**Economic Analysis of Vaccination Programs**

**Running Title**: Economic Analysis: Vaccination Programs

# ISPOR Good Practices Task Force

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**Precis:** This report provides recommendations by an ISPOR Task Force for decision makers requiring economic analyses of new vaccination programs to allocate scarce resources in low- middle- and high-income countries

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**Abstract**

Objectives: This report provides recommendations for budget holders and decision makers in high-, middle, and low-income countries requiring economic analyses of new vaccination programs to allocate scarce resources given budget constraints.

Methods: The Economic Evaluation of Vaccines Designed to Prevent Infectious Disease: Good Practices Task Force of the International Society for Pharmacoeconomics and Outcomes Research Task Force wrote drafts and solicited comments on them from external reviewers.

Results: Cost-effectiveness analyses use decision analytic models to estimate cumulative changes in resource use, costs, and changes in quality- or disability-adjusted life years attributable to changes in disease outcomes. Constrained optimization modeling uses a mathematical objective function to be maximized or minimized for a target population for a set of decision variables and within established constraints. Fiscal health modeling estimates changes in net present value of government revenues and expenditures attributable to changes in disease outcomes. The Task Force recommends that those designing economic analyses for new vaccination programs take into account the decision maker’s policy objectives and country-specific decision context when estimating: uptake rate in the target population; vaccination program’s impact on disease cases in the population over time using a dynamic transmission epidemiologic model; vaccination program implementation and operating costs; and the changes in costs and health outcomes of the target disease(s).

Conclusions: The three approaches to economic analysis are complementary and can be used together to generate a more complete picture of a vaccination program’s economic value for national, regional, or subregional decision makers in high-, middle- and low-income countries.

**Highlights:** This report provides guidelines for using three analysis methods—cost-effectiveness analysis, constrained optimization modeling, and fiscal health modeling—to assess the economic and health consequences of vaccination and comparator programs and inform decision makers and budget holders. These three approaches are useful to decision makers with different policy objectives working in different decision contexts. Our guidelines are applicable to high-, middle-, and low-income countries. These complementary approaches can provide information in a useful format for meeting policy objectives based on the best available evidence.

# Introduction

Many new vaccines for a wide range of infectious diseases are being introduced around the world. Their introduction requires increasing amounts of public health funds at a time of increasing pressure on healthcare budgets globally. Low-income countries have been supported in their vaccination programs by organizations such as Gavi, the Vaccine Alliance ([www.gavi.org](http://www.gavi.org)). However, that support might decline when a low-income country makes the transition to middle-income status [1].

Budget holders and decision makers responsible for adding or changing vaccination programs in high-, middle-, and low-income countries are requesting economic analyses of new vaccination programs to help allocate scarce resources in the context of budget constraints. These economic analyses should include not only cost impacts, but also direct health benefits and broader health system consequences [2, 3].

Vaccines can prevent infectious diseases by stimulating an individual’s immune system, thereby reducing morbidity and possibly increasing life expectancy [4]. The populations eligible for a new vaccine may be very large and, although individual benefits are uncertain and may occur many years in the future, population-level direct and indirect health system benefits may be substantial.

Globally, changes in vaccination programs are made in very different public health environments, and governmental involvement in regulating and financing these programs varies. Decision makers everywhere need to base their decisions about changes in vaccination programs on their policy objectives as well as their perceived interests (eg, values, preferences) and obligations (eg, policies, regulations, constraints), which we call their “decision contexts” [5]. Table 1 presents examples of decision makers and their policy objectives for vaccination programs.

# Purpose of This Guidance

We present guidance for economic analyses of new vaccination programs using methods that are relevant to decision makers with different policy objectives within different decision contexts. These objectives and contexts are not exclusive to vaccination, but some unique issues regarding vaccines that prevent infectious diseases must be taken into account in the economic assessments. In particular, vaccination programs can generate substantial “externalities” (indirect effects on third parties) that are not necessarily observed with other types of medical interventions, such as for treatment or prevention of noninfectious diseases (Table 2). These indirect effects should normally be considered in a full economic assessment of the vaccination program. Epidemiologic models designed to estimate the full health outcomes of a vaccination program are required to assess the indirect health effects on third parties [6].

# Proposed Economic Analysis Methods

This report presents guidelines for conducting three types of economic analyses for vaccination programs in high-, middle-, and low-income countries: cost-effectiveness analysis (CEA), constrained optimization (CO), and fiscal health modeling (FHM). Each of these methods provides information in a format likely to be useful to some decision makers in Table 1. Published guidelines for evaluating new vaccination programs are not yet available for CO and FHM, and recent CEA guidelines are available only for Europe [7]. However, the World Health Organization is currently updating its CEA guidelines for vaccination programs published in 2010 [8]. The three methods are briefly described below.

CEA evaluates and compares a new intervention with an existing situation, other relevant comparators, or even a null choice in an analysis of the change in total costs, vaccination program and disease related, and the clinical benefit, frequently measured as quality-adjusted life years (QALYs) gained or reductions in disability-adjusted life years (DALYs) [9-11]. A country-specific threshold value, if available, representing the opportunity costs of interventions to be displaced within a fixed budget or the country’s willingness to pay for increased clinical benefits is then used convert the clinical benefits to costs and the vaccination program and disease-related costs subtracted to compute the new intervention’s net benefits. Alternatively, the incremental cost effectiveness ratio (ICER), the ratio of the difference in total costs divided by the difference in clinical benefit measured as QALYs or DALYs is computed. Interventions with positive net benefits or ICERs below a threshold value are considered cost-effective and are candidates for reimbursement. In countries without a specified threshold value, ICERs can be compared with those for other currently funded interventions in the country to determine their acceptability for reimbursement. Decision makers using CEA should select interventions that maximize a population’s health outcomes while keeping costs within the available healthcare budget.

CO modeling includes budget and other constraints [12, 13]. The CO problem’s mathematical formulation has an objective function that optimizes a goal (policy objective) for a disease under study (eg, reduce numbers of cases or deaths, increase numbers of QALYs, or averted DALYs) with a mix of different interventions that must comply with a list of constraints. Constraints to consider in addition to budget include resources, logistics, disease criteria, target group selection, and maximum vaccine coverage or screening rates. Specific analysis methods are used to identify the right mix of interventions and the level of each intervention that provides the optimum value for the policy objective within the constraints. Alternatively, the objective function can be formulated to choose the optimum intervention mix that minimizes the total cost while producing a target disease outcome.

