

# Using Cost-Effectiveness Analysis to Support Research and Development Portfolio Prioritization for Product Innovations in Measles Vaccination

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**Background.** Several potential measles vaccine innovations are in development to address the shortcomings of the current vaccine. Funders need to prioritize their scarce research and development resources. This article demonstrates the usefulness of cost-effectiveness analysis to support these decisions.

**Methods.** This study had 4 major components: (1) identifying potential innovations, (2) developing transmission models to assess mortality and morbidity impacts, (3) estimating the unit cost impacts, and (4) assessing aggregate cost-effectiveness in United Nations Children's Fund countries through 2049.

**Results.** Four promising technologies were evaluated: aerosol delivery, needle-free injection, inhalable dry powder, and early administration DNA vaccine. They are projected to have a small absolute impact in terms of reducing the number of measles cases in most scenarios because of already improving vaccine coverage. Three are projected to reduce unit cost per dose by \$0.024 to \$0.170 and would improve overall cost-effectiveness. Each will require additional investments to reach the market. Over the next 40 years, the aggregate cost savings could be substantial, ranging from \$98.4 million to \$689.4 million.

**Conclusions.** Cost-effectiveness analysis can help to inform research and development portfolio prioritization decisions. Three new measles vaccination technologies under development hold promise to be cost-saving from a global perspective over the long-term, even after considering additional investment costs.

The current measles vaccine has been in use for nearly 40 years and has successfully eliminated measles in many countries. However, as recently as 2001, measles was estimated to be the largest cause of vaccine-preventable illnesses worldwide [1]. It is still true today that millions of infants face a significant risk of death from measles, particularly in highly populated, low-income countries. The current measles vaccine technology—a reconstituted, lyophilized, live-attenuated vaccine delivered

by subcutaneous injection—has been the standard for the past 4 decades in developing countries and is relatively inexpensive. However, because of its inherent limitations in terms of thermostability, infant age at administration, and requirements for aseptic technique, syringes, and needles for delivery, international experts have made the case for new measles vaccine formulations and delivery devices that aim to accelerate control efforts by simplifying distribution and administration to reduce personnel needs, as well as by improving injection safety and infectious waste disposal [2, 3]. In addition, a number of research and development (R&D) efforts have aimed to improve or replace the standard measles vaccine. Important incremental innovations, such as auto-disable syringes and vaccine vial monitors, have helped with these limitations, and other researchers have pursued alternatives to address injection and other perceived shortcomings, such as the protection of susceptible infants <9 months of age. During the 1980s, the Pan-American Health Organization and others began work on aerosolized delivery in

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Mexico; in 2000, the Bill & Melinda Gates Foundation awarded grants for basic research on a DNA vaccine; and in 2003, the Grand Challenges in Global Health program awarded several grants aimed to improve child vaccines, aiming for earlier, needle-free delivery and eliminating or reducing cold-chain dependence.

Similar to pharmaceuticals, basic and translational research on vaccines and their delivery is uncertain and risky, both in terms of demonstrating scientific proof of principle and of realizing a commercially viable target product profile. Among these risks are changes—some intended and some not—in the broader landscape that could affect the usefulness of a specific innovation. Although measles was virtually eliminated in the Americas during the 1990s, the significant remaining global burden of disease prompted the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and other groups to form the Global Alliance for Vaccines and Immunization (GAVI) and the Measles Partnership in 2001. Since 2000, substantial investments in “second opportunity” vaccination programs have been made, and during 2000–2006, estimated mortality associated with measles worldwide decreased from an estimated 757,000 to 242,000 deaths, a reduction of 68%, compared with a targeted 90% reduction by 2010 [4, 5]. Although Africa had an estimated 91% reduction in measles-associated mortality during 2000–2006, Southeast Asia had a reduction of only 26%. These recent efforts, relying on the current measles vaccine, have had a significant impact and raised questions about the importance of parallel issues, such as increased infant risk of infection resulting from decreasing maternal antibodies. However, the sustainability of long-term financing and the strengthening of public health delivery systems in these countries remains a concern [6].

