Appendix C: Supporting Information on Best-Practice Recommendations for Cost-Effectiveness Analysis

The cost-effectiveness analysis (CEA) guidelines presented in the task force report complement general CEA guidelines for all health conditions (Drummond et al., 2015; Neumann et al., 2017; Wilkinson et al., 2016) and guidelines developed for vaccination programs, such as those used in Europe (Ultsch et al., 2016) and by the World Health Organization (Walker et al., 2010).

All of these guidelines informed the Task Force report, although the primary sources used for our recommendations are those of Ultsch et al. (2016) and those for low- and middle-income countries (LMICs) of Wilkinson et al. (2016). The best-practice guidelines presented in this task force report result from discussions among task force members and input from International Society for Pharmacoeconomics and Outcomes Research members and others with experience in economic evaluations of vaccines.

Guidance for the CEA of vaccination programs is required because of the nature of the specific characteristics of infectious diseases encountered in evaluating vaccination programs, although these characteristics are not necessarily unique to vaccination programs. These characteristics include indirect health effects such as herd effects (because a vaccine received by one person can affect the health of others) or sero-type replacement, transmitted resistance and disease age distribution effects resulting from the receipt or nonreceipt of vaccines that depend on immunization coverage rates. Immunization coverage rates might depend on provider and individual choices and jurisdiction requirements. Therefore, complex epidemic models to estimate the health outcomes of vaccination programs are desirable if resources and data to support these models are available (Pitman et al., 2012). However, these resources and data are

frequently limited, especially in LMICs. In addition, uncertainty analyses can be difficult to complete for complex epidemic models.

Several studies also have identified the potential economic benefits of vaccination programs beyond health improvement, including increased productivity, reduced financial risk for households, increased educational attainment, increased equity in health outcomes, and reduced risk of disease for tourists (Vuerget et al., 2016; Bärnighausen et al., 2014; Jit et al., 2015; and Ozawa et al., 2012). A tutorial for performing "extended cost-effectiveness analysis" is provided by Verguet and colleagues (2016). Although these benefits might be important for decisions about investment in vaccination programs and can be included in economic analyses, they are also associated with other types of healthcare interventions. Analysts should therefore be cautious in applying these broader benefits only to vaccination programs if their decisions could also affect funding for interventions targeted at other diseases. In this task force report, our focus is on recommendations for cost-effectiveness analysis using health outcomes as the only measure of effectiveness for vaccination programs.

Decision Problem

Framing a decision problem requires the analyst to identify the decision maker(s) and characterize the decision context (i.e. the objectives of and constraints on choices). The analyst must also identify individuals and organizations likely to be affected by the decisions (i.e. public health departments, the target population, people in contact with the target population, and providers). It is also necessary to examine the infrastructure needed to support a new health care intervention (e.g. delivery system and staff for vaccination programs compared with testing

facilities and staff for screening programs for cervical cancer) and the nature and expected size of the impact (eg, number of disease cases or deaths prevented).

Perspective

The CEA perspective defines the scope and types of costs, health outcomes, and other outcomes to be investigated. The perspective depends on decision maker objectives and the decision context. A perspective that encompasses all possible factors that might influence the welfare of all those affected by the decision is rarely practical (Culyer 2014). It is more common for the perspective to be defined by the legal and professional concerns of the commissioning agency. For example, a minister of health might require the scope to include only the costs and health effects for which he or she is politically responsible. These outcomes might include all health system costs attributable to the vaccination program but not the costs to, for example, the education sector if the program is implemented in schools. A trade union might consider only the costs and effects of a workplace vaccination program to workers, whereas an employer might also consider the impact on business profitability. A member of the target population for the vaccination program might only consider the possible side effects, the vaccination price, and its impact on the risk of a disease and its outcomes.

Model Structure

The literature on model structures for vaccination programs has distinguished between cohort models, focusing on the lifetime costs and health outcomes of a single vaccinated cohort, and population models, focusing on the cumulative population costs and health outcomes over the chosen time horizon (Ultsch et al., 2016; Jit and Brisson, 2011) (see Table C1). Flowcharts that provide best-practice guidelines for choices between cohort models and population-based models

have been published (Ultsch et al., 2016; Jit and Brisson, 2011). A population-based model that uses the results of a dynamic transmission epidemic model to estimate the direct and indirect health outcomes of the vaccination program on the population of interest is recommended when indirect effects are expected, although there may be resource and limits to data availability to develop these models especially in LMICs.

