HHS Public Access

Author manuscript

Appl Health Econ Health Policy. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Appl Health Econ Health Policy. 2022 July ; 20(4): 457–465. doi:10.1007/s40258-022-00718-z.

Data-related challenges in cost-effectiveness analyses of vaccines

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Abstract

Cost-effectiveness analyses (CEAs) are often prepared to quantify the expected economic value of potential vaccination strategies. Estimated outcomes and costs of vaccination strategies depend on numerous data inputs or assumptions, including estimates of vaccine efficacy and disease incidence in the absence of vaccination. Limitations in epidemiologic data can meaningfully affect both CEA estimates and the interpretation of those results by groups involved in vaccination policy decisions. Developers of CEAs should be transparent with regard to the ambiguity and uncertainty associated with epidemiologic information that is incorporated into their models. We describe selected data-related challenges to conducting CEAs for vaccination strategies, including generalizability of estimates of vaccine effectiveness, duration and functional form of vaccine protection that can change over time, indirect (herd) protection, and serotype replacement. We illustrate how CEA estimates can be sensitive to variations in specific epidemiologic assumptions, with examples from CEAs conducted for the United States that assessed vaccinations against human papillomavirus and pneumococcal disease. These challenges are certainly not limited to these two case studies and may be relevant to other vaccines.

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Authors' contributions: All authors contributed to the study conception and design. The first draft of the manuscript was written by Jamison Pike, Scott Grosse, and Andrew Leidner. Harrell Chesson and Charles Stoecker provided subject matter expertise. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of interest/Competing interests: Authors declare that they have no conflict of interest.

I. Introduction

Vaccines have resulted in dramatic decreases in the incidence of vaccine preventable diseases and corresponding declines in morbidity and mortality worldwide. Each year in the United States, vaccinations save thousands of lives and avert billions of dollars in health care costs [1, 2]. Many vaccinations, particularly the common childhood vaccinations, have been estimated in economic assessments to be cost-saving when compared to the previous standard-of-care [3, 4]. Health technology assessors typically prepare modeling studies to quantify the expected health-related impacts and economic values to inform advisory committees considering new vaccination policies [5, 6].

Economic value is estimated in a cost-effectiveness analysis (CEA) by comparing estimated changes in costs and health for two or more strategies. For comparisons where a strategy (e.g., a vaccine product with a specified schedule of doses targeted to a specific population) is associated with increases in health and total costs relative to a comparator strategy, the incremental cost-effectiveness ratio (ICER) will be an estimated cost per health outcome gained, e.g., cost per quality-adjusted life year (QALY) gained. Estimated outcomes and costs of vaccination strategies depend on economic and epidemiologic assumptions, e.g., vaccine efficacy and disease incidence in the absence of vaccination, and limitations in epidemiologic data and understanding can affect the estimates and their interpretation.

CEAs incorporate epidemiological models of disease transmission and host-pathogen characteristics to yield estimates of health outcomes, or effectiveness, that are combined with cost estimates to calculate economic value of potential vaccination strategies. Epidemiological models and economic models are based on inputs and assumptions. Limitations in data and evolving scientific knowledge create uncertainty, which can be addressed through sensitivity and scenario analyses. Conclusions of CEAs should acknowledge the dependence of findings on methodological choices and assumptions and discuss challenges to generalizability.

In this paper we describe selected challenges to conducting CEAs for vaccination strategies, with a focus on issues related to epidemiological inputs and assumptions. The overarching purpose of this review is to call attention to the importance of appropriate interpretation of the uncertainty of epidemiologic data, either from lack of data or true uncertainty of the future impact, in the formation and interpretation of CEAs for vaccination strategies. The reliability of cost-effectiveness results may be more dependent on data inputs than on the methodological sophistication of the modeling techniques. The “quality” of a CEA as assessed using standard checklists may provide little indication of the reliability of the findings.

Researchers should be mindful of these issues as both consumers and producers of CEAs. The following section provides an overview of previous discussions of these methodological challenges. That section is followed by discussion of US case studies from two recent Advisory Committee for Immunization Practices (ACIP) vaccination policy considerations of vaccinations against human papillomavirus (HPV) and pneumococcal disease. These methodological challenges are not limited to our two case studies and may be relevant to

other vaccines. All values referenced have been inflated to 2020 US dollars using the overall US Consumer Price Index [7].