FHM evaluates the public economic or fiscal consequences for a government that invests in healthcare. For an investment in a vaccination program for a birth cohort, FHM estimates the changes over a lifetime in tax revenues and transfer costs attributable to changes in the birth cohort’s morbidity and mortality rates due to the new intervention [14-17]. The analysis therefore focuses on the acceptable return on investment in terms of reduced government expenditures (ie, public economic impact) for healthcare and disability (transfer payments) and increased taxation revenue in a net present value or internal rate-of-return calculation. The model allows budget holders, such as ministries of finance, that allocate general tax revenues from all members of society to compare returns on investment from vaccination programs and other government projects for different segments of society [3, 18].

The three methods are therefore designed to compare the outcomes of new vaccination programs with those of alternative health and nonhealth interventions in a useful format for achieving different policy objectives (Figure 1).

The three approaches are complementary and can be used together to generate a more complete picture of a new vaccination program’s economic value for national, regional, or subregional decision makers in high-, middle-, and low-income countries. Our recommendations therefore take a global perspective within which the decision maker along with the policy objective and decision context determine which method(s) to use and how to operationalize each method and identify the input data needed.

Other economic analysis methods for vaccination programs have also been reported in the literature [19-28]. Examples include extended CEA; cost-benefit analysis that monetizes all benefits and costs from a broader perspective than FHM, which estimates government financial impacts only; multicriteria decision analysis; and macroeconomic modeling. We did not include these methods in this report because methods guidelines for vaccination programs have been published recently for extended CEA [23] and cost-benefit analysis [25]. In addition, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task forces have published methods guidelines that can be applied to vaccination programs for multicriteria decision analysis [21, 22]. CO modeling has been the subject of two ISPOR task force reports [13, 29]. The 2017 report describes types of CO analyses used in different healthcare fields, such as capacity management, facility location, efficient supply delivery, and outpatient scheduling. The 2018 report presents examples of studies of healthcare interventions using CO, including an example of a CO analysis for a vaccination program. We have aligned our presentation of CO methods, vocabulary, and guidelines with those used by the CO task force.

# Recommendations

In this report, we present 14 categories of best-practice recommendations and explanatory information for the guidelines on CEA, CO, and FHM. We have grouped our recommendations into four main topics:

* Decision description (policy objective, decision context and perspective)
* Disease modeling approaches (model structure, time horizon, comparators, data requirements and sources, outcome measures)
* Data evaluation (analysis method and interpretation, discount rates, uncertainty analysis, validation)
* Logistics (software, transparency, reporting)

Appendix A illustrates the disease modeling approaches and data evaluation steps for each method with examples. Online Appendix B summarizes the literature supporting our value framework for economic analysis of vaccination programs. Online Appendices C, D, and E provide additional background information for our recommendations for CEA, CO, and FHM, respectively.

# Decision Description

## *Policy Objective and Decision Context*

Each of the three methods can provide useful information for decision makers at different levels and in different types of countries (high, middle, and low income). Our recommendations provide a global view whereby users can identify the method or methods to use to address specific policy objectives and decision contexts and determine how to obtain the input data needed and operationalize the approach.

The policy objective and decision context should be described for all three methods and the country of interest. The policy objective differs by method, whereas the decision context differs by country.

For CEA, the policy objective focuses on maximizing net health benefits or achieving an incremental cost per unit of health gained below an acceptable threshold value for a vaccination program (or a combination of interventions; see [30]). The net health benefits from the vaccination program are computed using the opportunity costs of new investments in health or willingness to pay for increased health. These are sometimes, but not always, represented by a country-specific threshold value [7, 31-33] or opportunity costs [34]. However, it is not clear whether current threshold values used in high-, middle-, or low-income countries represent the opportunity costs of new investments in or willingness to pay for increased health through vaccination programs [35-40].

For CO, the policy objective requires the selection of the best combination of interventions to optimize a decision maker’s objective subject to a set of constraints. Examples are maximizing QALYs gained within a given budget or minimizing costs to achieve a QALY-gain target [13, 41-48].

In FHM, the policy objective is to determine the value for a government of an investment in a new vaccination program expressed as a public-sector impact. Changes in money transfers and tax revenues are measured as the net present value of lifetime tax income, net of government transfers for health and disability payments and pensions for a targeted cohort [14-16, 49].

For each country, the decision context is based on the local government and health system structure, healthcare provider or funder policies and regulations, and societal values and preferences.

## *Perspective*

The perspective for the economic analysis should be based on the type of decision maker(s), their policy objectives, and the relevant decision context. The analysis perspective should always be specified.

For CEA, at least two perspectives should be considered: that of the healthcare payer as the decision maker and that of society [50, 51]. For CO, only the budget holder’s perspective must be considered [12, 13], whereas the government’s perspective is appropriate for FHM because it assesses the impact on public accounts [14].

Within a societal perspective for a CEA, a broad set of benefits might be evaluated. These include the health effects of vaccination programs on disease control, elimination, or eradication; reduction of antimicrobial resistance; and improvement in quality of care. These benefits also include nonhealth effects on improved educational attainment, increased work productivity, reduced household financial risk, and increased attractiveness of tourism. Inclusion of a broad range of health and nonhealth costs and effects in the societal perspective might only be possible with qualitative statements if quantitative data are not available.

A budget holder’s perspective for CO could limit the analysis to healthcare costs and disease cases studied, or it could consider a broader range of inputs, outputs, and constraints that are not healthcare related, such as maximizing work productivity by reducing absenteeism.

FHM considers the government perspective, while recognizing that all individuals pay taxes but receive public benefits, such as healthcare services, as well as specific support in case of disability and pensions. From the government perspective, expenditures for vaccination programs leading to program-related reductions in morbidity and mortality improve tax revenues and reduce healthcare and disability payments but may increase pension payments.

Table 3 presents our recommendations for decision descriptions for the three methods.

# Disease Modeling Approach

## *Model Structure*

For any economic analysis of a new vaccination program that prevents an infectious disease, the model’s structure is primarily determined by the impact of the new program on the epidemiology of the disease studied estimated using an epidemiologic model. Inputs for the epidemiologic model include disease incidence, disease prevalence, and clinical trial data on vaccine efficacy to estimate the likely changes produced in the number, severity, and/or age distribution of disease cases.