A static cohort model should only be used in place of a dynamic model, if either (a) the vaccine has no effect on the transmission of a disease (such as vaccines against non-communicable diseases such as therapeutic cancer vaccines), or (b) if all the following conditions hold:

- The vaccine has no negative direct or indirect health effects (such as changes to the average age of infection, serotype replacement or changes to the periodicity of outbreaks that may affect health care resource needs), and
- Even without the positive herd effects or other indirect health effects the vaccine is cost-effective, and
- The evaluation is simply used to decide whether or not to introduce a vaccine, and not for price negotiations, budget impact analysis or budget optimization

For example, a cost-effectiveness analysis of a herpes zoster infection vaccination program, assumed that the program did not affect the disease transmission rate because this rate was assumed to be very low or nonexistent (Blank et al., 2017).

Cohort-based model structures are typically based on disease incidence and short- and long-term outcomes using, for example, decision trees, Markov models, and patient-level simulation models (Wilkinson et al., 2016). The model structure is designed primarily to represent the new and comparator interventions' impact on disease incidence and associated outcomes for a single

cohort receiving these interventions. A cohort model compares the costs and health outcomes of the vaccination program for the targeted cohort with a relevant comparator intervention based on estimates of clinical efficacy and durability of effect, validated surrogates for these clinical outcomes derived from immune response if no clinical outcomes data are available, and adverse events.

Once a vaccination program is implemented, individuals in the cohort who are eligible for vaccination, regardless of whether they are vaccinated, and other members of the population in contact with the eligible cohort experience health effects. To include health effects for those not vaccinated in a CEA, a population-based dynamic-transmission modeling approach is required. Population-based CEAs for vaccination programs use the outputs of dynamic-transmission epidemic models as inputs into the economic analysis. The economic analysis combines estimates of the resource use associated with the vaccination program and the disease prevented along with the health outcomes from the epidemic model to calculate incremental costs and health outcomes. These costs and health outcomes are based on the cumulative costs (vaccination and disease related) and cumulative health outcomes for the population of interest over the selected time horizon(s), regardless of whether everyone in the population is vaccinated (Kim et al., 2008; Mauskopf et al., 2012).

The economic calculations can be integrated into the epidemic model or used in a separate model. For some diseases, the economic analysis might require a disease progression model describing changes in the disease over time in addition to the epidemic model (e.g. for a vaccination program for prevention of human papillomavirus [HPV] because not everyone infected with HPV will develop the final health outcome, cervical cancer) (Nygard et al., 2014). For vector-borne diseases, such as malaria, the epidemic model might include interactions

between humans and the vector (Tediosi et al., 2006). Dynamic transmission models can be deterministic (eg, a compartmentalized susceptible-infectious-recovered model for the population) or stochastic (eg, an agent-based simulation model following all individuals in the population). Stochastic models can track individuals in the epidemic model and therefore accommodate individual variability but require more data than deterministic models (Ultsch et al., 2016; Pitman et al., 2012).

Dynamic transmission models are designed for a specific disease and vaccination program. These models take into consideration type of vaccine efficacy (reducing infectiousness of those vaccinated who still get the disease versus changing the number of people susceptible to infection; Longini et al., 1996); cases avoided and other outcomes (eg, hospitalizations or deaths); whether the vaccine provides all-or-nothing protection versus partial protection; herd effects; validated surrogates for clinical outcomes derived from immune response if no clinical outcomes data are available; adverse events from vaccination and the vaccination program's impact on serotype replacement or age shifts; and comparative effectiveness of different vaccination programs or other interventions (Ultsch et al., 2016; Pitman et al., 2012).

Time Horizon

The time horizon for CEA is the maximum number of years after the vaccination program starts for calculating estimates. For interventions without external health effects (eg, those that target noncommunicable diseases or that are designed for communicable diseases using a cohort model structure), a time horizon of the duration of the illness or of the vaccination program's impact for a typical individual or cohort should be adopted (Drummond et al., 2015). However, when a population approach with a dynamic transmission model is used for programs designed to prevent communicable diseases to capture relevant externalities and to estimate changes in

infection force and number of disease cases for the whole population, a specific time horizon must be selected for which to present cumulative costs and health outcomes for the population. In this case, the vaccination program's effects that continue beyond the selected time horizon are not captured (Pitman et al., 2012; Mauskopf et al., 2012).

