenting the total costs, total outcomes (e.g. QALYs) for each strategy, as well as incremental results comparing the strategies under consideration. The results should be further disaggregated to allow readers to understand the relative contribution of different factors to these overall results. By breaking down the total costs into different categories of resource use, the different elements contributing to the overall results can be more easily understood (e.g. comparing the total cost savings from the prevention of influenza inpatient visits versus the savings from prevention of outpatient visits, etc.). The outcomes results should also be disaggregated when they are reported. For example, the total QALYs gained for prevented influenza mortality and the QALYs gained from prevented influenza morbidity could be reported separately. Further advice on the presentation of cost-effectiveness results can be found in [10].

Incremental cost-effectiveness ratios

The influenza strategy being considered for implementation should be compared to an appropriate alternative or to several potential alternative strategies (see below). For instance, the alternative for comparison may be the costs and consequences of “no vaccination” (i.e. do nothing) for this group or those for “current practice” uptake of influenza vaccination in this group.. This will allow an incremental cost-effectiveness ratio (ICER) to be calculated, representing the difference in costs between the alternatives divided by the difference in health outcomes [2].

In practice there are various ways of calculating these differences in a model. For example, one simple approach to calculating the differences in total costs between a vaccination strategy and “no vaccination” is to estimate the health-care savings of the vaccination strategy under consideration. The difference in total costs between the alternatives can then be calculated by subtracting these savings from the costs related to the vaccination programme under consideration. Another approach is to calculate the total costs from influenza illness and any programme-related costs in each alternative. In this approach, the vaccination strategy would include both the cost related to the programme and the costs from the (remaining) influenza illness. The “no vaccination” option would include the costs from influenza illness estimated under this strategy. The differences in total costs between the alternative strategies can then be calculated. When applying either of these approaches, the same ICER should result when the appropriate calculations are made. A more detailed discussion of how to calculate an ICER can be found in Methods for the economic evaluation of health care programmes [2].
Multiple strategies

Two forms of comparison are often discussed and are worth describing clearly to avoid confusion. The first is when comparing between mutually exclusive alternatives within an economic evaluation. This is what is discussed above, as the new influenza vaccination strategy in the target group and the “no vaccination” in this group cannot be implemented simultaneously. However, there may be more than two strategies that should be considered for this target group; for instance one may also want to consider “current practice” uptake or immunization with an alternate vaccine (e.g. LAIV or TIV) in this group. The ICERs should then be calculated by comparing each strategy to the next best alternative, after excluding dominated strategies (see [14] for detailed advice on this process). Only strategies that are mutually exclusive would generally be considered as comparators within a single economic evaluation [2].

The second form of comparison is when comparing between the results of completed economic evaluations. Each of these evaluations should have compared mutually exclusive alternative within the analysis. However, once the evaluations are completed one can examine the ICERs estimated for the different interventions to help determine which of these independent options represents better value for money. If all the evaluations have used the same methods and have calculated results in the same units (e.g. DALYs averted) then the one with the lower cost per DALY averted represents better value for money, all else being equal. This is where one can compare the value of different types of health programmes, such as comparing vaccination for influenza in group X with vaccination for prevention of another disease in group Y (see the section on interpreting economic evaluation results below). However, care must be taken when comparing the results of different studies because the reference case applied may not be consistent (e.g. they may have applied different perspectives).

In most situations in LMICs, a practical approach to economic evaluation is to treat each target group as independent (e.g. pregnant women, children aged 6 months to 2 years, children aged 2 years to 5 years, etc.). In this way, a different economic evaluation would be completed for each group that may be considered for vaccination, and within each evaluation the influenza vaccination strategy would be compared only to alternatives for that group. The ICER results for each evaluation can then be interpreted separately against an appropriate threshold. If applying a dynamic modelling framework, there is also the potential to evaluate influenza strategies for different target groups against each other, accounting for herd effects that the vaccination of one group can have on another and on the wider population [3]. When evaluating multiple strategies, it may be useful to present the results on a cost-effectiveness plane to allow readers to see where strategies fall relative to each other in terms of total costs and outcomes.