Because infections may be transmitted back and forth across all members of the population, a vaccination program may change the disease dynamics for those not vaccinated in the target cohort and in the general population. Thus, a deterministic or stochastic dynamic transmission epidemiologic model that accounts for changes in population disease dynamics when a vaccination program is introduced (including herd protection, serotype replacement, and changes in age distribution of cases over time) is recommended (see [6] for guidelines on developing a disease transmission model). In a dynamic transmission epidemiologic model, vaccine coverage rates affect the vaccination program’s outcomes. Because vaccine uptake rates depend on the target population’s willingness to be vaccinated, the epidemiologic modeling should take factors influencing this willingness into account.

The economic analysis structure can use a cohort design or a population design [31, 32, 52]. A cohort design follows a group of individuals as they age until they reach a certain endpoint, which could be death or a fixed age. A population design builds its evaluation as cross-sectional assessments of all persons in the population of interest in a specific geographical area that are followed annually during a certain period. The advantage of a population over a cohort design for infectious diseases is that changes in disease dynamics (eg, force of infection) for those vaccinated and those not vaccinated in the target population and the general population can all be captured.

A cohort model only follows one cohort or a small number of cohorts within the population. It may or may not capture the vaccination program’s impact on disease dynamics in the cohort over time. To account for the impact of population disease dynamics on the cohort, population dynamic transmission epidemiologic models can be programmed to estimate the effects on a single cohort [53]. But most cohort models either assume no effects on cohort disease dynamics or approximate these effects using a variety of static approaches [54, 55].

In some settings (particularly in low- and middle-income countries [LMICs]), there may be limitations in data and/or technical capacity to perform evaluations using dynamic transmission models. A cohort model using a static epidemiologic model may be used in place of a dynamic transmission epidemiologic model if the vaccine has no effect on a disease’s transmission (eg, vaccines for noncommunicable diseases, such as therapeutic cancer vaccines) or the vaccination program has no potential negative direct or indirect health effects (eg, changes in the average age of those infected, serotype replacement, or changes in outbreak periodicity at different coverage rates) that may affect healthcare resource needs or health outcomes.

Using a static epidemiologic model for vaccination for a communicable disease can lead to misleading conclusions, as happened in Greece when low coverage rates for rubella vaccination led to increased rates of congenital rubella. A static epidemiologic model predicted fewer cases of congenital rubella for any coverage rate [56]. For many infections, transmission rates are particularly high in LMICs, making dynamic transmission epidemiologic modeling even more important and highlighting the need to invest in better data collection and local researcher training to broaden use of dynamic transmission epidemiologic models in these settings. Analysts are advised to use previously developed flow diagrams (eg, [7, 8, 57]) to choose the appropriate model structure.

Dynamic transmission or static (where appropriate) epidemiologic models are used to estimate vaccination programs’ health outcomes to generate the health outcomes inputs for both CEA and CO economic analyses. For FHM, where the comparators might be other investments not directly related to health (eg, in infrastructure, education, or defense), a static cohort model structure allows direct comparison of annual expenditures for the vaccination program for the targeted cohort with those for other government investments [14]. However, a static cohort model may underestimate the vaccination program’s value to the government if, for example, the herd protection effect is large. A static cohort model can also overestimate the vaccine program’s value if it has negative indirect effects; in this case the use of a static cohort model is inappropriate.

In CEA models, both cohort and population analyses use decision trees, Markov models, or simulation models to estimate cumulative changes in resource use, costs, and changes in QALYs or DALYs attributable to changes in disease outcomes over the chosen time horizon [58]. CO models use a mathematical objective function to be maximized or minimized for a target population related to a set of decision variables, including the vaccination program and other interventions, with a set of constraints, such as budget limits. The objective function includes changes in disease outcomes from the epidemiologic model for each alternative intervention. FHM models estimate changes in the net present value of government revenues and expenditures attributable to the changes in disease outcomes of the cohort estimated by the epidemiologic model over the selected time horizon.

## *Time Horizon*

In a cohort CEA model, the duration of the vaccination program’s impact can be analyzed over a short time horizon or a lifetime horizon [51]. The time horizon depends on the duration of vaccine effectiveness and any reductions in a disease’s long-term effects, such as chronic sequelae (eg, deafness or neurological deficits after meningitis) or delayed disease outcomes (eg, cervical cancer or decompensated liver disease) attributable to the new vaccination program. In a population CEA model, the time horizon used to estimate cumulative costs and benefits should be long enough to include the time when changes in disease outcomes attributable to the new vaccination program become stable (ie, annual estimates of a disease’s long-term outcomes and sequelae should not change if the time horizon is extended) [7].

For both cohort and population model structures, different time periods after the vaccination program begins should be tested in sensitivity analyses. Alternatively, using a population model, a 1-year time horizon can be selected to compare, using the epidemiologic model, the new vaccination program’s costs and outcomes with those of relevant comparators when both short- and long-term disease outcomes reach a steady state [31].

Population models can also provide estimates of changes in vaccination- and disease-related population costs each year after the new vaccination program is initiated (ie, the vaccination program’s annual expected budget impact) [31].

A critical time horizon in CO is the one defined by specific constraints. For example, budget limits could be evaluated over a period of interest to the budget holder, such as 3 to 20 years, allowing an estimate of the new vaccination program’s optimal impact during the budget time horizon [41].

In FHM, the time horizon should cover the period during which health gains attributed to vaccination accumulate and are likely to have a public economic impact. If the tax money spent on the vaccination program reduces mortality rates, a lifetime horizon is needed.

## *Comparators*

All three analytic methods should include all relevant comparators, including prevention or treatment interventions used currently and alternatives that could be considered in a near future [7, 51]. Examples of comparators include alternative dosing schedules or target age groups for the new vaccine, bed nets for malaria, increased resources for human papillomavirus infection screening, and community activities to influence health-related behaviors. For CEA and CO, these alternatives generally consist solely of interventions that target health outcomes. For FHM, the comparators might include interventions designed to achieve other types of policy objectives. such as better education, less unemployment, or higher gross domestic product.

In CEA, the vaccination program is compared to each comparator individually, and a ranking algorithm is used to compare the results of each of these analyses. For FHM, the vaccination program and all relevant comparators are analyzed separately, and the results are compared. For CO, all relevant comparators are included as decision variables in a single analysis that identifies the combination of interventions that optimizes the decision maker’s objective function. For CO, comparison of the optimum solution with those generated using an alternative process for decision making, such as random selection of prespecified criteria, should also be included.