This study, entitled the Global Measles Vaccination Innovation Strategies (GMVIS) Study, had 2 major goals: (1) to identify and assess the most promising new measles vaccination technologies—potential innovations—on the horizon and (2) to use prospective cost-effectiveness analysis based on measles transmission mathematical modeling and microcosting analysis to explore the health and economic impacts of 4 product innovations for measles control to inform investment decisions. This should help to (1) inform the community of public and private decision-makers, including developing country governments, who are investing in measles innovations and programs, and (2) improve understanding of the strengths, weaknesses, and challenges of applying this approach to R&D portfolio prioritization.

## METHODS

This study had 4 major components: (1) identifying potential innovations in measles vaccination, (2) developing measles transmission models to assess the potential impact of the innovations on measles-associated mortality and morbidity in 6 low-income countries, (3) estimating the unit cost impacts

in those 6 countries, and (4) assessing the potential cost-effectiveness of the innovations, both in the 6 countries and in all 84 countries receiving single-antigen measles vaccine from UNICEF. The economic evaluation (via cost-effectiveness) of these new technologies required the construction of several mathematical models—for both the current and new technologies—that covered measles transmission, the costs of vaccination, the health outcomes of measles with and without vaccination, and the impact in specific countries and globally for those countries using the UNICEF vaccine [7].

### Identifying Potential Innovations

The potential innovations were identified on the basis of a review of the literature and consultation with experts [8–16]. The technologies selected for economic evaluation were those that were determined to be demonstrating clear progress in the development pipeline and with the potential to launch by 2020 at the latest. On the basis of available evidence and expert advisor interviews, innovation target product profiles were developed for each of the innovations that were evaluated. These profiles described key features and characterized parameter assumptions related to efficacy, effectiveness, safety, storage needs, delivery mechanism, immunization schedule, and vaccine product costs and other costs associated with immunization activities.

### Projecting Impact on Mortality and Morbidity

Building on the extensive measles modeling literature [17–25], a dynamic (age-structured, compartmental) measles transmission model was constructed for 6 different countries: Cambodia, Ghana, India, Morocco, Nigeria, and Uganda [26]. It was tailored to each country by using country-specific data on demographic characteristics, measles epidemiology and disease burden, delivery systems, and vaccine coverage environments [27]. A dynamic model is capable of capturing herd immunity, which is especially important when vaccine coverage approaches the elimination threshold. As a result, dynamic models predict the impact of alternative vaccine delivery scenarios on measles cases and deaths and infection-associated costs more accurately than methods that do not account for herd immunity, such as cohort models [28, 29].

The parameterized model was then validated against data on case reports over time for each country and used to project measles cases, deaths, and vaccine doses in each country under various scenarios (Figure 1) for improving routine immunization (RI) coverage, introduction of second dose of measles-containing vaccine, frequency and coverage of supplemental immunization activities (SIAs), impact of vaccine innovations on vaccine coverage, age of first dose (for DNA vaccine), and the timeline for field deployment of vaccine innovations.

We explored increased coverage assumptions with use of this dynamic model but found that, if the current trends toward increasing coverage continue, it will be difficult for any of the new innovations to have a major impact on coverage.

1. Scenarios (21) with <u>current vaccination</u> : a. MCV1 coverage improves by <b>1% or 3% per year</b> (additive), from 2007 onward. b. Follow-up SIAs are scheduled every <b>4, 6 or 8 years</b> . c. MCV2 is introduced once MCV1 coverage reaches <b>70%, 80% or 90%</b> . d. Three additional scenarios corresponding to stagnant RI coverage: Follow-up SIAs are scheduled every <b>2, 4 or 6 years</b> . MCV1 coverage remains constant from 2007 onward and MCV2 is not introduced.
2. Alternative scenarios (16) with the <u>three innovations</u> that simplify administration a. MCV1 coverage improves by <b>1% or 3% per year</b> (additive), from 2007 onward. b. Follow-up SIAs are scheduled every <b>4 or 6 years</b> . c. MCV2 is introduced once MCV1 coverage reaches <b>70% or 80%</b> . d. Simplified administration due to new technologies improves baseline MCV1 and MCV2 coverage by <b>2% or 5%</b> from 2012 onward.
3. Alternative scenarios (8) with a <u>new vaccine</u> providing early coverage (before 9 months of age) a. MCV1 coverage improves by <b>1% or 3% per year</b> (additive), from 2007 onward. b. Follow-up SIAs are scheduled every <b>4 or 6 years</b> . c. MCV2 is introduced once MCV1 coverage reaches <b>70% or 80%</b> . d. DNA vaccine is introduced in countries upon the start of MCV2 coverage, but not before 2020.