II. Epidemiologic challenges in vaccination cost-effectiveness analyses: overview

Health economists and other researchers have developed checklists for assessing the quality of reporting of economic evaluations. These checklists typically focus on technical aspects of decision-analytic methods and the extent of documentation provided regarding data sources, model inputs, and methodological choices [8]. The ACIP provides guidance for economic evaluations to assure that they meet minimum technical standards and are transparent and understandable [9], and separately assesses the strength and quality of epidemiologic evidence using the Grading of Recommendations Assessment, Development and Evaluation approach [10]. The accuracy of CEA study findings may also depend crucially on the availability and quality of the underlying data, sources, and assumptions for epidemiologic model parameters. Economic evaluation checklists do not address those issues, although the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Quality Assurance for Modeling Studies Task Force designed a questionnaire for use in assessing the credibility of CEA models, including consideration of factors such as the validation of data sources, assumptions, and model results [11]. However, a single CEA may involve multiple model parameters and parameter values that are derived from more than one study or based on expert opinion. It can be challenging to fully assess the rigor or validity of how epidemiologic information is incorporated into a CEA model, especially key features such as the model structure, parameter values and assumptions applied in the model, and the data sources used to inform the model.

Efforts to model the cost-effectiveness of vaccine products can encounter a range of data-related challenges of which researchers should be cognizant [5, 6]. Some challenges are especially salient for diseases for which no vaccines currently exist. Those include limited population-based data on the incidence of infection, clinical outcomes, and associated healthcare use. Modelers should be aware of potential biases in sources of observational data and avoid assumptions that might overstate disease burden [12].

We focus here on four issues that add complexity to the health economic analysis of vaccinations where randomized control trial (RCT) data exist. First, trial data on vaccine efficacy may not generalize to real-world health outcomes because of differences in behavior or physiology between trial subjects and target populations or because trials may not yield data on important clinical outcomes, including adverse effects. A second issue involves generalizing to outcomes beyond the trial follow-up period; in particular, vaccine-conferred immunity can wane over time. A third issue is the extent to which the proportion of strains, serotypes, or types of a vaccine preventable infection that circulates in the environment will remain constant or will be affected by serotype replacement, where non-vaccine type disease may become more dominant in the environment following the introduction of a vaccine. Fourth, the magnitude of disease prevented by a vaccine may depend on the extent to which the vaccine modifies disease transmission in the community, i.e., indirect effects of

vaccination. Indirect effects can either reduce disease burden, e.g., reduction of community transmission, or potentially raise it, such as by shifting the age distribution of infections to groups with greater risk of complications [13].

a. Efficacy vs. effectiveness and generalizability

In the development of a new vaccine product, one or more RCTs are typically conducted to assess vaccine efficacy. While RCTs can produce high quality estimates of efficacy under controlled conditions, results do not necessarily translate into effectiveness in real-world settings because of behavioral or physiological differences between trial subjects and demographic groups being considered by policy makers [14]. RCT participants may have higher levels of access and utilization of health care than the general population. One common example of this comes from trials of multi-dose vaccines. RCT participants generally have high levels of vaccine dose series completion, or adherence. For example, in trials of the recombinant zoster vaccine (RZV), series completion rates were 96% [15] and 94% [16]. In contrast, real-world completion rates for the two-dose RZV vaccine have been reported to be 86% [17] and 80% [18]. Imperfect adherence to multidose vaccines can introduce a number of complicating factors to a modeling effort, such as identifying the appropriate level of vaccine effectiveness for individuals who do not complete a vaccine series and the most likely level of series completion in the real-world setting. These kinds of differences are not trivial for economic assessments of multi-dose vaccines, particularly when alternative vaccines are available or when those alternative vaccines require a different number of doses.

If a vaccine is less effective in some population groups than in the RCT population, a CEA that does not account for patient heterogeneity and differential effectiveness may generate overly favorable cost-effectiveness estimates of the vaccine compared to no vaccine. In particular, vaccine efficacy may be reduced for immunocompromised and/or older individuals. Further, efficacy may vary among different groups of immunocompromised individuals. For example, people who have received organ transplants may generate a lower immune response to the vaccine than those with well-controlled HIV [19, 20]. The relative sizes of the populations which have a muted vaccine response can influence the overall ICER.