## *Data Requirements and Sources*

Three types of input data should be considered: current epidemiologic data for the disease and competing causes of death in the population of interest; vaccination trial results, such as efficacy and protection duration; and economic and health outcome inputs, such as prevention-program–related and disease-related resource use and costs and disease-related QALYs or DALYs.

To identify input parameter values, data should be collected from clinical trials; observational, modeling, and qualitative studies; and compendia of disease-related information, such as the World Health Organization’s CHOICE [30] and other online resources (eg, U.S. Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, World Bank, Organisation for Economic Co-operation and Development, Eurostat).

Data needed to construct static or dynamic epidemiologic models for the disease(s) of interest include current disease incidence and mortality rates as well as vaccine coverage and efficacy over time. Additional data needed to construct dynamic transmission models include social contact matrices and measures of infectivity, which are now available for many countries worldwide (for social contact matrices [59-61] and for infectivity [62]). Vaccine-related data, especially on long-term duration of protection and serotype replacement, should be selected based on scientific plausibility of product characteristics or observational data, when available. The impact of the assumptions should be tested in sensitivity analyses.

When country-specific data are unavailable for dynamic transmission model inputs, the input values assumed should ensure that the model outcomes without the vaccination program match observed, age-specific disease incidence rates (model calibration) [6]. When data on cost and other outcomes are not available, treatment algorithms, expert opinion, or key informant interviews should be used (and promotion of special interests avoided whenever possible to prevent bias).

Specific constraints in CO should be determined with decision makers (budget holders who will use the analysis results) and based on local conditions, such as the available budget and vaccine access and screening platforms.

Additional sources of data for FHM are needed and vary by country. Ministries, such as of economics, planning, and finance, may be good sources for data on cost transfers by age (eg, taxes or disability payments) based on health outcomes.

## *Outcome Measures*

For all economic evaluations, both intermediate and final outcomes over the time horizon selected for the analysis provide important information for decision makers. Thus, for vaccination programs and their comparators, the health outcomes of the disease(s) of interest, QALYs and life years gained or DALYs averted, with the disaggregated and total intervention-related and disease-related costs should be presented [63-65].

The health outcomes should include disease-related outcomes, such as numbers of patients with the disease by age and severity as well as numbers of deaths, hospitalizations, and physician visits. Vaccination-program–disaggregated costs should include costs of vaccine acquisition, vaccine delivery, cold chain implementation and maintenance, program infrastructure, and high coverage rates. Economies or diseconomies of scope or scale (eg, related to delivery of multiple vaccines in one provider visit), vaccine spoilage rates (eg, from cold-chain failure), and rates of vaccine-related adverse events for the cohort or population over the chosen time horizon should be presented. Costs of comparator programs other than vaccination programs might include those of program infrastructure, implementation, and supplies (eg, bed nets for malaria prevention). Disease-related costs might include costs of inpatient stays, outpatient visits, and long-term sequelae as well the value of productivity lost by patients and caregivers. FHM includes additional intermediate and final cost outcomes, such as lifetime tax revenues and transfer payments from a modeled cohort for vaccination and comparator programs.

Although many intermediate health outcomes and aggregated and disaggregated costs are similar for the three methods, the final outcome measures are different. The cost-effectiveness final outcomes include net monetary benefits or incremental cost per QALY gained or DALY averted (ICERs) for the new vaccination program compared with those of each comparator. These outcomes are compared with a country-specific threshold value or estimated opportunity costs (eg, for the UK [34] and for LMICs [33]) or with ICERs for currently used healthcare interventions.

A CO model’s final outcomes include the best mix and level of alternative interventions that optimize the decision maker’s objective within budgetary and other constraints. The decision maker’s objective might be a single outcome (eg, maximum number of disease cases or deaths avoided or minimum vaccination budget needed) or a composite outcome with weights for each outcome clearly specified (eg, disease cases and mortality rates).

The final outcomes for FHM are the net present value of the interventions using the discounted cash flow for gross and net taxes after the initial investment is made in a new vaccination program as well as benefit-to-cost ratios and (internal) rates of return for the government.

Table 4 presents our recommendations for disease modeling approaches for the three methods.

# Data Evaluation

## *Analysis Method and Interpretation*

Because CEA, CO, and FHM produce different types of results, it is important to understand each model’s analysis method and how to interpret the results.

CEA can produce two different types of results. The first type is the net monetary benefit for the new vaccination program compared with the alternative [66]. The opportunity cost for the marginal investment in health (λ) must be placed into the decision context, where the benefit is converted into local currency before the net costs, (λ \* ΔQALYs – Δcosts) or (λ \* ΔDALYs – Δcosts), are subtracted. This opportunity cost could be a best local estimate or a generally accepted cost-effectiveness threshold representing willingness to pay in the relevant jurisdiction ([34, 38, 67] for the UK, [33] for LMICs, [40, 68]).

The other type of result is the estimated incremental total vaccination program and disease-related cost per QALY gained or DALY averted ratio (the ICER) of the new vaccination program when the total costs and QALYs or DALYs are compared with each alternative intervention. The ICER is compared with a cost-effectiveness threshold that reflects the opportunity costs appropriate for the jurisdiction or the willingness to pay for health gains to determine the acceptability of funding the vaccine program. For countries where threshold values or local estimates of opportunity costs are not available, the ICER can be compared with ICERs for currently used healthcare interventions. Sensitivity analysis with alternative cost-effectiveness thresholds should be explored to identify prices that make the vaccination program cost-effective.

For CO, depending on the optimization problem (level of complexity), an appropriate analysis method should be selected for obtaining an exact or heuristic (approximate) solution.

Simple optimization problems with a clear objective function expressed with few decision variables and few related constraints, expressed as linear functions, could be solved with an exact solution using the simplex method [13]. Other exact analysis methods (eg, interior point method) in linear programming can be used for more complex and extended problems. Details on these methods can be found elsewhere [69].

