The Net Economic Benefit of a Vaccine Coverage Level Increase for a Full Childhood Routine Immunization Schedule in Gavi-eligible Countries

Abstract

Background: Gavi is assessing what resources would be required to achieve its stated strategic objective of a broad coverage level increase. While there is a large volume of literature on the cost-effectiveness of vaccines, little research has been done by looking at the immunization schedule holistically. Additionally, vaccination scenarios are almost always compared to those of no vaccination, which is less relevant in today's Gavi-eligible countries where scenarios should be separated by incremental changes in coverage level. The objective of this study is to quantify the net economic benefit of an increase in coverage level, across the full spectrum of routine childhood immunization, for archetypal Gavi-eligible countries from the decision making perspective of country health officials.

Methods: We constructed a decision tree model that incorporated cumulative incidence of vaccine-preventable disease, vaccine effectiveness, indirect effects of vaccination, distributions of possible outcomes for each disease and treatment costs. Data was aggregated from previous research completed in Gavi-eligible countries.

Results: The cost of a coverage level increase from 85% to 89% in an average Gavi-eligible country is $1.21 per child in the cohort. The number of cases of vaccine-preventable disease (VPD) decreased from 0.1108 cases per child in the low coverage scenario to 0.1056 cases in the high coverage scenario, for a cost per case avoided of $233. Through a series of sensitivity analyses, the cost of the vaccines strongly dominated the result and other variables—including cumulative incidence of disease, vaccine effectiveness, and the magnitude of indirect effects—did not substantively alter the result.

Conclusion: The cost to raise coverage levels, even with a narrow perspective on the benefits of vaccination, is quite low. Vaccine cost is the largest contributor to this result, which suggests that the net economic benefit will improve over time as vaccine cost goes down. This analysis, particularly the framework of looking at the full immunization schedule, can be used going forward by countries to make better decisions about health resource allocation

Introduction

The level of performance of vaccine systems in low- and middle-income countries (LMICs) is routinely judged by coverage level, defined as the percentage of eligible children who receive a particular vaccine. Specifically, coverage levels are used to monitor the performance of immunization systems, to aid in the development of strategies to control vaccine-preventable diseases, and to identify underperforming components of the vaccine delivery system.[1] It remains one of the most widely used methods to evaluate relative performance of one geographic unit to another as well as trends over time within a given location.[2] Coverage levels are used at different levels of the health system, from individual health facilities all the way up to national reporting.

National vaccination agencies are pressured to raise coverage levels directly by external donors and indirectly by peer country performance.[3; 4] This pressure is pushed down the hierarchy of the health system until it ultimately arrives at the district, the level at which it can best be translated into specific and actionable decisions. In other words, "districts"—loosely defined as the first administrative region above that of individual facilities, and usually comprised of one dozen to several dozen primary care facilities—have the best ability to directly affect vaccine coverage levels; they are closer to the realities of their served communities, they have control over shifting human and financial resources among individual facilities, and they can allocate physical vaccine stock to specific outlets.[5] However, districts are financially significantly more restricted than higher levels of the health system and they make resource allocation decisions using different criteria.

Economic evaluation and the various forms of cost-effectiveness analysis are routinely used in the evaluation of vaccine systems.[6; 7] Immunization, compared with other health interventions, is particularly well-suited to this type of analysis since the connection between cause and effect is more direct and more easily measured. However, the vast majority of research has looked at the impact of

individual vaccines; furthermore, a scenario of vaccination is often compared to one with no vaccination. We have not found any research that looks at the economics of a full immunization schedule nor have we seen research that compares two levels of immunization coverage.

The motivation for this study is to determine the net economic benefit to the health system of an increase in the vaccine coverage level. In other words, as districts are pressed to deliver higher coverage levels, how much are they economically justified in investing to "buy" that increase?

