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# Return On Investment From Immunization Against 10 Pathogens In 94 Low- And Middle-Income Countries, 2011–30

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**ABSTRACT** Estimating the value of global investment in immunization programs is critical to helping decision makers plan and mobilize immunization programs and allocate resources required to realize their full benefits. We estimated economic benefits using cost-of-illness and value-of-a-statistical-life approaches and combined this estimation with immunization program costs to derive the return on investment from immunization programs against ten pathogens for ninety-four low- and middle-income countries for the period 2011–30. Using the cost-of-illness approach, return on investment for one dollar invested in immunization against our ten pathogens was 26.1 for the ninety-four countries from 2011 to 2020 and 19.8 from 2021 to 2030. Using the value-of-a-statistical-life approach, return on investment was 51.0 from 2011 to 2020 and 52.2 from 2021 to 2030. The results demonstrate continued high return on investment from immunization programs. The return-on-investment estimates from this study will inform country policy makers and decision makers in funding agencies and will contribute to efforts to mobilize resources for immunization. Realization of the full benefits of immunization will depend on sustained investment in and commitment to immunization programs.

**T**he Decade of Vaccines (2011–20) is nearing an end. This was a strategic period led by the Bill & Melinda Gates Foundation, Gavi, the United Nations Children’s Fund (UNICEF), the National Institute of Allergy and Infectious Diseases (US), and the World Health Organization to expand access to immunization in low- and middle-income settings. As the first step, the global health and development community, under the aegis of the Decade of Vaccines Collaboration, developed the Global Vaccine Action Plan, which outlined ambitious goals to extend “by 2020 and beyond full benefits of immunization to all people” and was endorsed by 194 member states of the World Health Assembly in 2012.<sup>1</sup>

During the Decade of Vaccines the global com-

munity made significant strides toward these goals, vaccinating more than twenty million additional children and helping more than a hundred countries reach at least 90 percent national uptake (known as “coverage”) of the three-dose diphtheria-tetanus-pertussis vaccines.<sup>2</sup> The Decade of Vaccines also contributed to increased recognition of the socioeconomic benefits of immunization beyond reducing the vaccine-preventable disease burden, as well as to increased demand for data and analytical methods to quantify the economic impact and to support decision making.<sup>3,4</sup> Among such methods are return on investment and investment cases that have been actively used by global health stakeholders to link the impact and costs of specific investments in health.<sup>5</sup> Sachiko Ozawa and col-

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leagues previously estimated the return on investment (ROI) for immunization programs during the Decade of Vaccines to be \$16 per dollar invested using a cost-of-illness approach and \$44 using a full-income approach in ninety-four low- and middle-income countries.<sup>6</sup> These figures have been cited as key evidence of high rates of return, and thus as justification for donor pledges of US\$7.5 billion to Gavi for the period 2016–20.<sup>7</sup>

In the coming decade funders and governments will continue to face high demand for health investments to make progress toward the United Nations Sustainable Development Goals and the achievement of universal health coverage by 2030, to which all 193 United Nations member states reaffirmed a global political commitment in 2019.<sup>8</sup> In addition, new challenges such as emerging infectious diseases, humanitarian crises, climate change, and vaccine hesitancy require further political commitment and contributions to protecting hard-won gains achieved during the past decade. As the global community works toward establishing a new vision and strategy for the next decade,<sup>9</sup> estimating the value of global investment in immunization programs is critical in the mobilization and allocation of resources to realize the full benefits of immunization.

To achieve this purpose, we estimated the ROI of vaccines and immunization programs against ten pathogens for ninety-four low- and middle-income countries from 2011 to 2030. As an update to the study by Ozawa and colleagues, this study incorporated historical vaccine coverage and price data for the period 2011–17 that were unavailable in previous studies,<sup>6,10</sup> as well as forecasts for 2018–30. We further leveraged newly available data for model parameters and updated methodological approaches to estimating economic benefits and immunization program costs to be consistent with recently developed international best practices.<sup>11</sup> In particular, we applied two analytical approaches—the cost-of-illness approach and the value-of-a-statistical-life approach—to capture different aspects of the economic benefits that inform policy decisions in countries and at funding organizations. The cost-of-illness approach captures the observable impact of immunization programs on household costs, health care costs, and labor productivity, while the value-of-a-statistical-life approach reflects societies' willingness to pay for saving lives.