A heuristic solution is obtained using more complex analysis techniques for more complex situations, such as when optimization conditions are nonlinear, multiple objectives need to be optimized, dynamic transmission models are used to estimate changes in disease incidence due to the vaccination program, or more than 100 decision variables and constraints are assessed. The solutions produced are almost but not quite optimal. Heuristic analysis techniques include genetic algorithms, neural computing, and fuzzy logic. Software has been developed to support these analyses, but the process requires substantial time, resources, and hardware. Moreover, these analysis methods do not always make clear how close their results are to the optimal solution. Extended validation processes and testing are needed to interpret the resulting solution for the CO analysis.

For complex problems, such as how to prevent infectious diseases, dynamic models to measure the indirect herd effect are difficult to use directly in an optimization model that searches for an exact solution. An alternative approach is to develop a simple construction using the output of dynamic transmission models as direct inputs into the optimization model. We recommend, in this case, that model users explain what has been constructed and how the results of the dynamic transmission model are integrated into the CO model’s objective function. It remains essential to evaluate the plausibility of the results obtained through any optimum analysis method (see validation section).

For FHM, simple calculations should be used to combine the input parameter values for calculations of net present values as well as the cost-benefit ratio, return on investment, and rate of return on the investment in a vaccination program for a population cohort.

## *Discount Rates*

Because assumptions about discount rates are different in different countries and different decision contexts, our primary recommendation is to use discount rates for all three methods for vaccination programs that are consistent with those used for other interventions in the country of interest for similar healthcare policy objectives, unless use of alternative rates can be justified.

However, because of ongoing research on the appropriate values for both benefits and costs [70-73], models should be programmed to allow users to change the base-case discount rates for both benefits and costs. Alternatives to present in sensitivity analyses might include differential discounting for costs and benefits [7], lower discount rates when time horizons are longer than 30 years [51], and 0 discount rates, especially for short-term analyses that use CO analysis. Furthermore, when nominal costs or budgets are used in the CO analysis, no discount should be applied, but discounting can be applied to the outcome measures to be maximized over time (eg, QALYs gained or DALYs averted).

## *Uncertainty Analysis*

For CEA, conventional one-way sensitivity analyses should be used with plausible ranges to test the impact on the results of the uncertainty of the input values for the epidemiologic models and economic calculations for which the modeler expects variability. A series of multiway analyses should also be performed that change structural forms and/or use multiple input values in the model to represent alternative credible scenarios (eg, [74]).Scenario analyses should be performed in both cohort and population models with varying time periods to assess the cumulative costs and health outcomes.Scenario analyses of population subgroups should be considered if costs, health, or other outcomes of the vaccination program might vary. Probabilistic sensitivity analyses should be done whenever possible but are likely more feasible in cohort models based on static epidemiologic models than in population models based on dynamic transmission models.

For CO, software packages (eg, Microsoft Excel’s Solver add-in, Lindo, MATLAB) use standard reporting formats for sensitivity analyses of critical variables that affect the outcome [12, 75]. These formats include the decision variable parameters that affect whether the decision variables should still be considered in the analysis as well as changes in constraints, vaccine price, and variables that can change the outcome measure during the analysis period. It remains important to note that sensitivity analyses are only available on specific variables when the problem has been set up accordingly. The reports provide standard outcome results but need careful evaluation to ensure that they are interpreted correctly. Sensitivity analysis is cumbersome to perform with stochastic variables in optimization models, especially when the equations are complex because, for example, they have too many variables or are nonlinear. These analyses might require more powerful software that presents more precise combinations of interventions for the constructed algorithms, and heuristics might be more appropriate than methods aimed at identifying exact solutions.

One-way and multiway scenario analyses can be performed for FHM analyses using best estimates of parameter ranges. Probabilistic sensitivity analysis is not recommended with FHM because such analyses are not typically presented for other types of government expenditures.

## *Validation*

Validation is important for any economic analysis and includes the following steps [76]:

1. Arrange for experts in modeling or prevention program design and operation to assess the model’s face validity.
2. Verify the model program’s internal validity to ensure that it has no errors and planned calculations are executed correctly.
3. Assess the model’s external validity to ensure that its results are compatible with the data used to derive the inputs as well as observational data from other datasets, where available, or outcomes from similar published economic analyses.

Table 5 presents our recommendations for data evaluation for the three methods.

# Logistics

## *Software*

Software that is widely available, such as Microsoft Excel, or in the public domain, such as R, should be used if possible for CEA and FHM analyses. Integrated epidemiologic and economic CEA or FHM analyses should be programmed and used to generate base case results with uncertainty analyses.

When dynamic transmission epidemiologic models and uncertainty analyses are developed with MATLAB, R, or C/C++, a program code should be added to calculate the costs, effects, and final outcomes. Programs built with commercial software should include full documentation to guide reviewers. For transparency, the model code should be made available to decision makers, where feasible.

For CO, a wide variety of software options are available, some of which can be used with Microsoft Excel (eg, INFORMS or Solver).

## *Transparency*

Economic evaluations are provided to decision makers who might not be familiar with economic modeling techniques or the terminology used to describe them. Therefore, the models must be described in ways that those who are not familiar with the methodology can understand. Sufficient details should also be provided so technical users of the method can readily understand the model’s structure, assumptions, input parameter values, and derivations. The model’s structure and assumptions should be as simple as possible while meeting decision context needs.

## *Reporting*

Technical reports and publications on models should follow the Consolidated Health Economic Evaluation Reporting Standards [77]. 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 those of 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 or with and without a herd protection factor in static cohort models if the results are sensitive to these assumptions.

Table 6 presents our recommendations for logistics for the three methods.

# Discussion

This report provides guidelines for using three analysis methods—CEA, CO and FHM—to assess the economic and health consequences of vaccination and comparator programs and inform decision makers and budget holders. We chose these three approaches for their utility to decision makers with different policy objectives working in different decision contexts. We also provide guidelines applicable to high-, middle- and low-income countries. These complementary approaches can provide information to budget holders and other decision makers in a useful format for meeting their policy objectives based on the best available evidence. Table 7 summarizes the economic principles and relationships among the methods for informing decision makers with different policy objectives.

These guidelines do not propose normative rules that identify desirable policy objectives or recommend methods to achieve each policy objective. However, decision makers in different decision contexts can use the best practices for the analyses described in this report in an evidence-based framework rooted in decision-theoretic principles to make sound decisions about a vaccination program. The three methods included in this task force report include only a limited number of the potential extended benefits of vaccination programs described in the recent literature [18, 23, 25, 73]. The data needed to include the extended benefits of vaccination programs in economic assessments are currently very limited.