Data and Methods

Framing

We have framed the analysis as an institutional, rather than societal, perspective in an effort to better reflect the decision making of district-level health officials of Gavi-eligible countries; all of our choices about what to include in or exclude from the model are based on that underlying perspective. The study is also motivated by an acknowledgement that, going forward, increasing the benefit of immunization systems will come from incremental changes in coverage levels; it is no longer applicable to use a counterfactual of no vaccination.

The vaccine schedule used for the model was selected to be reflective of that used by the majority of Gavi-eligible countries. We have included BCG, measles, pneumococcal, oral polio, pentavalent (DTP-Hib-Hep B) and rotavirus vaccines. We simplified the vaccination status of a child to a binary state of either having received no vaccines or having received all recommended vaccines (i.e. "fully immunized"). The analytic horizon of the study is five years from the completion of the full immunization schedule so the model uses a five-year cumulative incidence as the risk of disease. We also incorporated indirect effects of vaccination—i.e. herd immunity, or additional protection afforded to the unvaccinated portion

of the cohort as a result of reduced prevalence and reduced transmission coming from having part of the cohort directly protected from the disease by the vaccine.[8]

Costs

Consistent with the perspective of the analysis outlined above, we are including only those costs that would appear in the districts' decision making calculus: namely hard costs and those that occur in the near term. More specifically, we are choosing to look only at the direct costs for which some entity within the health system would have to pay. Indirect costs and benefits (e.g. time savings, future earnings) are outside the scope of this analysis because these do not take from nor contribute to a district's pool of financial resources and are therefore unlikely to be incorporated in the decision making calculus of those district health officers. Furthermore, as opposed to the empirical nature of direct costs, indirect costs are largely theoretical concepts and have not been adequately characterized; government officials have admitted that these economic benefits are rarely brought up in policy discussions.[9]

In a survey of government health officials and vaccine policy makers, "burden of disease" (under which are included health care cost savings and governmental savings) was identified as the most powerful evidence type in support of vaccine decisions among five categories of economic impact.[9] Productivity-related gains and other indirect effects were rated as the least powerful.

This is not to say the health officials should not consider these more distal benefits but that in the majority of today's vaccine decisions, these indirect costs are not given serious weight. The purpose for framing the study this narrowly is to reflect the nature of actual decision making in these settings and then to use the results as a foundation on which to build a more compelling argument for vaccination that does appropriately include the wide array of indirect benefits. It has been noted that even when indirect costs are included, cost-effectiveness analyses of vaccine programs still undervalue the total benefit delivered.[10; 11]

There are two categories of costs that we have incorporated into the model. The first category is the purchase cost of the vaccines, including associated consumables (e.g. auto-disable syringes). We calculated an average per-dose price for each of the vaccine formulations using reported amounts from UNICEF Supply Division for volume and value of vaccines procured in 2014.[12] Increased service delivery and other overhead costs—including labor, cold chain, and transportation—were modeled proportionally to the coverage level increase. We have accounted for vaccine wastage by formulation; for example, for a vaccine with a formulation-specific wastage rate of 15%, a country would need to buy seven vaccines to administer an additional six.

Table 1: *Vaccine characteristics*

Vaccine	Doses[13]	Cost per dose[12]	Wastage rate
BCG	1 (birth)	$0.0864	43.0%[14]
OPV	4 (birth, 6/10/14 weeks)	$0.1312	13.5%[14]
Pentavalent (DTP-Hep B-Hib)	3 (6/10/14 weeks)	$1.9109	6.9%[14]
PCV	3 (6/10/14 weeks)	$5.4442	5.0%[15]
Rota	3 (6/10/14 weeks)	$2.8704	5.0%[15]
Measles	1 (9 months)	$0.0864	32.6%[14]
Total		**$34.15**	

The second category is the cost of various treatment outcomes. Vaccine cost-effectiveness analyses vary widely with how they account for treatment costs. In an effort to make our analysis generalizable to the full cohort of Gavi-eligible countries, we have chosen to define outcomes as the average number of outpatient visits and/or inpatient days for a course of treatment; these treatment courses are less likely to differ between countries. We can then use the WHO CHOICE[16] database of country-specific health service delivery costs to determine the monetary cost of that treatment.