An additional limitation of RCT estimates used as CEA inputs is that RCTs primarily assess short-term outcomes, which can limit generalizability. That is particularly the case when biomarkers are used as proxies or predictors of the health outcomes of interest. For example, HPV RCTs assessed histological changes such as cervical intraepithelial neoplasia, which can progress to cervical cancer [21], to predict health gains. Until long-term studies are available, modeling is required to estimate the magnitude of reduction in the incidence of cervical cancer that can be attributed to HPV vaccination.

Uncertainty in the vaccine efficacy estimates from RCTs in combination with uncertainty in disease burden can lead to very wide ranges of estimates of outcomes, whether numbers of avoided cases of disease or antibody levels, and of cost-effectiveness. If differential vaccine effectiveness is a concern, cost-effectiveness modelers would ideally report scenario analyses that utilize alternative assumptions of vaccine efficacy for population groups that

may not have been included in the RCT to calculate an ICER reflective of the overall population.

b. Duration of protection

At the time a new vaccine is introduced there is uncertainty as to what the long-term effects are going to be both for persons vaccinated as well as the total population. The lack of long-term follow-up data from vaccine RCTs can be a problem for economic vaccine models which project vaccine effectiveness over an individual's lifetime. Some clinical trials have a long-term case ascertainment component beyond the primary trial end, but long-term follow-up is uncommon. A review of 46 publications reporting on 13 RCTs found most clinical trials had a maximum follow-up period of 4 years, with two reporting follow-up of 6–8 years [22]. Even if long-term outcomes are tracked the findings are not available to inform CEAs until long after a vaccine is approved. Because of substantial uncertainty regarding the duration of vaccine protection or waning immunity beyond a vaccine's clinical trial, a range of plausible assumptions could be used. CEA modelers may extrapolate effectiveness over longer periods of time based on available clinical trial data, data from similar vaccines, expert opinion, or a combination.

Varying assumptions regarding the duration and degree of protection (vaccination effectiveness) have been shown to influence CEA results. For example, in a study of RZV among 60- to 69-year-old U.S. adults, a sensitivity analysis that varied initial vaccine efficacy from 0.95 to 1.0 and waning duration (modeled as the number of years of gradually decreasing protection until no protection remains) from 10 to 30 years found the estimated cost per QALY gained to range from $8,500 to $89,100 [23]. In a CEA assessing the use of PCV13, the base case yielded a value of $593,100/QALY, but a scenario that assumed a slower reduction in the degree of protection yielded an ICER of $235,700/QALY [24].

c. Serotype or genotype replacement

Many vaccines, such as the influenza, HPV, and pneumococcal conjugate vaccines, protect individuals from specific variants or types which are a subset of all the disease-causing agents that are known to cause a particular disease. Changes to the mixture of disease types circulating in the environment following the implementation of a vaccination program may influence the economic value of vaccinations but, like decreases over time in the degree of protection, is generally not known with much certainty for new vaccines. Depending on the disease under consideration, this phenomenon is generically referred to as replacement but is commonly referred to as serotype replacement in the context of pneumococcal disease [25, 26], or genotype replacement, which has been used in the context of HPV disease [27]. Serotype or genotype replacement is the process by which the absolute occurrence of non-vaccine-type disease in the population change over time following vaccine implementation. If there is a high rate of non-vaccine type replacement, non-vaccine type disease could become the most common form of a given disease, which would render a vaccine less effective overall and hence less cost-effective. New information on serotype replacement and serotype-specific vaccine efficacy can lead to substantially different ICER estimates. The issue of replacement is relevant primarily to the pneumococcal vaccine and is discussed in the case studies section. Substantial amounts of replacement disease were observed after

introduction of PCV7 in 2000 [28], although evidence of replacement disease after the introduction of PCV13 has been mixed [29]. The HPV vaccine currently used in the United States, Gardasil 9, protects against 9 HPV types that cause most of the disease due to HPV [30]. The non-vaccine types of HPV and pneumococcal infection could plausibly lead to types replacement and attenuation of the benefits of vaccination over time, but so far there is no evidence of notable HPV type replacement [25–27].