We have discussed three complementary approaches in the context of vaccination program investments. Vaccination programs provide examples of large programs that are usually publicly funded and often vertically integrated, so they lend themselves naturally to these three approaches. However, restricting the scope of the analysis to vaccination programs is unlikely to lead to globally optimal outcomes. The approaches we describe are equally valid for evaluating other preventive and therapeutic interventions. Indeed, knowing about the other interventions is often necessary to understand the context for the three analytic approaches, such as the value of the opportunity cost of health in CEA, the basket of options and resource constraints in CO analyses, and the size of a positive net present value or return on investment that would lead to an investment in FHM analyses.

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Table 1: Decision makers and their policy objectives

|  |  |
| --- | --- |
| **Decision Makers** | **Policy Objectives** |
| * Those responsible for developing new vaccines (commercial or public enterprises)
 | * Allocate funding to vaccine research for different diseases based on potential outcomes and return on investment
 |
| * Those responsible for allocating funds available for vaccination programs within a country
 | * Allocate limited funds to vaccination programs by investing in the direct purchase and delivery of vaccines as well as surveillance, information gathering, and other activities to support successful vaccine implementation and use
 |
| * Medical specialists (eg, in infectious diseases and pediatrics)
 | * Provide counsel to policy makers and other decisions makers by serving on advisory councils
 |
| * Those responsible for health planning, budget development, and management of community-based programs
 | * Choose the amount of healthcare resources to commit to vaccination programs while taking into consideration claims on budgets for health promotion and other prevention and treatment interventions
 |
| * Ministries of health, health technology assessment agencies, national immunization technical advisory groups (in the public sector), and leaders of public and private insurance plans
 | * Choose vaccine or other prevention or treatment programs for public or private insured bundles
 |
| * Senior officers of industrial federations, trade unions, or local workers’ compensation boards
 | * Decide whether to introduce a new workplace vaccination program to reduce employee productivity losses
 |
| * Senior administrators of public service organizations
 | * Decide whether to require employees to be vaccinated to protect employees and others who are in contact with them, such as patients or family members
 |
| * Leaders of international funding agencies (donors) or nongovernmental organizations
 | * Determine whether to fund vaccine development and delivery programs through domestic institutions or vertically (eg, in their own facilities or through other nongovernmental providers) or other priorities
 |
| * Ministers of finance with broad social objectives
 | * Appraise the claims for funding vaccination programs and the health sector more generally and compare those claims with those for funding other needed infrastructure
 |
| * General population
 | * Decide on vaccination preferences for themselves and their family
 |

Table 2: Factors affecting economic analyses of vaccination programs

| **Category** | **Factors** |
| --- | --- |
| *Impact of vaccination program on disease outcomes for specific vaccine coverage rates* |
| Narrow effects | * Avoidance of cases or events
* Shift of severe to less severe cases or events
* Reduction in medical resource use for those who are vaccinated
* Increased productivity for those who are vaccinated and their families
 |
| Broad effects (may be positive or negative)  | *Positive* * Herd protection (reduced infection rates in unvaccinated and susceptible individuals because of reduced disease transmission resulting from a high level of immunity [herd immunity] in the population through vaccination or prior infection) [78]
* Reduced antimicrobial resistance
* Improved capabilities (eg, education, learning, and work)
* Protection of households from catastrophic health expenditures
* Improvement in quality of healthcare
* Macroeconomic benefits (eg, increased foreign investment and economic output throughout the economy)

*Positive or negative* Age shifting of the infection and disease condition* Serotype replacement (eg, because of vaccine coverage of only a subset of disease serotypes)
* Changes in health-related behaviors (eg, those pertaining to risk exposure)
 |
| *Determinants of vaccine coverage rates* |
| Program objective | * Disease elimination, eradication, or maintained outbreak control
* Increased investment cost for high vaccine coverage rates to achieve the objectives of disease elimination and eradication
 |
| Cost | * Payment for the vaccine through copayments or public or private third-party insurance payments
 |
| Risk of vaccine side effects | * Balance between the benefit of a public good and individual risk aversion toward vaccine side effects
 |
| Individual freedom | * Freedom to decide whether to undergo vaccination versus social obligations
 |
| *Impact of vaccination program on healthcare costs* |
| Budget | * Impact on total healthcare costs of prevention versus treatment
 |
| *Analysis process requirements* |
| Epidemiologic model | * Comprehensive epidemiologic model needed to estimate all direct and indirect disease-related effects, which can lead to complex model constructions
 |
| Uncertainty analysis | * Complexity or difficulty of full sensitivity analysis because of uncertainty about some of the vaccination program’s broad effects when the program starts (eg, vaccine coverage rates, herd protection, serotype replacement)
 |

Table 3: Recommendations for decision descriptions

|  |  |
| --- | --- |
| **Policy Objective and Decision Context** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Describe the country-specific decision context, including relevant policies, regulations, values, and preferences.
 | ✓ | ✓ | ✓ |
| * Identify the decision makers, decisions to be made, persons affected by the decisions, and likely size of the impact; use the decision makers’ policy objectives and decision context to guide the choice of analysis method(s) (see Table 1).
 | ✓ | ✓ | ✓ |
| * Present the policy objective as:
	+ An estimate of net health benefits or incremental cost per unit of health gained with a new vaccination program when compared with alternative interventions and the opportunity cost or willingness to pay for health gains
 | ✓ |  |  |
| * + An optimization exercise to select a combination of interventions to optimize health, nonhealth, or budget goals within known feasibility constraints
 |  | ✓ |  |
| * + An estimate of public return on investment measured as the net present value of lifetime tax income and government transfers for a population cohort that is eligible for vaccination
 |  |  | ✓ |
| **Perspective** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Select a perspective that reflects the decision maker’s policy objectives within the decision maker’s decision context.
 | ✓ | ✓ | ✓ |
| * Include at least the following two perspectives in CEA:
	+ Healthcare program payer for direct and indirect health effects of the vaccination program
	+ Societal perspective for direct medical and nonmedical cost and cost of work-productivity loss
 | ✓ |  |  |
| * Include the budget holder’s perspective with constrained budget, other constraints if relevant, and health or nonhealth outcomes goals to optimize.
 |  | ✓ |  |
| * Include the government’s perspective for decisions about tax revenue distribution among public programs.
 |  |  | ✓ |