WHO CHOICE reports cost per bed-day and cost per outpatient visit at different levels of health facilities in purchasing power parity-adjusted 2008 US dollars for 193 countries. We then used World Bank estimates for country-specific annual inflation rates[17] to convert the WHO CHOICE costs into 2015 US

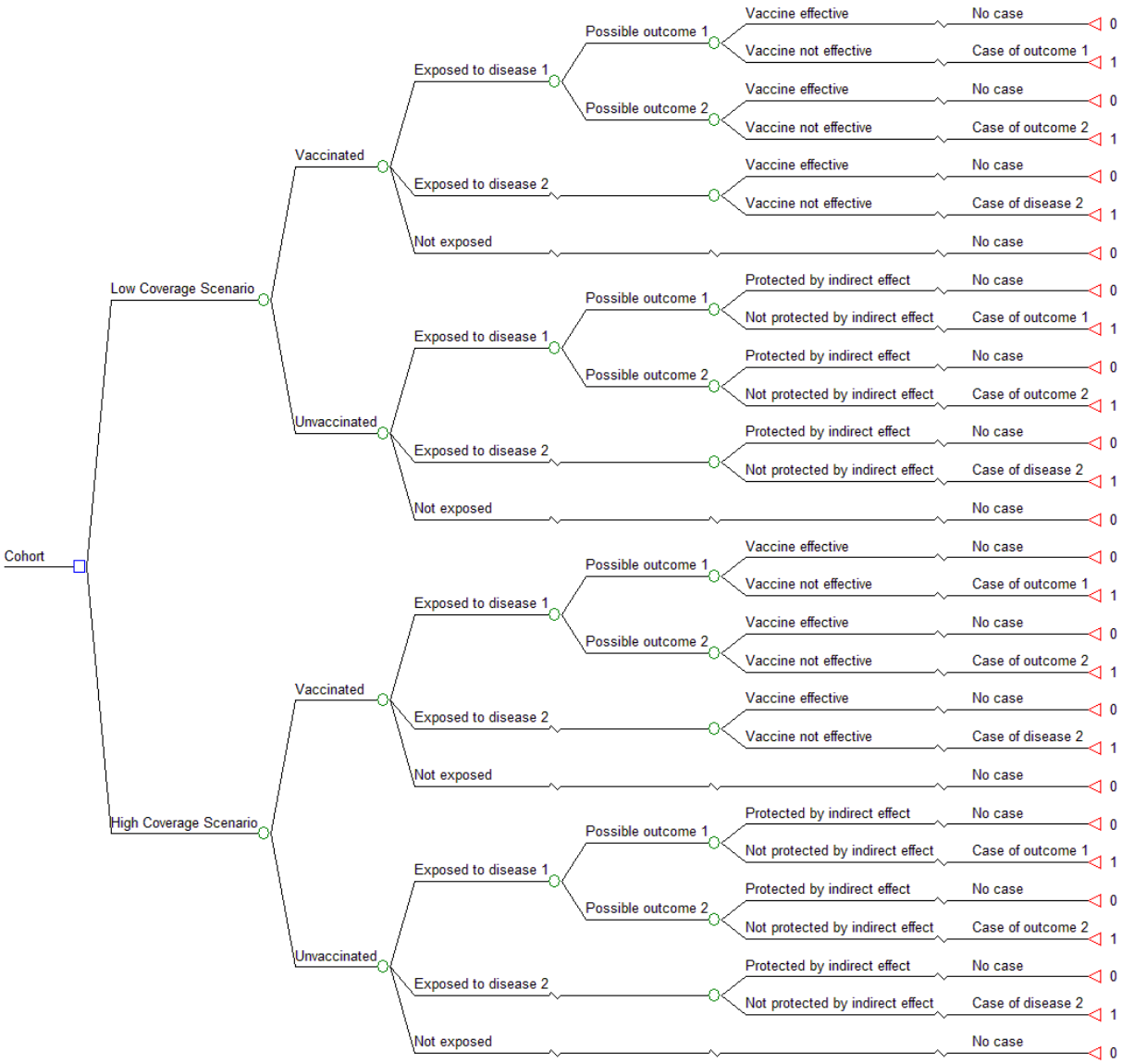
dollars. Finally, we calculated a weighted average cost using the size of the annual birth cohorts of the Gavi-eligible countries. In the end, we have a cost per bed-day for primary-level, secondary-level and teaching hospitals (average: $11.56) and a cost per outpatient visit for a health center (no beds), health center (with beds), primary-level hospital and secondary-level hospital (average: $3.12) in 2015 US dollars that represents the average for all children born in Gavi-eligible countries.