d. Indirect effects

Community protection is a potential indirect benefit of vaccination against infectious disease. For most vaccine preventable diseases, unvaccinated individuals experience a reduced risk of infection due to vaccinated individuals being less likely to be infectious. For some diseases, the indirect effect from a vaccine can provide almost complete protection against disease transmission in the community, referred to as “herd immunity.” The threshold proportion of the population that needs to be vaccinated to reach herd immunity may be difficult to assess for a given disease and vaccine [31], but any level of vaccination in the community confers some indirect protection even if herd immunity in the classic sense is not attained. Varying assumptions on indirect effects can have important implications for the results of an economic assessment. For example, Ultsch et al. [32] cited an analysis of seasonal influenza vaccination in Spain that used both a static model without indirect effects and a dynamic model approach that incorporated indirect effects and found that the former greatly underestimated the cost savings from vaccination [33]. A systematic review of CEAs of immunizations in low- and middle-income countries found that among 16 studies that calculated ICERs with and without indirect effects using static models, all ICERs were lower (more favorable) when indirect effects were modeled [34].

The treatment of indirect effects differs between static and dynamic models of disease transmission. Dynamic models of disease transmission incorporate indirect effects by modeling how the infection risk to a susceptible individual varies with the levels of immunity and exposure among their contacts [35]. In contrast, static models typically assume a constant risk of acquiring infection. However, analyses that use static models can incorporate adjustments to approximate indirect effects, such as by applying a higher estimate of vaccine effectiveness or by assuming that reduced incidence can occur as a function of vaccination coverage rates [34, 36]. For example, a recent CEA of pneumococcal vaccines that used static models assumed a lower incidence of disease in older adults as a result of vaccinations in children [24, 37]. Static models that do not in some way account for indirect effects may substantially underestimate the number of cases of infection prevented by a vaccine relative to models with dynamic disease transmission. Dynamic models therefore generally provide a higher (and more accurate) estimate of the number of infections averted by vaccination, typically resulting in more favorable cost-effectiveness estimates of vaccination [38–40]. Experts typically recommend that CEAs of immunization programs incorporate dynamic models whenever feasible [5]. While dynamic models are not always feasible, especially when the data supporting the dynamic transmission assumptions are limited, the impact of potential indirect effects on economic models can be explored using scenario analyses that modify vaccine effectiveness and incidence assumptions.

III. Epidemiologic challenges in vaccine cost-effectiveness analyses: case studies

a. Recent HPV and pneumococcal vaccine developments

Three vaccines that protect against HPV infection and disease have been approved in the United States, but since 2017, only the 9-valent HPV is available. A range of cost-effectiveness data have been presented to ACIP over time to inform HPV vaccine recommendations, including vaccinating adolescent females and young adult women vs. no vaccination, adding adolescent and young adult males to a female-only vaccination program, 9-valent HPV vaccination vs. quadrivalent vaccination, and adding mid-adult HPV vaccination (ages 27 to 45 years) to an existing program for adolescents and young adults [41–44].

The first pneumococcal conjugate vaccine, PCV7, which protected against seven types of pneumococcal virus, was recommended for children in 2000, and in 2010, PCV13, which protects against six additional types, was recommended by ACIP in place of PCV7. In 2014, the recommended age range for PCV13 was expanded to include adults 65 years of age and older in conjunction with the 23-valent polysaccharide vaccine (PPSV23), recommended since 1984 [43, 45]. The recommendation for routine use of PCV13 for all 65+ year-olds was replaced in 2019 with a recommendation of shared clinical decision-making after evaluating evidence that PCV13 use in children had substantially reduced the vaccine-type disease burden among 65+ year-old adults through reduced carriage and transmission from vaccinated children (i.e., indirect effects from the childhood vaccination programs) [46].

b. Challenges in assessing HPV vaccines

Assumptions regarding duration of vaccine protection can have a notable effect on estimates of the health impact and cost-effectiveness of HPV vaccination. A 2010 study that compared several approaches to modeling a 12-year-old female-only HPV vaccination program identified the potential waning of vaccine protection as an important assumption [47]. Available empirical data suggest that the duration of protection is at least 10 years for the bivalent and quadrivalent HPV vaccines, with no evidence of decreasing effectiveness within that period [48–51]. Evidence for the duration of protection for the 9-valent vaccine is qualitatively similar [48, 52, 53]. Extrapolating or projecting vaccine protection beyond the horizon of available data remains an important challenge for modelers, although assumptions regarding duration of protection are more evidence-based now than in the earlier years of HPV vaccine modeling.