In published studies, a rationale given for choosing the number of years of costs and health outcomes to include in population models has been the number of years after initiation of the vaccination program until the annual number of disease cases estimated using the epidemic model has reached a steady state (i.e. does not change further over time) (Mauskopf et al., 2012; Ultsch et al., 2016; O'Mahony et al., 2015). An alternative approach sometimes used in population CEAs is to compare the costs and quality-adjusted life years (QALYs) using the costs and outcomes for the epidemic model for a single year after the model has reached a steady state with the vaccination program with the costs and QALYs for a single year without the vaccination program.

Comparators

The comparators should include the new vaccination program, current prevention interventions for the disease(s) of interest, and changes in other interventions under consideration, such as increased resources for current prevention programs or for disease management, based on the stated decision problem (Drummond et al.,2015; Wilkinson et al., 2016). Features of alternative vaccination programs under conservation can also be compared; these might include programs with different vaccine doses and schedules, expected coverage rates, delivery mechanisms, catch-up programs (e.g. a catch up program in adolescents 11-17 years of age for meningitis and routine use in those 11 years of age [Ortega-Sanchez et al., 2008]) and population subgroups targeted (e.g. certain age or risk groups for pneumonia vaccines [Porchia et al., 2017] or different

sexes for HPV vaccine [Ben Had Yahia et al., 2015]). When several population subgroups can be targeted by a vaccination program, an incremental analysis of possible combinations of subgroups should be considered in addition to analyses of each subgroup separately if contact rates among subgroups are significant (WHO, 2016).

Outcome Measures

QALYs and disability-adjusted life-years (DALYs) are multidimensional ratio scale measures of health that capture longevity and aspects of health-related quality of life, such as morbidity and absence of pain; their measurement is described extensively elsewhere (Gold et al., 2002; Augustovski et al., 2017). The measure used in the decision context should also be used for the CEA. QALYs and DALYs have been used frequently in CEAs of vaccination programs (Mauskopf et al., 2012; Augustovski et al., 2017). Intermediate outcomes, such as reductions in disease incidence (cases avoided), long-term sequelae, hospitalizations, or deaths, should also be presented in all analyses if they are relevant to the disease and decision context and of interest to the decision maker.

Vaccination program–related and other prevention program-related costs should include those of implementing the program, including, where relevant, costs of vaccines (or what the costs would be if the vaccines are donated), delivery, cold chain, program infrastructure, economies or diseconomies of scope or scale (e.g. those related to the delivery of multiple vaccines in one provider visit [vaccine bundling]), vaccine spoilage from cold-chain failure or other causes, achievement of high coverage rates, and treatment for vaccine-related adverse events. Disease-related costs should include those of healthcare resources for inpatient and outpatient treatment.

Additional individual, family, and population vaccination program–related outcome measures could be included in the CEA depending on the disease, perspective, and decision context if

credible data are available for the vaccination program and its comparators. These outcome measures might include productivity losses for parents from a vaccination program for children and from diseases in children; changes in productivity and educational attainment attributable to reduced incidence of disease and its complications; changes in financial risk to the household because of reduced rates of premature mortality, acute symptoms, or long-term disease complications; changes in antibiotic resistance in the population because of changes in the need for antibiotic therapy; and elimination of disease that might have other macroeconomic effects, such as industrial development or tourism (Verguet et al., 2016; Bärnighausen et al., 2014). When including these measures, the results can be presented as shown in the Tutorial on extended cost-effectiveness analysis by Verguet and colleagues (2016). Alternatively, these outcomes can be presented in an impact inventory list of the magnitude of the different cost and effectiveness outcomes expected instead of a cost-effectiveness ratio or net-benefits analysis, as recommended by the Second U.S. Panel on Cost-effectiveness in Health and Medicine (Sanders et al., 2016; Neumann et al., 2017).

Data Sources

Because many input parameters are needed to estimate the cost-effectiveness of a new vaccination program, these data should be obtained using a comprehensive and transparent process from published information when possible. When input data needed for cohort or population models are not available for the epidemic and economic estimates with and without the new vaccination program or its comparators, inputs should be selected that allow validation of the disease incidence rate without the new program against observed values, if available, or against values extrapolated from those available for similar populations. In addition, when only very limited data are available on vaccine durability, herd immunity, and other long-term indirect

effects, estimates of vaccine efficacy over time should be based on scientific plausibility or expert experience with similar vaccines.