Interpreting results of economic evaluations

The interpretation of economic evaluations and how they can inform policy depends on how they value health outcomes. In the case of cost-benefit analysis, where both costs and consequences are valued in dollars, a positive net benefit from an evaluation would suggest that a programme offers value for money. However, in the case of a cost-utility analysis, where results are calculated as the ICER per DALY averted (or QALY gained), a threshold for “value for money” can be considered. Although the original purpose was not for use at country level, willingness-to-pay thresholds applied in LMICs have sometimes been based on criteria set out by the WHO Commission on
Macroeconomics and Health [46]. The values of 1–3 times per capita GDP have been widely cited in the literature for LMIC when assessing value for money for vaccination programmes [47], with ICERs per DALY averted below one times GDP per capita considered “very cost-effective” and under three times considered “cost-effective”. However, as these absolute thresholds do not explicitly account for the available health budget or the opportunity cost of the allocation of these health resources to the vaccination programme in a given country context, applying these strict thresholds may not be appropriate [47].

There is currently no consensus as to what approach should be used to establish thresholds in LMICs. Ideally thresholds in LMICs should be informed by the alternative ways the health resources could be allocated, as well as local budget constraints [47]. As a result, it is important to consider the findings of budget impact analyses for the various influenza vaccination strategies under consideration. There may also be locally-established thresholds for decision-makers which should be considered (as in Thailand [48]). The estimation of thresholds for LMICs is an area of research that is evolving quickly, and new recommendations may soon emerge. WHO recommends against imposing a strict threshold as a decision rule for policy options. While cost-effectiveness ratios are undoubtedly informative in assessing value for money, countries should be encouraged to develop a context-specific process for decision-making that is supported by legislation, has stakeholder buy-in and is transparent, consistent and fair.

Assessment of uncertainty

It is vital to assess and appropriately present uncertainty when estimating the cost-effectiveness of influenza vaccination programmes. The base-case results from an economic evaluation should be seen as only one of the many potential outcomes for the strategy under consideration. Uncertainty within economic evaluation of influenza vaccination flows from several sources, and these different sources can be used to categorize the types of uncertainty [49]. Detailed instruction on different methods of sensitivity analysis and how to perform them can be found elsewhere [14] and this section focuses on outlining three key types of uncertainty that should be assessed: parameter uncertainty, methodological uncertainty and structural uncertainty.

Parameter uncertainty is the most frequently-discussed form of uncertainty [49]. This type of uncertainty reflects doubt about the true (numerical) value of parameter inputs used in an economic model. Part of this uncertainty may be due to sampling uncertainty that arises from the sources used for the input parameters. For instance, most estimates of disease burden will not be drawn from the whole population but from a sample of this population. However, uncertainty in these estimates will often go beyond this sampling uncertainty to include other factors such as the representativeness of the sample and of the appropriateness of the study methodology used to create the estimate. For this reason, when conducting sensitivity analysis, it may be appropriate to consider values outside the confidence intervals generated from sampling uncertainty alone. Common parameters that should be varied include (but are not limited to) those related to the vaccine (cost of doses, cost of administration, uptake and efficacy) and those related to the disease (probabilities of events and the costs and consequences attached to these events, such as influenza hospitalizations).

Methodological uncertainty refers to uncertainty in the choices made by an analyst when conducting an economic evaluation [49]. Many of the methodological choices that an evaluation
applies will be driven by the relevant guidelines for the setting and/or country under evaluation. However, for other decisions, choices will not be explicitly stated in the guidelines, or perhaps multiple approaches may be deemed acceptable [49]. For instance, there may not be country-specific advice on the discounting rates to apply in some settings. In this case, choices will need to be made by an analyst, and uncertainty in these choices may have a substantial impact on cost-effectiveness projections. This form of uncertainty may be explored in scenario analyses where alternative approaches (e.g. different discounting rates) are applied and model results are presented for these choices.