If HPV vaccine protection is not lifelong, the shape of the function that characterizes vaccine protection over time can have a notable effect on effectiveness estimates [47]. For example, if the average duration of protection is assumed to be 20 years, vastly different results can be obtained in a scenario in which all vaccine recipients are protected for exactly 20 years versus a scenario in which duration of protection is uniformly distributed from 1 to 39 years across vaccine recipients. An alternative assumption is that the degree of protection gradually wanes over time. Regardless of the functional forms used to represent waning of vaccine protection, assumptions regarding the duration of protection are often

based on expert opinion in addition to available empirical data, especially for new vaccines. Sensitivity analyses can illustrate the impact that these duration assumptions have on the estimated cost-effectiveness of vaccination.

As with many modeling studies of infectious disease, modeling assumptions that affect HPV transmission dynamics have important implications for the economic assessment of HPV vaccines. The issue of transmission dynamics is particularly notable for HPV vaccines, given that female vaccination was licensed several years before male vaccination. When HPV vaccines were licensed for use in males, assessments of the cost-effectiveness of male vaccination needed to account for transmission dynamics, including the indirect benefits of the status-quo female-only vaccination program in preventing adverse HPV-attributable health outcomes in males. In an early study of the use of the bivalent HPV vaccine among adolescents, vaccination of 12-year-old females was predicted to reduce cumulative HPV-16/18 prevalence among unvaccinated males by 86% at 30 years post-intervention [47]. More recently, a systematic review and meta-analysis of HPV models suggested that measurable indirect protection is possible even with fairly low vaccination coverage rates of 20% among females, which may reduce the incremental benefit of vaccinating males [54]. This review also found that the HPV models assessed were generally consistent in their predictions of the direct and indirect effects of females-only vaccination, even though models differed in structure, settings, and data used for calibration. Recently, economic models used to investigate the use of HPV vaccination among the mid-adult (age 27 to 45 years) US population models found that historical and ongoing adolescent vaccination programs are expected to confer both direct protection for those in the mid-adult population who were vaccinated at younger ages and some indirect protection on the unvaccinated mid-adult population by reducing the prevalence of HPV in their sex partners [55–57].

In addition to duration of protection assumptions and transmission dynamics, HPV modelers face other challenges, such as limited data regarding sexual behavior over the life course, duration of naturally acquired immunity, rates of progression from HPV infection to cancer, and the uptake and frequency of screening for cervical cancer. For example, among women with cervical cancer, the median age at which women acquired their “causal” HPV infection cannot be determined with available epidemiologic data, and mathematical models can differ substantially in their estimates of this median age. Often the only way to address such challenges is to ensure that the sensitivity analyses adequately represent the degree of uncertainty in the model inputs. For example, HPV vaccination of adults ages 27 to 45 years had ICERs ranging from $400,000 to $1,000,000 per QALY in one study[55], with an even wider range suggested in another study, depending on factors such as those related to the median age of causal HPV infection [58].

c. Challenges in assessing pneumococcal vaccines

Certain challenges in pneumococcal disease modeling overlap with challenges encountered when modeling HPV disease. Some challenges, such as selecting the shape of the function that characterizes vaccine protection over time, may be encountered when assessing almost any new vaccine product. As with HPV modeling, the assumed duration of protection from vaccination can play an important role in economic assessments of pneumococcal

vaccinations. In a 2016 study, Belgian researchers examined multiple scenarios for adults ages >50 years: constant vaccine efficacy for at least 10–11 years and constant vaccine efficacy for 5 years followed by an exponential decay [59]. They found that PCV vaccination in this population was not economically attractive unless vaccine efficacy was either constant or had a relatively slow rate of decay. The researchers also noted that previous analyses that projected that PCV13 would be cost-effective in adults assumed high rates of vaccine effectiveness that were not empirically supported.