Three major categories of data are needed to populate the economic models:

1. Epidemic and population data to estimate the current age-specific incidence, mortality, severity, virus serotypes or genotypes, and other disease outcomes in the population of interest
2. Input data to estimate the vaccination program's impact on the age-specific incidence, mortality rate, severity, virus serotypes or genotypes, and age distribution of disease cases as well as vaccination-related adverse events or cold-chain distribution failure rates
3. Data on all vaccination and comparator program-related and disease-related costs and health outcomes to estimate changes in costs and QALYs or DALYs associated with the vaccination program and its comparators and, for the broader perspective, data on nonhealth effects, such as productivity losses (eg, parents' lost work time to vaccinate a child or care for a child with the disease), reduced educational attainment, antimicrobial resistance, and family financial risk, depending on the availability of credible data and the interests of the decision maker

Input Data Needed to Estimate Current Disease Epidemiology and Vaccination Program Impacts

For a static cohort model, the information and data required to estimate the current disease incidence rate and expected changes with the new vaccination program include the current age-specific disease incidence by severity, vaccine coverage rates and the vaccine's efficacy in reducing age-specific disease incidence rates and severity over time since the vaccination.

For a population or cohort model using the outputs from a dynamic transmission model, the data required to model current age-specific disease incidence rates and the changes in disease incidence include population mixing patterns, contact rates by age group, disease duration and infectivity for each contact, duration and waning of immunity to the disease for those infected, vaccine uptake rates, the vaccine's ability to create immunity at first, annual immunity waning rate for those vaccinated, and vaccination externalities, including herd effects and serotype replacement for the whole population (Ultsch et al., 2016; Pitman et al., 2012).

Suggested sources of epidemic and vaccination program impact data include the following:

- National clinical and/or serological observational studies of annual age-specific disease incidence and age-specific prevalence of immunity to the disease in the country of interest or in a country with similar characteristics
- Age- and country-specific population mixing and contact patterns, such as those estimated in the POLYMOD study in eight European countries (Mossong et al., 2008). In addition, the number of social contact surveys being conducted is rapidly increasing, although still limited, especially in LMICs. A recent systematic review (Hoang et al., 2018) found 64 surveys in 24 countries (8 in LMICs i.e. China, Thailand, Vietnam, Kenya, South Africa, Zambia, Zimbabwe and Peru). For countries without these data, contact matrices have been proposed that make use of demographic and social activity data to construct synthetic matrices (eg. Prem et al., 2017).
- Published epidemic models for the disease of interest in the country of interest or in a country with similar characteristics. Dynamic models are usually fitted to measures of either past infection (eg. seroprevalence) or current infection (eg. culture or DNA detection). Since these data are also needed to understand the aetiology of syndromic surveillance for respiratory,

enteric and other diseases, they are becoming more common, and global laboratory surveillance networks have been set up for many organisms (http://www.who.int/immunization/monitoring_surveillance/burden/laboratory/en/). In cases where these are not available, analysts may have to rely on more general surveillance pyramids and/or symptomaticity rates in the literature.

- Estimates of vaccine coverage rates in the target population based on coverage rates observed in similar vaccination programs in the country of interest or in countries with similar culture and demographics
- Estimates of serotype replacement based on observed data in other countries or based on plausible assumptions.
- Clinical trials or observational studies of vaccine efficacy and efficacy waning (immune response, clinical cases avoided, or both). For example, for pneumococcal pneumonia vaccination in adults Bonten et al. [2015] report clinical outcomes and Juergens et al. [2014] present immunogenicity data from randomized trials.

Input Data Needed to Measure Costs and Health and Nonhealth Outcomes

Data on the costs and outcomes of implementing a vaccination program could come from multiple sources, including published studies, local and central government agencies, healthcare agencies, and community organizations. Cost and health and other outcomes data required to use the epidemic model results to estimate the vaccination program's cost-effectiveness might include the following:

- The full costs of implementing the vaccination program, including the costs of the vaccines (or what the costs would have been if the vaccine is donated), delivery, cold chain, program

infrastructure, and treatment for vaccine adverse events; economies or diseconomies of scope or scale related, for example, to the delivery of multiple vaccines in one provider visit (bundling of vaccines); vaccine spoilage from cold-chain failure or other causes; and costs of achieving high coverage rates (if relevant), disease progression rates after infection (e.g. after HPV infection), and long-term complication rates and costs of the disease (e.g. meningitis).