**Figure 1.** Dynamic model scenarios for the six countries. (Note: MCV1=1<sup>st</sup> dose of measles-containing vaccine; MCV2 = 2<sup>nd</sup> dose of measles-containing vaccine, routine administration; SIA=supplemental immunization activity, ie, a campaign).

Consequently, for this article, we focus on costs and provide limited information on transmission modeling results.

### Estimating the Unit and Aggregate Cost Impacts

To estimate the potential incremental impact on mean cost per dose for each of the 6 countries, we used an ingredients-based modeling approach to estimate current measles vaccination costs and the potential cost impacts of the new innovations [29, 30]. The ingredients-based model primarily considered the following cost elements: vaccine price, cost of measles vaccine wastage [31], cost of the vaccine delivery device, cost of distributing vaccinations by RI, and cost of infectious waste management [32, 33]. The estimates were modeled on the basis of previous reports [34–37] and WHO measles cost reports.

The aggregate global investment cost model was a straightforward calculation:

Aggregate cost savings=

Aggregate costs with existing vaccination technology–

Aggregate costs with new vaccination technology, where

$$\text{Aggregate costs} = (I \cdot C \cdot V \cdot M) \sum_{it} B_{it} / (1+r)^t$$

where:

$\sum_{it}$  = summation over [i] countries over t years (i=84 UNICEF countries); t= 20 or 40)

B = projected number of births in country i in year t

I = constant factor for the average proportion of births surviving to 9 months

C = constant factor for the average vaccination coverage rate

V = constant factor for the mean number of vaccinations received per inoculated child

M = constant calculated as the weighted mean incremental unit cost impact per dose (based on the proportion of RI vs SIA vaccinations).

r = discount rate (3% in base-case) The base case values for these parameters are shown in Table 1.

### Assessing Potential Health Outcomes and Cost-Effectiveness

Health outcomes were measured in terms of disability-adjusted life-years (DALYs) averted. The primary analysis focused on the more widely used aggregate DALY weight of .152 for a period of 2 weeks, representing the disability impact associated with a typical measles-infected patient [38].

Cost-effectiveness was defined and assessed from 2 perspectives. First, similar to an analysis of a hypothetical thermostable vaccine by Levin et al [34], cost-effectiveness in use was considered: if a new technology were to meet its target product profile, would it offer good incremental value for money in a variety of country settings? Second, cost-effectiveness from an R&D investment perspective addressed this question: would the projected aggregate advantages of the innovation in terms of cost savings and/or improved health outcomes be likely to outweigh the additional costs of completing R&D and introducing it in the global market?

Cost-effectiveness in use for each potential innovation was assessed by evaluating the incremental cost per DALY averted as the primary outcome measure, although the cost per dose delivered, cost per measles case avoided, and cost per death avoided were also estimated for each country.

**Table 1. Base Case Values and Data Sources in Aggregate Cost Model**

Variable	Definition	Base Case Value(Range)	Data Sources
B	Projected number of births in 84 UNICEF countries	4.2 billion total	United Nations Database
I	Average proportion of births surviving to 9 months	0.95(.90–.98)	Assumption based on typical infant mortality; WHOSIS
C	Average vaccination coverage rate	0.90(.85–.95)	Assumption
V	Mean number of vaccinations per inoculated child	1.98(1.75–2.75)	Assumption and Policy Goal
M	Mean cost per vaccination (based on proportion RI vs. SIA)	\$2.52(\$3.26 for RI and \$0.79 for SIA) [RI (\$1.75–\$3.50); SIA (\$0.69–\$0.00)]	Assumptions based on cost report analysis [Ranges]
–	Proportion of vaccination delivered via SIA	30%(20%–40%)	Assumption
–	Discount rate	3%(1%–6%)	Assumption

To assess R&D investment cost-effectiveness, an aggregate global cost model was constructed. Key base-case assumptions are summarized in Figure 2: the impact of varying them was assessed through scenario and sensitivity analyses.