Another important issue for PCV is the degree of serotype replacement, which can be an influential assumption for estimates of cost-effectiveness. Following introduction of PCV7, the significant reduction in invasive pneumococcal disease caused by vaccine serotypes in immunized children was largely offset by a larger than expected increase in disease caused by non-vaccine pneumococcal serotypes [60]. Subsequently, the PCV13 vaccine added six more serotypes. Van Hoek et al examined the cost effectiveness of replacing PCV7 with PCV13 versus discontinuing PCV7 vaccination; in a conservative scenario assuming complete serotype replacement and not including non-invasive disease endpoints, they found PCV13 borderline cost effective (with 53% of the simulations below the £30,000 per QALY threshold commonly applied in the United Kingdom) [61]. If replacement serotypes were assumed to be less invasive or virulent, cost-effectiveness estimates would be more favorable.

In 2016, Stoecker et al projected that indirect protection for older adults resulting from pediatric PCV13 use would over time greatly reduce the incidence of pneumococcal disease, which in turn would make the cost-effectiveness of routine PCV13 vaccination in adults at age 65 less favorable [37]. In 2019, the ACIP conducted a reassessment of the vaccination recommendation for the age 65 group, and a modified CEA by Stoecker et al. reported a less favorable cost-effectiveness ratio attributable in part to the observed magnitude of indirect protection from childhood vaccination being twice as large as expected, resulting in half as much benefit from adult vaccination, and in part new data showing no vaccine effectiveness for the newly dominant serotype 3 [24]. The updates in the 2019 model present an example of how modeling of economic value can be updated to reflect evolving scientific understanding and epidemiologic information. The historical modeling of pneumococcal vaccines demonstrates the importance of not only modeling various scenarios to capture uncertainty in duration of protection, indirect effects, and serotype replacement, but the necessity of updating the CEA model as new information becomes available.

IV. Conclusion

Epidemiological models and economic models are based on inputs and assumptions which are intended to provide the best practical representation of the health effects and costs of vaccination in the real world. These inputs and assumptions are based on scientific knowledge that will be incomplete, evolving over time, or both. When research findings that pertain to a given model input are mixed, choosing the most appropriate assumption is a challenge for modelers. Developers of CEAs should be transparent regarding the sensitivity of their estimates to variability in epidemiologic data. We have provided illustrative examples of how ICER estimates for vaccines can be sensitive to variations

in specific epidemiologic assumptions. In the absence of robust data, CEA modelers can make assumptions and use sensitivity analyses to understand how variability in specific model assumptions might alter estimates of economic value and conclusions, with particular focus on those assumptions that appear most influential, e.g., indirect effects. For example, analysts using static models could make simple adjustments to their model to approximate transmission dynamics (such as assuming lower incidence of disease in unvaccinated persons in the vaccination scenario than in the no vaccination scenario) in order to assess the degree to which the inclusion of indirect effects might affect their results. Contrary to a recent article in this journal [34], we do not consider it feasible or desirable for CEAs using dynamic models to attempt to separately estimate direct and indirect effects. Changes in the distribution of PCV serotypes have been found to be an important source of variation in CEA estimates in some cases. That illustrates the importance of updating CEAs of vaccines as warranted by the appearance of new epidemiologic data and improved scientific understanding.

It can be challenging to interpret the epidemiologic literature and consider which assumptions to apply in an economic model. In particular, in cases where vaccines are newly developed or being considered for new populations, the epidemiologic literature may be without a clear consensus on several potentially important aspects of the vaccine-disease system being modeled. We have discussed duration of protection, generalizability of vaccine effectiveness estimates, indirect effects (i.e., transmission dynamics), and serotype replacement as four examples of potentially influential epidemiologic parameters or modeling choices, each of which is associated with uncertainty. We focused on these because of evidence of their influence on CEA results in some settings. Other epidemiological assumptions may also warrant consideration.

Acknowledgments:

The authors thank Rafael Harpaz, Kai Hong, Lauri Markowitz, and Sarah Pallas for comments on previous versions.

Funding:

No funding/support was used for this study

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Key points for Decision Makers:

- We describe selected data-related challenges to conducting cost effectiveness analyses (CEA) of vaccination strategies.
- We illustrate how CEA estimates can be sensitive to variations in specific epidemiologic assumptions, with examples from CEAs conducted for the United States that assessed vaccinations against human papillomavirus and pneumococcal disease.
- Developers of CEAs are encouraged to acknowledge epidemiologic variability in model inputs and present a range of estimates along with caution in interpreting results regarding cost-effectiveness.