- Age-specific costs of treatment and QALYs or DALYs lost because of the disease of interest without the vaccination program based on estimates of the proportion of cases at different levels of severity
- Extent of long-term complications
- Costs of treatment and of QALYs or DALYs lost because of breakthrough cases of the disease of interest (depending on disease severity and age)
- Productivity losses for parents of childhood vaccination-related and disease-related care and for adults of undergoing vaccination and preventing disease
- Changes in antimicrobial resistance, educational attainment, or family financial risk levels

Discount Rates

Several related contentious issues have arisen about discounting for vaccination and other healthcare programs, including whether differential discount rates should be used for costs and effects, whether lower discount rates should be used when long-term outcomes data are available, and the appropriateness of various discount rates (Jit and Mibei, 2015).

Recommendations about differential discount rates vary among current guidelines. Ultsch et al. (2016), for example, recommend differential discounting with a discount rate for benefits that is 50% lower than for costs and lower discount rates for both costs and health effects with longer time horizons. In contrast, Wilkinson et al. (2016) recommend discounting costs and health

effects at the same rate (3%) in the base case as well as sensitivity analyses that use lower discount rates when the time horizon is longer than 30 years. However, there is no obvious reason why the discount rates used for vaccination programs should differ from those applied to evaluations of other healthcare interventions in the same country.

Debate continues about the methodological merits and shortcomings of differential discounting (O'Mahoney and Paulden, 2014; Claxton et al., 2011) and the bases for discount rates. Claxton and colleagues (2011) demonstrated that the implications of discounting differ by whether the decision maker's goal is to maximize health (extrawelfarist approach) or the consumption value of health (welfarist approach).

The study by Claxton et al. (2011) showed that discounting of both costs and health effects at the discount rate for future consumption when the goal is to maximize health is only appropriate if the cost-effectiveness threshold stays constant over time and the level of willingness to trade current and future health is the same as that for willingness to trade current and future consumption. Because the level of willingness to trade current and future health is probably lower than that of willingness to trade current and future consumption, the discount rate for costs and health effects should be lower than that for future consumption. In addition, an increase in the threshold value for the cost-effectiveness ratio over time would support use of a lower discount rate for the health effects than for the costs (Claxton et al., 2011).

Claxton et al. also showed that the effects on discount rates are similar when the decision maker's goal is to maximize the consumption value of health. Thus, the discount rates for both costs and health effects are likely to be lower than those for future consumption if the consumption value of health increases over time. Moreover, the discount rates for health are

likely to be lower than those for costs if the threshold value for the cost-effectiveness ratio increases over time (Claxton et al., 2011).

Given the findings of Claxton and colleagues, the discount rate for both costs and health effects for many decision contexts in healthcare should be lower than the discount rate used for future consumption. However, the discount rates for health effects should be lower than for costs only if the cost-effectiveness threshold is expected to increase over time.

Analysis and Interpretation of Results

How results are reported in CEAs reflects their central aim of identifying and recommending for funding interventions for which benefits exceed opportunity costs.

When the chosen measure of benefit is health change (eg, QALYs or DALYs gained or lost), an intervention should have a positive net health benefit (NHB) compared with the comparators to be cost effective (Phelps et al., 1991; Stinnett et al., 1998), such that

$$\text{NHB} = \text{incremental health gains} - \text{incremental health costs} > 0$$

$$\text{NHB} = Q - C/\lambda > 0$$

In this equation, Q is the expected incremental health gains (eg, QALYs or DALYs averted) resulting from the intervention, C is the incremental cost of the intervention (eg compared with comparators), and λ is the cost-effectiveness threshold representing the opportunity costs of health forgone (ie, cost per QALY or DALY of interventions that can no longer be provided because of resources that are no longer being available). Alternatively, net benefit can be expressed as net monetary benefit ($Q^*\lambda - C$). The comparator offering the greatest net benefit or net monetary benefit is deemed most cost-effective. Alternatively, positive funding

recommendations can be made if the cost per QALY or DALY gained of the intervention (the ICER) is less than the cost-effectiveness threshold, λ. For countries in which a specific threshold value has not been determined, the opportunity costs of the new vaccination program should be estimated using available data on healthcare spending and mortality rates (Revill et al., 2015) or alternative values based on expert opinion and used as the value of λ.