Model Overview

The model (fig. 1), a decision tree built using TreeAge software, is structurally similar to those of traditional vaccine cost-effectiveness studies.[7; 18] A cohort is exposed to some risks of vaccine-preventable diseases and then the vaccinated group is partially protected by the vaccines' effectiveness. Collectively, these result in a number of disease states and treatment outcomes, each of which has some costs. Using the taxonomy of cost-effectiveness analysis models proposed by Kim and Goldie[19], our model is a closed, static, deterministic, aggregate model.

Our model expands on previous work by combining all of the selected EPI vaccines. The output of the model is the difference in expected cost between two scenarios: one of a base coverage level of 85% and one of an incrementally higher coverage level (89%).

Figure 1: *Model structure example*



For each vaccine-preventable disease, we aggregated data about cumulative incidence in post-vaccine introduction situations, vaccine effectiveness, distribution of disease outcomes and average courses of

treatment for each outcome from previous research. Those served as the primary model variables and are summarized in table 2.

Table 2: *Primary model variables*

Antigen	Outcome	5-year cumulative incidence	Vaccine effectiveness	Costs*
Polio (assumes all OPV)	Poliomyelitis	0.000716%†	91%[21]	168 IP[22]
BCG	Tuberculosis meningitis (extrapulmonary)	0.075%[23]	73%[23]	8 OP + 180 IP[24]
	Miliary tuberculosis (pulmonary)	0.0375%[23]	77%[23]	8 OP + 15 IP[24]
Diphtheria	Diphtheria	0.020%[25]	98%[26; 27]	10.7 IP[28]
Tetanus	Tetanus	0.00175%[29; 30]	99.9%[31]	13.2 IP[28]
Pertussis	Mild	0.575%[18; 32; 33]	96%[34; 35; 36]	2 OP[18]
	Severe	0.425%[18; 32; 33]	96%[34; 35; 36]	14 IP[18]
Hib	Meningitis	0.790%[37]	90%[38]	13 IP[39]
	Severe pneumonia	1.320%[37]	99.6%[40]	6.42 IP[41]
	Non-severe pneumonia	7.805%[37]	99.6%[40]	2 OP
Hepatitis B	Non-fulminant acute hepatitis B	2.226%[42; 43]	95%[44]	1 OP[43]
	Fulminant acute hepatitis B	0.01344%[42; 43]	95%	1 OP + 8.4 IP[43]
Pneumococcal	Non-bacteremic pneumonia	1.90325%[45]	37%[45]	6.42 IP[41]
	Bacteremic pneumonia	0.1409%[46]	70%[45]	6.42 IP[41]
	Meningitis	0.06405%[46]	92%[45]	12.26 IP[41]
	Sepsis	0.0878%[46]	92%[45]	6.42 IP[41]
Rotavirus	Severe	3.45%[47; 48]	42.5%[49; 50]	1 OP + 3 IP[51]
	Moderate	7.50%[47; 52]	25.4%[49; 50]	1 OP[51]
Measles	Measles	0.8%[53]	85%[54]	2.4 IP[55]