**CEA, cost-effectiveness analysis; CO, constrained optimization; FHM, fiscal health modeling**

Table 4: Recommendations for disease modeling approaches

|  |  |
| --- | --- |
| **Model Structures** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Justify the choice of cohort or population model.
 | ✓ | ✓ | ✓ |
| * Preferentially use a model structure with the vaccination program’s impact on disease outcomes estimated using a dynamic transmission process.
 | ✓ | ✓ | ✓ |
| * Consider using a cohort model based on static estimates of vaccination program efficacy only when the vaccination program is likely to have no negative indirect effects.
 | ✓ | ✓ | ✓ |
| * For a CEA model with a population-based model, assess cumulative population costs and disease outcomes based on a dynamic transmission epidemiologic model that estimates the health outcomes over the selected time horizon.
 | ✓ |  |  |
| * For a CEA model with a cohort-based model, estimate cohort costs and health outcomes over the selected time horizon based on a dynamic transmission epidemiologic model, unless a static epidemiologic model can be justified.
 | ✓ |  |  |
| * For a CO model, estimate the optimum combination of interventions over the selected time horizon; obtain the estimates of disease outcomes for each intervention type (decision variables) in the objective function based on a dynamic transmission epidemiologic model unless use of a static epidemiologic model can be justified.
 |  | ✓ |  |
| * For an FHM model, estimate changes in net government revenues by age and sex using changes in disease outcomes for the cohort of interest; include indirect effects on cohort members using a dynamic transmission epidemiologic model unless use of a static epidemiologic model can be justified.
 |  |  | ✓ |
| **Time Horizon** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * For a cohort CEA or FHM model, choose a time horizon that is long enough to capture the vaccine’s duration of effectiveness and long-term effects of avoided cases; if the effects assessed include mortality rates, use a lifetime time horizon.
 | ✓ |  | ✓ |
| * For a population CEA model, choose a time horizon that is long enough to include the point at which the population’s net health benefit from the new intervention becomes stable.
 | ✓ |  |  |
| * If there is a budget constraint for a CO model, select a time horizon that is relevant to the budget holder, which could be at least 3 years or at most 20 years.
 |  | ✓ |  |
| **Comparators** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Include as a comparator a scenario that evaluates the prevention and treatment programs currently in use with their level of implementation for the disease of interest but does not include the new vaccination program.
 | ✓ | ✓ | ✓ |
| * Include other new prevention or treatment interventions or changes in current interventions that target the disease of interest if this is part of the policy objective.
 | ✓ | ✓ | ✓ |
| * Include vaccination programs for different diseases if these diseases are part of the policy objective.
 | ✓ | ✓ | ✓ |
| * Compare the model results for population subgroups if these subgroups are part of the policy objective.
 | ✓ | ✓ | ✓ |
| * Compare the results of the optimization modeling process for the available interventions with the results of a process that uses selection criteria other than optimization to demonstrate the difference in the end results between the two methods.
 |  | ✓ |  |
| * Consider comparing the vaccination program’s effects on public investments with those not related to healthcare.
 |  |  | ✓ |
| Data Requirement and Sources | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Use a comprehensive and transparent approach to select input data from the best available source.
 | ✓ | ✓ | ✓ |
| * Obtain estimates of vaccine coverage, efficacy, waning, and infectious disease externalities from evidence and/or assume these based on scientific plausibility.
 | ✓ | ✓ | ✓ |
| * Obtain estimates of resource use, costs, and health outcomes from published studies and/or prevention or treatment strategies.
 | ✓ | ✓ | ✓ |
| * Ask budget holders to identify constraints based on local conditions.
 |  | ✓ |  |
| * Assess government cost transfers by age based on health outcomes using country-specific health ministry and other government data.
 |  |  | ✓ |
| **Outcome Measures**  | **Analysis Method** |
| **Recommendations**  | **CEA** | **CO** | **FHM** |
| * Measure changes in numbers of cases, hospitalizations, deaths, and medical visits over time that are relevant to the disease of interest.
 | ✓ |  | ✓ |
| * Measure changes in QALYs, DALYs, or life years.
 | ✓ | ✓ |  |
| * Measure changes in health-related resource use and disaggregated and aggregated costs, including prevention- and treatment-related resource use and costs.
 | ✓ |  | ✓ |
| * Measure changes in government revenue and transfer costs over time.
 |  |  | ✓ |
| * Compute net monetary benefits as (λ x ΔQALYs – Δcosts) or (λ x ΔDALYs – Δcosts) for the new vaccination program compared with all comparators, where λ represents the threshold value or opportunity cost of a QALY gained or a DALY averted if available.

OR Measure incremental cost per QALY gained, DALY averted, or life year gained for the new vaccination program relative to all comparators. | ✓ |  |  |
| * Measure changes in a broader set of outcomes, including work productivity, levels of educational attainment, household financial risks, antibiotic resistance, and disease eradication, if these data are available.
 | ✓ |  |  |
| * If a single disease-related outcome is to be optimized, measure the absolute and relative changes in outcomes over the selected time horizon, and compare the current and optimum combinations of interventions selected within the specified constraints.
 |  | ✓ |  |
| * If a composite outcome is presented as a single value, clearly describe the process for determining the weighting factors and make sure that this process is easily replicable.
 |  | ✓ |  |
| * Rank and estimate the disease impact magnitudes of each intervention included in the analysis that optimize the chosen outcomes.
 |  | ✓ |  |
| * Calculate net present value for a single cohort and the return on investment, cost–benefit ratios, and internal rate of return to the government.
 |  |  | ✓ |

# CEA, cost-effectiveness analysis; CO, constrained optimization; FHM, fiscal health modeling; QALY, quality-adjusted life year; DALY, disability-adjusted life year