## RESULTS

### Identifying Potential Innovations

Of a variety of potential measles vaccinations reviewed, 4 promising technologies were identified and evaluated: (1) aerosolized delivery of the current lyophilized vaccine via nebulizer (WHO) [39]; (2) needle-free, jet injection of the current lyophilized vaccine (PATH) [40]; (3) inhalable, more thermostable dry powder vaccine (Aktiv-Dry) [41]; and (4) DNA vaccine for early administration with 2 doses (University of Maryland) [42].

The key features of their target product profiles and their status in development are summarized in Figure 3.

### Projecting Impact on Mortality and Morbidity

In scenarios using the conventional vaccine alone, cases are predicted to remain very low in Cambodia, Ghana, Morocco, and Uganda, compared with historical norms as long as SIAs are held every 4 years and RI coverage continues to improve. Thus, the model projections are generally consistent with the experience of Latin American countries, where measles was eliminated in recent decades through similar efforts with use of the conventional vaccine. However, for Nigeria and India, there is a probability of larger numbers of cases in the next 10 years: this period represents a window of vulnerability pending the achievement of higher (>80%) levels of coverage in the broad population of those countries [22]. More frequent SIAs may be required in these countries over the next decade to avoid major outbreaks.

Strong herd immunity attained in most countries under these scenarios of continued improvements in coverage means that the vaccination innovations are likely to have a small absolute impact, if at all.

### Estimating Unit and Aggregate Cost Impacts

Although the vaccine innovations are not predicted to have a significant impact on disease burden, some of them have implications for costs. The price of the current measles vaccine, estimated at \$0.21 per dose, does not vary across the 84 countries purchasing it through UNICEF [42–43]. However, the cost per delivered dose varies substantially depending on personnel costs and wastage rates, especially for RI. For the 6 specific countries analyzed, the estimated cost per RI dose of the current vaccine ranges from \$1.76 to \$2.56; for the SIA dose of the current vaccine, the range is \$0.70–\$1.00.

Across the 84 countries purchasing through UNICEF, the projected mean cost per RI dose is ~\$3.26, and the mean cost per SIA dose is \$0.79 (from the WHO Measles Strategic Planning Tool) [44].

The estimated unit cost impacts are shown in Table 2 for the 4 new technologies in the analysis. On the basis of the microcosting analysis, all but the DNA vaccine would have \$0.024 savings per dose for improved sharps waste management. The aerosol nebulizer also has SIA personnel cost savings, and the inhalable dry powder has an additional ~\$0.15 savings per dose because of reduced vaccine wastage. For the DNA vaccine, the mean cost increase is \$0.97 per each administration in conjunction with diphtheria-tetanus-pertussis vaccine at 6 and 10 weeks.

However, these cost impacts vary across countries in relation to variations in underlying factors, such as wastage rates (eg, 70% for RI in Cambodia vs 25% in Ghana). In the aggregate cost sensitivity analyses, we vary these impacts by  $\pm 50\%$ .

For the 3 potentially unit cost-saving innovations, although the savings appear to be small in absolute terms per dose, when multiplied by the >4.2 billion children (84 countries) estimated to be candidates for a new vaccine over the next 40 years, the aggregate cost savings could be substantial, ranging from \$98.4 million to \$689.4 million (Table 3). Considering discounting at 3%, two-thirds of the savings would be realized during the first 20 years.