**Structural uncertainty** refers to the design of the model and the extent to which it captures the relevant disease and intervention characteristics [49]. An example of structural uncertainty could be the choice to include influenza mortality only from hospitalized influenza cases. This is a choice concerning the structure of the model, where a decision is made to have no pathway from community cases to influenza death. While this choice may be appropriate in the base-case model in view of the available data, including an assumption about deaths in the community may also be reasonable (i.e. it potentially reflects reality) and could be explored in a separate scenario. Another key form of structural uncertainty is the choice of model type (dynamic or static, see Chapter 6). While it may not be feasible to explore the impact of different model types on the results, if a dynamic modelling approach is chosen the results can be presented both with and without herd protection.

**Inter-year variability in model results**

Alongside uncertainty regarding the true average (numerical) value of parameters in influenza vaccination models, there is also variation between influenza seasons in many values. This variation results from the inter-year variation in influenza virus transmissibility, virulence, prior immunity and vaccine match [6]. However, as economic evaluations generally seek to make decisions on whether to implement vaccination programmes for several years, one simple approach is to use of the average input values calculated from data collected over several years as the base-case value (e.g. for hospitalisation rates). However, the most appropriate approach to use should be carefully considered. Decision-makers should be aware that cost-effectiveness in any given year may vary substantially, as when an influenza vaccine match is poor vaccination strategies will be less cost-effective.
Estimating and presenting results of the economic evaluation

Box 1. Summary of methodological recommendations from guidelines

Disease burden
- Ideally, at least five years of data should be used to estimate the existing influenza disease burden [15]. However, a shorter period (minimum of a single calendar year) can serve as a starting point.
- WHO’s A manual for estimating disease burden associated with seasonal influenza [15] can be used to estimate some key outcomes, but further sources are required (e.g. to estimate non-medically attended influenza).

Economic burden
- Evaluations should ideally adopt a societal perspective, including all relevant costs and consequences irrespective of who incurs them. However, costs borne by different entities should be reported separately where possible [14].
- If productivity costs are included, they should be reported separately from other costs and cost-effectiveness results should be presented with and without indirect costs.

Programme costs
- The vaccine administration strategy should be carefully considered and outlined in detail. Key choices include who administers the vaccine, in what setting, and whether it is delivered opportunistically or at a separate encounter.
- Where possible, estimates of adverse events following immunization (AEFI) should be included in economic evaluations of influenza vaccination.

Programme impact
- Efficacy against confirmed influenza disease from a meta-analysis will often be the most appropriate estimate. This can be applied to all estimates of influenza-specific outcomes (e.g. influenza death).

Modelling approach
- Table 2 summarizes when to consider each modelling approach.

Discounting/horizon
- Costs and effects should be discounted at the appropriate level indicated in relevant guidelines for the setting under evaluation, but results should also be reported applying WHO-CHOICE recommendations in sensitivity analysis.
- A one-year time horizon may be appropriate in most cases; however long-term consequences from prevented influenza mortality that occur outside the one-year time frame must be fully incorporated into model results.

Results/presentation
- In most cases, strategies for each different target group (e.g. pregnant women) should be compared only to alternative strategies for that group.
- Total costs and outcomes should be presented for each strategy, as well as the incremental results comparing the strategies. These results should be further disaggregated to show the factors driving the results.
- Key types of uncertainty – including parameter, methodological and structural – should be explored. Inter-year variation also needs to be considered [39].

Other recommendations
- Consideration should be given to specific issues that may arise when evaluating a particular population subgroup (see [4] for a summary of potential issues).
9. CONCLUSION

Influenza vaccination strategies in LMICs offer substantial scope to reduce both morbidity and mortality. However, there are currently few published economic evaluations for LMICs that can help decision-makers understand the value for money that may be offered by different influenza vaccination strategies [10]. As many economic evaluations have been conducted in high-income countries [4], some of the lessons learned through this process can help to inform future evaluations for LMICs. However, there are important differences that also need to be taken into account when assessing vaccination programmes for LMICs. This report has outlined many of the influenza vaccine-specific challenges that should be considered and presents advice that should help to provide a framework for future evaluations in the area to build upon.
References