Table 5: Recommendations for data evaluation

|  |  |
| --- | --- |
| **Data Analysis and Interpretation** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Use a threshold value to compute net benefits or for comparison with the ICER that reflects the opportunity cost or willingness to pay for clinical benefits for the intervention; alternatively, compare ICERs with best local estimates of the opportunity cost based on published studies or ICERs for currently used healthcare interventions.
 | ✓ |  |  |
| * With simple linear optimization models, use the simplex method; with more advanced models, use more complex analysis methods that do not search for exact results but use heuristic searches to find a solution that is close to an exact result.
 |  | ✓ |  |
| * Compare the results with those of other public health and nonhealth programs.
 |  |  | ✓ |
| **Discount Rates** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Use discount rates that are consistent with those used for other programs in the decision context, unless use of different rates can be justified.
 | ✓ | ✓ | ✓ |
| * For CEA, use discount rates for benefits that are lower than for costs only if cost-effectiveness thresholds or opportunity costs are expected to increase over time.
 | ✓ |  |  |
| * For CO with a short time-horizon (eg, less than 3 years), consider using a 0-discount rate as the base case. When budgets are evaluated using nominal costs each year, no discount should be applied to costs.
 |  | ✓ |  |
| * For FHM, consider using discount rates that are equal to the country’s long-term bond rate.
 |  |  | ✓ |
| * Make sure that the model allows users to change discount rates for costs and benefits because of differences among decision makers in different decision contexts.
 | ✓ | ✓ | ✓ |
| * Perform sensitivity analyses for alternative discount rates (including no discounting and differential discounting).
 | ✓ | ✓ | ✓ |
| * Promote additional research on discounting where needed.
 | ✓ | ✓ | ✓ |
| **Uncertainty Analyses** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Perform extensive one-way sensitivity analyses and multiway scenario analyses using credible ranges for all input parameters.
 | ✓ |  | ✓ |
| * Perform scenario analyses with epidemiologic models using different combinations of assumptions and input values to assess outcome variability.
 | ✓ | ✓ | ✓ |
| * Perform probabilistic sensitivity analysis to generate acceptability curves.
 | ✓ |  |  |
| * When using a population approach, show the impact of the selected time period on the cumulative cost-effectiveness ratio.
 | ✓ |  |  |
| * If possible, conduct sensitivity analyses for population subgroups.
 | ✓ |  | ✓ |
| * Use the software that was used for the optimization analysis to generate the sensitivity analysis results; carefully examine the results for plausibility.
 |  | ✓ |  |
| **Model Validation** | **Analysis Method** |
| **Recommendation** | **CEA** | **CO** | **FHM** |
| * Arrange for experts in the jurisdictions to assess the face validity of the model’s structure, assumptions, input parameter values, and results.
 | ✓ | ✓ | ✓ |
| * Arrange for a second programmer who is not involved in the analysis to evaluate the internal validity of the calculations.
 | ✓ | ✓ | ✓ |
| * Calibrate input parameters for the epidemiologic model to ensure that the outcomes match those in the dataset used to generate input values.
* Where possible, compare disease outcomes to the values in a dataset not used to develop the model.
 | ✓ | ✓ | ✓ |
| * Compare disease-related costs estimated in the model with those in the dataset used to generate the input values
* Where possible, compare disease-related costs to those from a dataset not used to develop the cost estimates.
 | ✓ | ✓ | ✓ |
| * Develop dual formulations of the objective function (maximization or minimization of alternative objectives) and run both formulations to ensure that the optimum combination of interventions is the same for both models and assess whether the results for the optimal intervention mix fall within included constraints.
 |  | ✓ |  |

# ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; CO, constrained optimization; FHM, fiscal health modeling

Table 6: Recommendations for logistics

|  |  |
| --- | --- |
| **Software** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Use software that is widely available, such as Microsoft Excel, to create a linked disease and economic model for estimating the vaccination program’s impact. However, if the run time is too long, use MATLAB, R, or C/C++. Provide extensive documentation on all software used.
 | ✓ | ✓ | ✓ |
| * Choose software for CO based on the complexity of the problem to be addressed, budget limits, frequency of use, and technical support available.
 |  | ✓ |  |
| * Make the model’s coding available to decision makers.
 | ✓ | ✓ | ✓ |
| **Transparency** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Present a clear overview and flow diagram in the report for all models.
 | ✓ | ✓ | ✓ |
| * Provide all model equations and assumptions as well as input parameter base-case values, ranges, and distributions, including the data sources and derivations, in a technical appendix.
 | ✓ | ✓ | ✓ |
| * Provide simple descriptions and explanations of the model’s structure and assumptions.
 | ✓ | ✓ | ✓ |
| **Reporting** | **Analysis Method** |
| **Recommendations** | **CEA** | **CO** | **FHM** |
| * Follow Consolidated Health Economic Evaluation Reporting Standards reporting guidelines.
 | ✓ | ✓ | ✓ |
| * Present base-case and extensive uncertainty analyses for the key model outcomes that test the impact of parameter uncertainty and alternative model structural assumptions.
 | ✓ | ✓ | ✓ |

# CEA, cost-effectiveness analysis; CO, constrained optimization; FHM, fiscal health modeling

Table 7: Key attributes of CEA, CO, and FHM

| **Attribute** | **CEA** | **CO** | **FHM** |
| --- | --- | --- | --- |
| How the method achieves the policy objective | Shows how to optimize an outcome (net benefit or ICER) within a fixed budget by selecting the cost-effective interventions  | Shows how to optimize one or more outcomes by selecting an optimal combination of interventions that fall within desired constraints (typically including budget limits) | Shows how to optimize net fiscal transfers within the public-sector budget |
| Decision makers targeted | Health technology assessment agencies, ministers of health, donor agencies, and insurance companies | Budget holders for prevention programs and public health agencies | Ministers of finance and treasury |
| Underlying economic principles | Inherent tradeoffs between resources needed to achieve societal objectives  | Mathematical expression of a decision about alternative programs as a CO problem | Representation of instrumental value of health attributed to cross-sectoral public finance |
| Relationship among methods | The same input parameters—including disease epidemiology, resource use for disease(s) of interest, costs of vaccination program and disease treatment, and impact of the vaccination program and comparator interventions on disease epidemiology— are needed for all three methods. Budget constraints are specified in CO analysis but only implied in CEA analysis. Comparator interventions are included in a single CO analysis, whereas they might be included one at a time in a CEA or FHM analysis. FHM analysis focuses on government transfer payments and tax revenues, whereas CEA and CO analyses focus on changes in disease epidemiology and payments for the vaccination program and treatment of the disease(s) of interest. A broader set of benefits and costs can be included in CEA or CO analyses if data are available. |

# CEA, cost-effectiveness analysis; CO, constrained optimization; FHM, fiscal health modeling; ICER, incremental cost-effectiveness ratio

Figure 1. Selected Approaches to Economic Analyses of Vaccination Programs

ICER, incremental cost-effectiveness ratio; NPV, net present value; IRR, internal rate of return; ROI; return on investment