Indirect effects were modeled as a disease-specific percentage of the unvaccinated proportion not contracting a disease despite exposure. Few of the vaccine-preventable disease presented here have strong empirical evidence quantifying their indirect effects, with the exception of pertussis, Hib and pneumococcal (respective protective levels of 56%[56], 24%[57] and 68%[58] in the unvaccinated cohort). For all other diseases, using a method described elsewhere[59], the magnitude of the indirect effect was

* OP = outpatient visits; IP = inpatient days

† Imputed from total number of cases in 2015 (WPV and cVDPV)[20]

estimated as 20% of the magnitude of the direct effect (i.e. the vaccine effectiveness). Tetanus was assumed to have no indirect effect since it is not contagious and has an environmental reservoir.

Results

We calculated a negative net economic benefit (i.e. a net cost) of $1.21 per child in the cohort to increase the coverage level from 85% to 89%. BCG contributes the most to a positive net economic benefit, a result of its low vaccine cost, relatively high incidence of disease and a high cost to treat. On the other end of the spectrum is rotavirus, where the higher cost of the vaccine is not offset even though the incidence is very high, mostly because the cost to treat either outcome is relatively low.

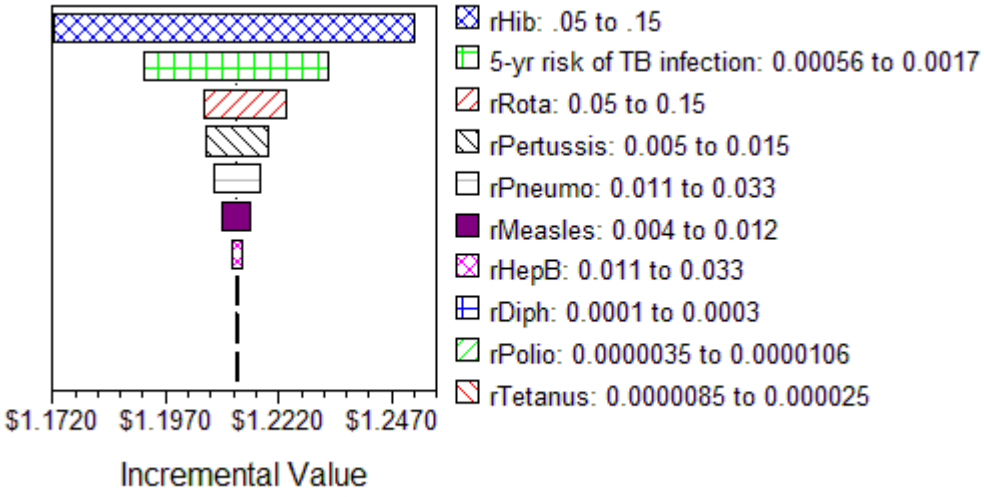
As a by-product of how the model was constructed, we were also able to calculate the number of cases of vaccine-preventable disease. In the 85% coverage level scenario, there were 0.1108 cases of VPD per child in the cohort compared with 0.1056 cases in the higher coverage scenario. This equates to approximately five fewer cases of VPD annually per 1,000 children. The coverage level increase came at a cost of $233 per case of VPD avoided. Almost 80% of cases in either scenario were rotavirus.