1. <b>Ongoing Measles Control.</b> Measles control will continue to improve in South Asia and sub-Saharan Africa on the trajectory assumed in the Measles Initiative's Measles Investment Case II.
<ul style="list-style-type: none"> <li>a. This assumes sufficient aggregate financial support for the coming decades for the 45 WHO-UNICEF priority countries.</li> <li>b. This assumes that countries will move gradually to improve routine immunization to the point where the need for supplemental campaigns will be eliminated.</li> <li>c. And, by implication, this assumes that measles will be eliminated on a sustained basis in these regions by 2020.</li> </ul>
2. <b>Cost/Budget Neutrality.</b> Each of the four new technologies is being developed under the assumption of cost or budget neutrality: the combination of the vaccine plus delivery device would not cost more than current combination.
<ul style="list-style-type: none"> <li>a. Their overall impact would, however, not be budget-neutral, as we assume potential cost impacts in other aspects of measles vaccination delivery.</li> <li>b. The two technologies that use the current vaccine but with a different device would be cost-neutral for the device (i.e., the syringes) only.</li> </ul>
3. <b>Coverage Impact.</b> For three of the four technologies—aerosol nebulizer, jet injector, and inhalable dry powder—there would be no improvement in coverage over the base case trajectory: only the DNA vaccine would improve coverage in the base case.
4. <b>Availability and Ramp-Up Costs.</b> Three of the four technologies were modeled as potentially available in 2010, while the DNA vaccine was modeled with introduction in 2020 in terms of coverage. No ramp-up or switching costs were projected.
5. <b>Cost Estimation and Resource Impacts.</b> For the country-specific cost analyses, estimates of routine immunization costs were constructed using both detailed cost report studies in a few countries and data from the Financial Sustainability Plans (FSP) submitted to GAVI. Our key cost assumptions for the each of the innovations are the following:
<ul style="list-style-type: none"> <li>a. For the jet injector device, sharps waste management costs would be eliminated</li> <li>b. For the measles aerosol device, waste management costs would be eliminated, and SIA personnel costs would be reduced by 20%.</li> <li>c. For the inhalable, dry powder device, waste management costs would be eliminated, RI and SIA observable wastage (including both open and closed vial) would fall to 10%, transportation costs would be reduced in RI and SIAs, and cold chain costs would be eliminated in SIAs.</li> <li>d. For the DNA vaccine, two additional primer doses would be needed at cost per dose equivalent to providing an SIA dose of the current measles vaccination.</li> </ul>
6. <b>Discounting and Perspective.</b> All costs and outcomes were discounted by 3% per annum to express comparisons in 2008 U.S. dollars. (Alternative discount rates of 0% and 5% were considered in sensitivity analyses.) The perspective of the payer for vaccines and their delivery is used in the base case, as the results would not be sensitive to either patient time costs or to the cost of treating cases of measles.

**Figure 2.** Key assumptions for base-case scenario.

### Assessing Potential Health Outcomes and Cost-Effectiveness

The consideration of morbidity and mortality is important in the measurement of the health outcomes of measles, particularly for resource-limited countries that tend to have substantially higher rates of complications from measles cases (i.e., 50–80% of cases). With mortality varying from 1% to 4% in the six countries, generally 99% of the disease burden was due to life years lost rather the morbidity associated with measles.

The rankings or assessments of the alternative new technologies were not sensitive to plausible alternative assumptions about either the morbidity or mortality associated with measles, because of the general base-case assumption of equal effectiveness for the innovations. Therefore, in terms of cost-effectiveness in use, the 3 cost-saving technologies will clearly be, similar to the conventional vaccine, highly cost-effective if coverage levels can be reached and sustained at levels sufficient to maintain herd immunity [45–49]. The proven effectiveness of

the current vaccine at appropriately high levels of use at a relatively low cost creates a significant clinical hurdle for new technologies seeking to enter the market.