The advantage of net benefit (either monetary or health) is that the magnitude of likely population health improvement or loss from vaccination programs or the change due to other constraints (e.g. limited health system capacity) affecting the delivery or receipt of those vaccines is made evident. This advantage can inform subsequent decisions about how to use cost-effectiveness information, such as for prioritizing implementation or health system–strengthening activities (e.g. increasing the availability of community healthcare workers) that are likely to be particularly important for vaccine delivery and for informing future research.

Cost-effectiveness thresholds or opportunity costs are likely to vary across and within countries depending on income level, healthcare spending, disease burden, claims on the budget, and the extent to which the budget is fixed (Cleemput et al., 2011; Revill et al., 2015; Woods et al., 2016; Glassman et al., 20916; Culyer, 2016; Robinson et al., 2017). For both net-benefits calculations and ICERs, a value of opportunity costs of health that are foregone is often used as a threshold value. Unfortunately, in many countries with health technology assessment agencies, the cost-effectiveness thresholds that have come to be recognized were never explicitly related to opportunity costs. The same is true for the previously recommended Commission on Macroeconomics and Health threshold values related to annual average gross domestic product per person (i.e. cost per QALY of either 1 or 3 times annual the per-capita gross domestic product [WHO, 2001]). An emerging area of research is now offering estimates of thresholds

representing opportunity costs for all countries (Woods et al., 2016; Ochalek et al., 2015; Revill et al., 2015), but uncertainty about these estimates remains. These estimates should therefore be applied with caution unless the decision makers have a clear and well-considered view of the opportunity costs.

An impact inventory list can be included for consideration in decision processes (see perspective and outcomes sections) (Sanders et al., 2016; Neumann et al., 2017), but its effect on decisions will depend solely on the judgments and discretion of the decision makers. If nonhealth effects are formally incorporated into a CEA, the opportunity costs of these nonhealth benefits generated by interventions foregone must be considered because resources were unavailable for other interventions.

Analysis of Uncertainty

Uncertainty analysis should be performed for the cost-effectiveness estimates to test the impact of variability in the model structure as well as assumptions and inputs used to estimate the health and economic outcomes (Bilcke et al., 2011).

For the cohort models, vaccination program, disease-related, and non–disease-related costs as well as the impact of credible ranges of all input parameter values on the cost-effectiveness ratios can be tested in one-way and multiway sensitivity analyses.

Disease dynamics, both real and modeled using dynamic transmission models, are inherently nonlinear, which means that they are sensitive to small changes in parameter values and starting conditions (e.g. changes in population demographics over time) (Pitman et al., 2012). This is particularly true when the disease is not in a stable endemic state. Thus, the impact on cost-

effectiveness ratios should be estimated in one-way sensitivity analyses varying a broad range of alternative inputs and structural assumptions for the dynamic transmission models. These inputs and assumptions include variations in structure to capture the potential impact of the vaccination program on the disease (eg, impact of varicella vaccination on herpes zoster incidence) and variations in input values for population-mixing matrices, disease duration and infectivity, vaccine coverage and efficacy, and immunity waning (Pitman et al., 2012).

Probabilistic sensitivity analysis is generally considered optimal to fully reflect decision uncertainty (Drummond et al., 2015; Sanders et al., 2016) but is likely to be unwieldy for cost-effectiveness models for new vaccination programs. This is especially true for CEA with a dynamic transmission model because of the large number of input parameters for which values are assumed because experimental or observational data are lacking and because of the importance of structural uncertainty due to the complexity of the relationships in the model. In addition, the probability distributions for many of the input parameter values are unknown when the vaccination program is first introduced. If probabilistic sensitivity analyses are not feasible, scenario analyses could be useful. In these analyses, multiple parameters are varied at the same time to reflect feasible alternatives (e.g. alternative estimates of contact patterns in the epidemic model and alternative estimates of disease-related outcomes and costs that might be observed in different countries). In addition, multiway sensitivity analyses can combine variations in structural and parameter uncertainty that cannot be combined in probabilistic sensitivity analyses.