Sensitivity analyses

We looked at two of the primary model variables—cumulative incidence and vaccine effectiveness—across the ten vaccine-preventable diseases to better understand their relative contribution to the net economic benefit. For vaccine effectiveness ranges, we used 95% confidence intervals reported in the literature, choosing wider ranges if there were multiple studies. Cumulative incidence ranges were set to ± 50% from the point estimates used in the base case. We also looked at the impact of the magnitude of the indirect effects; since they are less studied than other model variables and to understand the full range of their contributions, we set them to vary from zero—there is no indirect protection as a result of

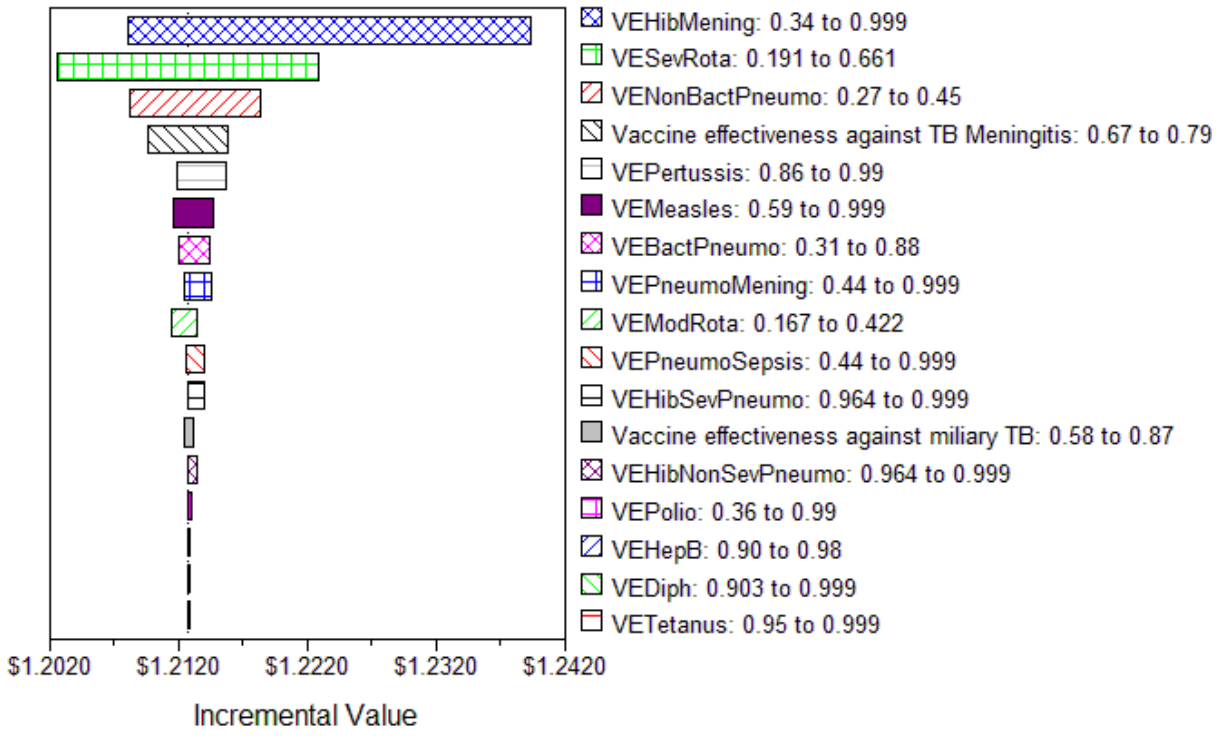
vaccination—up to 100%, or complete herd immunity (94% in the low coverage scenario to account for growth up to 100% in the higher coverage scenario).