Three of the 4 new technologies analyzed—aerosol nebulizer, jet injector, and inhalable dry powder—are projected to be cost-saving on a unit cost basis and per vaccinated child. As such, with more or less equal projected efficacy (and effectiveness), they would be considered to be dominant technologies in terms of cost-effectiveness in use. Among the 3 potentially cost-saving innovations, the inhalable dry powder is projected to have greatest cost savings in use, followed by the aerosol nebulizer and the jet injector. Their relative cost-effectiveness in use would therefore be in the same order. The DNA vaccine, according to the current target product profile, is very costly for the additional coverage provided, aiming to reach young infants who may be protected by general herd immunity anyway. As such, under the current assumptions, it is not projected to be cost-effective in use.



<p><b>1. Aerosolized delivery of the current lyophilized vaccine via nebulizer (WHO)</b></p> <ul style="list-style-type: none"> <li>• This new technology is being tested in Phase 2/3 non-inferiority clinical trials in India.</li> <li>• It relies on a delivery device that builds upon prior PAHO experience with aerosolized measles vaccine.</li> <li>• Major technological improvements have been incorporated, including disposables for all vaccine or patient contact surfaces, versatile power supply options, and a novel, firmware-controlled aerosol generator that limits device use to 8 hours.</li> <li>• It is expected to reduce unit costs per dose by eliminating the waste management activities associated with syringes.</li> <li>• It may also be possible to use less highly trained personnel in immunization campaigns, thus generating more cost savings, though difficult to quantify.</li> </ul>
<p><b>2. Needle-free, jet injection of the current lyophilized vaccine (PATH)</b></p> <ul style="list-style-type: none"> <li>• This new technology is in Phase 2 development.</li> <li>• The PATH project seeks to correct the disease transmission issues with prior, widely used jet injection systems.</li> <li>• It is more broadly targeted to a long-term goal for manufacturer-pre-filled disposable single-dose cassettes for administration of liquids, using recyclable plastics for the disposables.</li> <li>• For the measles vaccine, the cassettes will require aseptic filling at the time of use from reconstituted lyophilized vaccine.</li> <li>• It is expected to reduce unit cost per dose by eliminating the waste management activities associated with syringes.</li> <li>• Measles vaccine is a subset of PATH's broader initiative to use the jet injector for other vaccines in the WHO-UNICEF Expanded Program of Immunization (EPI).</li> </ul>
<p><b>3. Inhalable, more thermostable dry powder (Aktiv-Dry)</b></p> <ul style="list-style-type: none"> <li>• This new technology is in Phase 1 clinical development.</li> <li>• Aktiv-Dry has developed a freeze-drying technology that replaces lyophilization.</li> <li>• As the vaccine is delivered in dry-powder form, the reconstitution step with lyophilized vaccine is obviated.</li> <li>• All patient- and vaccine-contact surfaces are disposable.</li> <li>• It is expected to have substantial cost savings by reducing wastage, due to both open vial and closed vial losses, and by eliminating the use and waste management of syringes.</li> </ul>
<p><b>4. DNA vaccine for early administration at 6 and 10 weeks of age (University of Maryland)</b></p> <ul style="list-style-type: none"> <li>• DNA vaccine aims to address an observed window of vulnerability for infants due to a combination of two factors, having an immature immune system and having reduced maternal antibodies.</li> <li>• The goal of sufficient immune response for vaccine administered at birth has not, however, been realized in pre-clinical studies: the expected schedule for the DNA vaccine under development includes two additional early administrations to successfully prime the infant for two subsequent attenuated measles vaccine doses.</li> <li>• The current profile of two administrations alongside DTP at 6 and 10 weeks, followed by the conventional vaccine at 14 weeks and 9 months, means this approach will be cost-increasing.</li> <li>• In principle, mortality could be reduced in children less than nine months of age but at higher total cost.</li> <li>• These children would, however, likely be protected through herd immunity if coverage levels under the current vaccine are sufficiently high.</li> </ul>

**Figure 3.** Four target product profiles: key characteristics and stage of development.

Cost-effectiveness in use is only one criterion to consider, because all of these new technologies will require additional investments to reach the market. Therefore, the aggregate cost savings, as shown in Table 3, should be compared with the additional R&D investment expenditures. The latter was not estimated in this study, but it is likely to be on the order of tens of millions of dollars for any one of the 4 technologies, with some less than others.

