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Guidance on the economic evaluation of influenza vaccination



DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS

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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 lowincome 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).

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*.

Category	Publication	What it provides
Burden of disease	A manual for estimating disease burden associated with seasonal influenza	A standardized tool to estimate the respi- ratory burden of influenza
Economic burden	Manual for estimating the economic bur- den of seasonal influenza	A step-by-step guide and costing tool to estimate the cost of influenza
	Maternal seasonal influenza vaccination programme planning and costing tool	Specific steps and tools to cost maternal influenza vaccination delivery programmes
Programme cost	Guidelines for estimating costs of intro- ducing new vaccines into the national immunization system	A stepped approach to estimating incre- mental vaccination programme costs
	WHO-UNICEF guidelines for developing a comprehensive multi-year plan (cMYP)	Steps to develop a cMYP including plan- ning and costing tools
Foonemic evolution	Guidance on the economic evaluation of influenza vaccination (current document)	Specific guidance for the economic evalu- ation of influenza vaccination
	Guide for standardization of economic evaluations of immunization programmes	General guidance on the economic evalua- tion of vaccination programmes
Strategic health planning	WHO OneHealth iool	Supporting sector-wide integrated stra- tegic health planning, costing and health impact analysis

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

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 influenzaattributable 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 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]



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