Figure 2: *Sensitivity analysis of cumulative incidence*



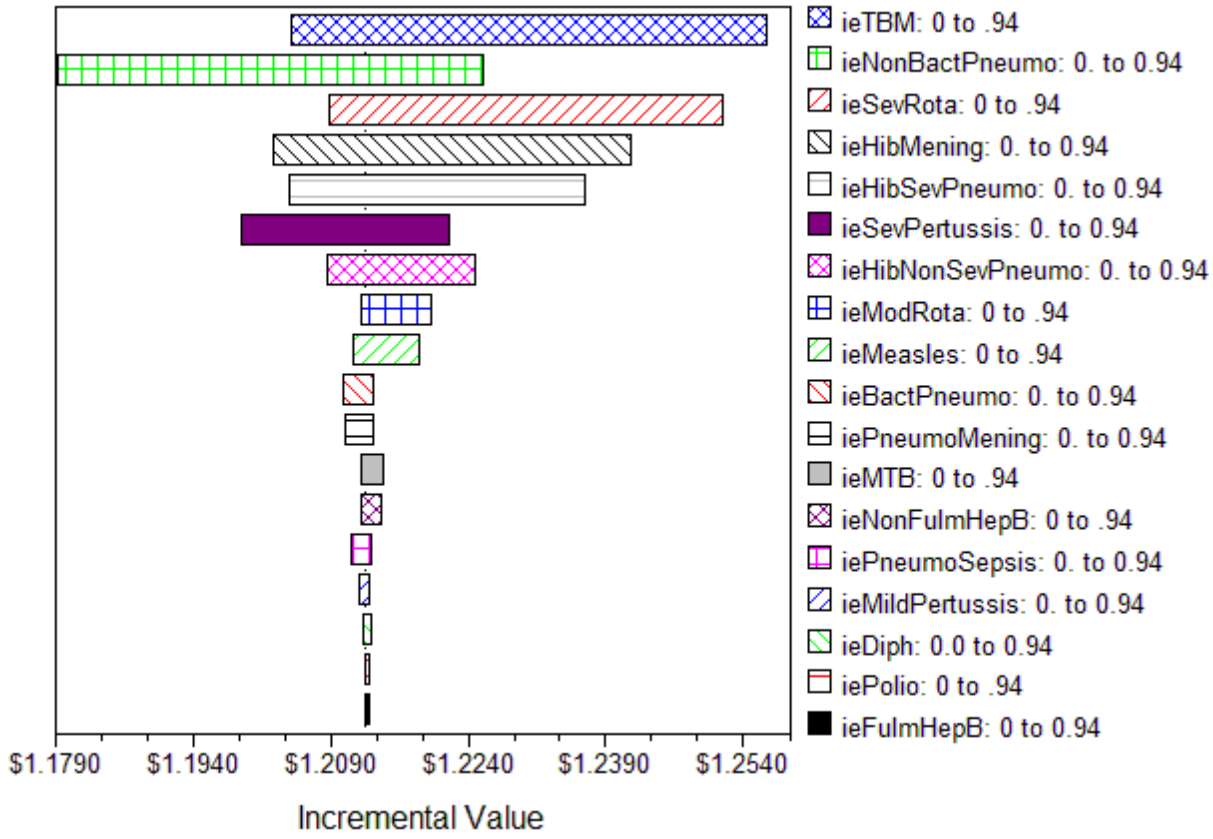
The cumulative incidences of Hib and TB had the biggest impact on the net economic benefit (fig. 2). This is because both diseases can result in meningitis, the disease outcome with the highest treatment costs among those included in the model. It should be noted that even at the ends of the spectrum for the cumulative incidence ranges, the net economic benefit does not change by more than 5%.

Figure 3: *Sensitivity analysis of vaccine effectiveness*



Vaccine effectiveness had even less of an impact on the net economic benefit (fig. 3). The effectiveness of vaccines against meningitis from Hib and against severe RVGE led to the widest range of possible outcomes, but even the most extreme scenarios were only 2% different than the base result. The indirect effect (fig. 4) had an equally negligible impact on the net economic benefit as the other variables in the sensitivity analysis—approximately 3%.

Figure 4: *Sensitivity analysis for indirect effects*



Ultimately, the net economic benefit is most sensitive to the cost of vaccines, which is large relative to the low cumulative incidence (especially post-vaccine introduction) and the low cost to treat these VPDs in Gavi-eligible countries. Reducing the cost of vaccines by 25% moves the net economic benefit 31% closer to positive. Reducing wastage rates is also a strategy that can lead to a more favorable net economic benefit, but wastage rates for the most expensive vaccines (pentavalent, pneumococcal conjugate and rotavirus) are already less than 7%, suggesting that the possible improvement is limited.