Because of an assumed differential impact on SIAs, compared with RI, the results for the aerosol nebulizer and inhalable dry powder are somewhat sensitive to the share of doses delivered by SIA, compared with RI; for example, for the aerosol nebulizer,

40 years savings vary from \$116.6 to \$191.8 million, when the proportion of SIA is varied from 10% to 50%.

The 2 primer doses of the DNA vaccine, adding ~\$2 additional spending per additional child, are expected to add roughly \$3.9 billion to current projected spending of \$10.2 billion over 40 years in the absence of these innovations. With use of a base-case assumption of high levels of coverage reaching herd immunity with the current vaccine, the improvement in health outcomes would be very limited. For example, in the case of India, the DNA vaccine is projected to avert an additional 1095 DALYs lost per year but at an annual incremental cost of \$75 million. The implied incremental cost-effectiveness ratio is

**Table 2. Estimated Unit Cost Impacts for New Technologies (\$ per Dose)**

	New Technology			
	Aerosol nebulizer	Jet injector	Inhalable dry powder	DNA vaccine
Routine immunization	-0.024	-0.024	-0.182	0.968
Supplemental immunization activities	-0.071	-0.024	-0.143	NA
Weighted mean	-0.044	-0.024	-0.170	NA

**NOTE.** NA, not applicable; Weighted mean assumes 30% of injections delivered by SIA; DNA vaccine given twice per children along with routine DTP at 6 and 10 weeks.

**Source:** Authors' estimates based analysis of cost reports and impacts on sharps waste management and personnel time.

\$68,500 per DALY averted, which would generally not be considered to be cost-effective in low-income settings.

### Critical Assumptions: Scenario and Sensitivity Analyses

Besides assuming successful clinical development, the most critical base-case assumptions are that (1) the Measles Investment Case II will succeed and be sustainable [50], (2) the bundled vaccine plus delivery device will be cost-neutral for 3 of the innovations, and (3) the ramp-up and switching costs (assumed to be zero) would not be a significant barrier to adoption. If the first does not hold, then all 4 innovations would be more valuable, although all could be adversely affected if overall financial sustainability becomes an issue. The innovations would be less valuable if ramp-up and switching costs were substantial.

In terms of the individual technologies, the unit cost savings for sharps (ie, used needles) waste management are a significant factor for both the jet injector and the aerosol nebulizer cost savings. This parameter is difficult to estimate reliably [33].

For illustrative purposes, Figure 4 presents the aggregate cost impact sensitivity analyses for the aerosol nebulizer. The unit cost impact and discounting assumptions are the most critical, but the results still indicate cost savings. Indeed, even in a simultaneous, multiway sensitivity analysis (not shown), the overall lower-bound estimate would still yield savings of \$34.0 million.

**Table 3. Aggregate Incremental Cost Impact of Potential Measles Innovations (Present Discounted Value for UNICEF Purchasing Countries; n = 84)**

TimeHorizon	New Technology			
	Aerosol nebulizer	Jet injector	Inhalable dry powder	DNA vaccine
20 years(2010–2029)	-\$101.4(-\$50.7—\$152.2)	-\$64.7(-\$32.4—\$97.1)	-\$453.7(\$226.9—\$680.7)	\$2,606(\$1303.0—\$3,909.0)
40 years(2010–2049)	-\$154.1(-\$77.1—\$231.2)	-\$98.4(-\$49.2—\$147.5)	-\$689.4(-\$344.7—\$1,034.1)	\$3,959(\$1979.6—\$5938.6)

**NOTE.** Spending discounted at 3%; Costs in 2008\$. Ranges shown are based on the population-weighted mean unit cost impact across the six countries plus or minus 50 percent with other parameters held at base case value.