In addition to structural and parameter uncertainty, the impact of the vaccination program on different population subgroups (e.g. different age groups or people living in different regions) might vary. Exploring subgroup variability might be especially important when a broader range

of outcomes is included in the analysis. Factors such as the costs of implementation might be uncertain and vary widely for different population subgroups, even within the same country, particularly if the vaccine is delivered by healthcare workers in hard-to-reach rural locations within LMICs. In these settings, sensitivity analyses of delivery and implementation costs should be undertaken.

Validation

An International Society for Pharmacoeconomics and Outcomes Research task force report on transparency and validation (Eddy et al., 2012) described five types of validity that are relevant to economic models: face, internal, cross, external, and predictive validity. The application of these types of validity to vaccination programs is discussed in the second appendix of that report. For vaccination programs, face validity requires experts to assess whether the model's structure, assumptions, and input parameter values appear credible based on their knowledge of the disease, population dynamics, and vaccination program impact. Internal validity requires careful checking of the computer programming of the dynamic transmission model and economic calculations to ensure that they are error free. Cross validity, external validity, and predictive validity all require comparing the results from the model or calculations with results from other similar models using current observational data or observational data collected after the vaccination program began.

In general, input parameters for dynamic transmission models are calibrated to fit real-world data so that the model outcomes reflect observed disease incidence, trends over time, or natural history. Matching the model outcomes to real-world data can help establish the model's credibility with decision makers (Pitman et al., 2012). It is also important, where possible, to validate the model using a different dataset from that used to calibrate the model (Ultsch et al.,

2016). In addition, where possible, the outcomes of the dynamic transmission model and the CEA results should be validated after the vaccination program is implemented. Kanpirom et al. (2017) point out that the cost-effectiveness results might change over time since the program began. Programs that initially appear not to be cost-ineffective might become cost-effective over time once program initiation costs are paid for and economies of scale and efficiencies are realized.

Software

The software used to create the model can affect the model's transparency and ease of use. Microsoft Excel and TreeAge Pro can be used for cohort models. Microsoft Excel can also be used to create a model that integrates the code for the dynamic transmission model and to calculate the costs and effects using health outcomes from the dynamic transmission model. However, changing structural assumptions after they are coded in an Excel spreadsheet program might be challenging, and solutions to the differential equations in the dynamic transmission model might be less accurate in Excel than with other methods. It is also difficult to implement modern uncertainty analysis and parameter inference methods (e.g. Markov chain Monte Carlo) efficiently in Microsoft Excel.

Software specifically designed for dynamic transmission models, such as Stella by isee Systems Inc. and Berkeley Madonna, are available. The health outcomes from these programs can be transferred to an Excel model to calculate the population costs and number of disease cases avoided with the vaccination program. However, these packages might prevent the programmer from incorporating all desired assumptions. Therefore, customizable code, such as MATLAB, R, or C/C++, might be preferred to allow programming of an integrated epidemic and economic

model, although this approach may be less transparent to policy makers. Regardless of the software used, the program code should be extensively documented so that another researcher familiar with the programming language can readily understand the model structure, assumptions, and calculations.

Transparency

Transparency means that both decision makers and other stakeholders understand how the analysis was performed, including underlying assumptions and likely limitations. A transparent process limits the possibility that researchers' idiosyncratic values will be imposed on those making decisions (Wilkinson et al., 2016). Because the computations in a dynamic transmission model are complex and involve mathematical calculations that might not be familiar to all decision makers, transparency for this model usually requires a clear written description of the model as well as a flow diagram of the model's structure and assumptions in a technical report. The equations used to drive the model and all input parameter values, including details about their derivation from the data sources, can be presented in a technical appendix.

In addition to providing a clear and complete description of the model and the computer program used, the model developers should declare any conflicts of interest. If the model is adapted from a model created for another country by other researchers, those adapting the model should determine all the assumptions in the original model and provide a detailed list of those assumptions in their description of the adapted model.

Reporting

Technical reports and publications on models should follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013). According to these

guidelines, a modeling expert should be able to replicate the model using the information provided, which requires that the model's structure, assumptions, input parameter values, and derivations be described in detail. In addition, because readers might not have access to the software used to develop the model, the results presented should include extensive uncertainty analyses. In particular, results should be reported for scenarios with different structural assumptions, such as different contact matrices or coverage rates in dynamic transmission models with population models or with and without a herd factor in cohort models if the results are sensitive to these assumptions.

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