Discussion

Meeting Gavi's goal of raising the coverage level from 85% to 89% only costs the average Gavi-eligible country $1.21 per child in the birth cohort. This is remarkably low compared to other costs in the vaccine delivery system, such as the purchase price of vaccines and the infrastructure required to

transport and properly store vaccines. Furthermore, our analysis took a particularly restrictive perspective on the benefits of vaccination, looking only at direct treatment costs avoided and then only capturing those that occurred within the first five years after immunization, and the end result is still only a marginal cost increase at worst.

While the cost per child may seem low, the total cost balloons quickly when applied to a full annual birth cohort of a country; this should be used as additional rationale for providing financial help to countries to help them meet the goals of increased coverage. The cost per child may be manageable, and potentially even a convincing argument by itself, at a district level, but more work needs to be done to translate the results to be more persuasive at the national level.

A negative net economic benefit should not be construed as an argument against increasing vaccine coverage. The cost-effectiveness of an intervention is but one of several factors that must be weighed.[60] The result here should, however, be used as motivation to build a more multi-faceted argument to convince health officials to invest in activities that raise coverage levels.

For a single vaccine with only one possible disease outcome and no indirect effect, the net economic benefit would be in favor of the higher coverage scenario if the cost of the vaccine (c_v) is less than the product of the disease incidence (r), the cost of treatment (c_t) and the vaccine effectiveness (v_e).

$$c_v < r c_t v_e$$

From this we can infer that higher coverage is more likely to generate a positive net economic benefit in those countries where incidence of or the cost to treat various vaccine-preventable diseases is higher. Nigeria, India and Nicaragua are examples of countries where the average health service delivery cost is in the top quartile of Gavi-eligible countries. There are additionally a small number of cases in which vaccine effectiveness might be higher for a particular population, which would also contribute to a more favorable net economic benefit.

Limitations

There are several limitations to our approach. Due to a relative paucity of the information required to build an integrated model like this, we necessarily pulled data—namely disease incidence, vaccine effectiveness and costs of service delivery—from a wide range of sources. Furthermore, many of the diseases addressed in the original 1970s Expanded Programme on Immunization have not been rigorously studied in the past few decades, certainly not to the same extent as the more recent vaccine additions like pneumococcal and rotavirus. By aggregating data from various time periods and across a number of different countries, the result is not perfectly representative of any one country. We are confident that the primary model drivers are similar enough across Gavi-eligible countries that the result should be a decent approximation for what a single country would experience.

We made simplifying assumptions about vaccine schedule completion and therefore levels of protection against vaccine-preventable disease. In reality, children frequently only partially complete the recommended schedule or fully complete it but with significant delays against the recommended timeline.

Conclusion

The ultimate output of the model is interesting insofar as it highlights that the direct economic benefit is not by itself a compelling argument for increasing coverage levels, at least when the benefit of vaccination is defined so narrowly. It does however help illuminate which diseases contribute to the cost-effectiveness of an entire vaccine schedule and which assumptions, if different in certain settings, could significantly alter results. It should also stimulate more robust conversations at the country level.

The approach proposed here can be used to better model the realities of vaccine decision making in today's world. Outside of a few new vaccines in development, there are no longer "no vaccination"

scenarios against which to compare vaccination. The decisions are about incremental changes to current coverage levels. And some of the key assumptions that drive vaccine cost-effectiveness—like disease incidence—need to reflect what is happening on the ground today, with some extant level of vaccination, rather than a hypothetical counterfactual.

More important than this particular analysis is validating the framework of an integrated, schedule-wide cost-effectiveness analysis, rather than the single-vaccine approach that has been done in the past. This can be used going forward by individual countries, with a better knowledge of their innate disease characteristics and costs, to evaluate vaccine programs holistically.

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