## DISCUSSION

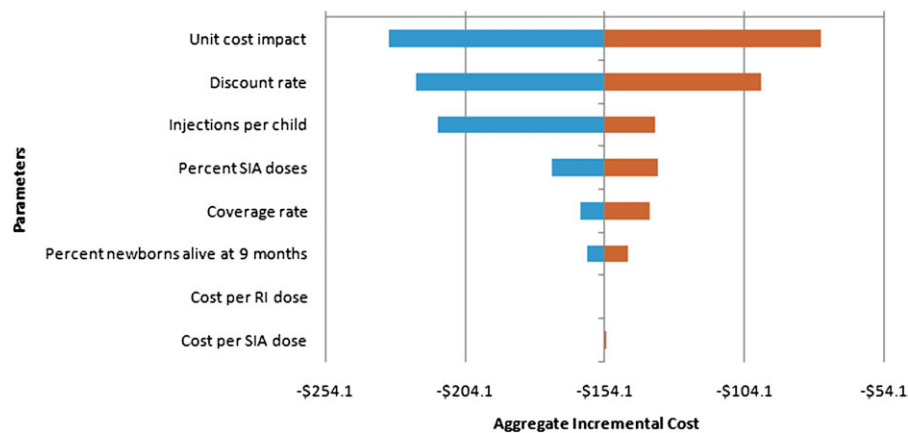
In summary, several of the new measles vaccination technologies on the horizon—aerosol nebulizer, jet injector, and inhalable dry powder—hold substantial promise to be cost-saving from a long-term global perspective, even considering additional investment costs. Although difficult to demonstrate in prelaunch, noninferiority clinical trials, the developers expect these innovations to also improve coverage and reduce disease burden. Choosing which ones to pursue would also require further research on the costs and likelihood of success in development and the costs and barriers to uptake (ie, switching to the new technology). It is much less clear that the DNA vaccine is a worthwhile investment from the standpoint of measles alone, because of the increased cost with no expected increase in measles coverage. It could, however, have additional value as a general scientific proof of principle and advancement, but this has not been quantified here.

The transmission modeling for the 6 countries indicated that the impact of the new technologies on absolute disease burden would be beneficial but very minimal in the aggregate, under most plausible scenarios for their impact on coverage and efficacy. By the time these new technologies can realistically be adopted, these 6 and most WHO-UNICEF priority countries are projected to have measles well under control. Of course, this assumes that progress toward GAVI vaccine coverage targets continues as it has for the past 5 years and is sustained for decades to come.

Another important caveat is that all 4 new technologies assume cost or budget neutrality with respect to the cost of the vaccine plus the delivery device. This assumes effective implementation of the relevant provisions or stipulations in the contracts with the developers and providers of the devices and vaccines.

In terms of other limitations, it is important to acknowledge that several factors of relevance in long-term R&D investment decisions were not included in the scope of this study:

(1) the probability that specific innovations are likely to meet their target product profile or the probabilities of achieving any of the steps in the development process (ie, probability of technical success); (2) the costs of further R&D to reach the point of approval for marketing; (3) the expected cost of



**Figure 4.** Sensitivity analysis for aggregate incremental cost impact for aerosol nebulizer for UNICEF purchasing countries over 40 year time horizon (2010–2049).

manufacturing the innovations; (4) the reaction of the marketplace to competing vaccine formulations in the future, including the costs and likelihood of encouraging users to adopt new technologies (ie, switching costs); (5) costs of regulatory submissions and review; (6) costs of ramp-up, switching, and other miscellaneous marketing, training, capital equipment, and other market-readiness costs; and (7) the value of scientific spillovers from gains in our basic science knowledge.

Three of the 4 new technologies are expected to be net cost saving, and although they are in different stages of development, they are all far enough along that the additional development costs are likely to be in the tens (not hundreds) of millions of dollars. In terms of immediate research needs, because of the importance of the assumption about the cost savings from sharps waste management, further research could be done relatively quickly to better test this assumption.

Finally, this analysis has demonstrated both the feasibility and usefulness of prospective cost-effectiveness modeling—combining infectious disease dynamic modeling with economic modeling—for informing decisions about vaccine innovation R&D. Real-world choices for health systems in low-income settings are, however, very difficult, and although potential cost-effectiveness should be given due consideration, it will seldom be decisive alone, because of the tradeoffs that must be made in allocating limited health care resources.

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