## Study Data And Methods

**SCOPE** This study measured the impact of immunization programs against ten pathogens (*Hae-*

*mophilus influenzae* type b, hepatitis B, human papillomavirus, Japanese encephalitis, measles, *Neisseria meningitidis* serotype A, *Streptococcus pneumoniae*, rotavirus, rubella, and yellow fever) in ninety-four low- and middle-income countries, including seventy-three current and former Gavi-supported countries across six World Health Organization regions for the period 2011–30 (see online appendixes 1 and 2).<sup>12</sup> Total investment and vaccine impact are compared with a counterfactual scenario of no vaccination. Our methods and data sources were reviewed and validated by an expert advisory group. All costs and economic benefits are presented in 2018 US dollars.

**IMMUNIZATION PROGRAM COSTS** Immunization program costs for routine immunization and supplemental immunization activities are divided into two components: vaccine costs, including injection supplies; and freight and immunization delivery costs, including labor, storage, transportation-related costs, and other capital and recurrent costs (see appendix 5).<sup>12</sup>

To estimate total vaccine costs, the number of doses was multiplied by the price per dose for each vaccine, country, and year. The number of doses was estimated, using the target population,<sup>13</sup> by vaccine coverage data provided by the Vaccine Impact Modelling Consortium, based on Gavi's operational forecast, version 16;<sup>14,15</sup> wastage rates;<sup>16</sup> and 25 percent buffer stock rates for routine vaccines.<sup>17</sup> For Gavi countries, historical weighted average prices of vaccines were extracted from Gavi-provided data for 2011–17.<sup>18</sup> Historical simple average prices from the Pan-American Health Organization (PAHO) Revolving Fund price list<sup>19</sup> and those from the UNICEF vaccine price list<sup>20</sup> were applied to PAHO countries and non-Gavi, non-PAHO countries, respectively. Future prices (2018–30) for Gavi countries were based on Gavi's projections,<sup>18</sup> and we generated price forecasts for PAHO and UNICEF data, assuming constant prices. Gavi's immunization supply cost for syringes and safety boxes, as well as freight cost, were applied to ninety-four countries.<sup>18</sup>

Immunization delivery costs were estimated by multiplying the number of doses by immunization delivery cost per dose for each vaccine, country, and year. For routine immunization, we extracted comparable cost components from eighty-nine comprehensive multiyear plan costing tools<sup>21</sup> and 135 cost estimates for routine immunization from the Immunization Delivery Cost Catalogue<sup>22</sup> (see appendix 5).<sup>12</sup> Multilinear regression was used to predict the cost per dose for countries missing data (see appendix 6).<sup>12</sup> The incremental cost per dose for *S. pneumoniae*, human papillomavirus, and rotavirus vaccines

from the Immunization Delivery Cost Catalogue were applied to the introduction years to capture introduction costs. Supplemental immunization activity delivery cost per dose for measles, measles-rubella, *N. meningitidis* serotype A, Japanese encephalitis, yellow fever, and human papillomavirus multi-age cohorts was based on the average of estimates from the Immunization Delivery Cost Catalogue,<sup>22</sup> a systematic review,<sup>23</sup> and budget estimates from country proposals submitted to Gavi<sup>24</sup> (see appendix 7).<sup>12</sup> We applied constant delivery cost per dose estimates across two decades.

#### **ECONOMIC BENEFITS**

► **COST-OF-ILLNESS APPROACH:** The cost-of-illness models used estimates of cases and deaths averted provided by the Vaccine Impact Modelling Consortium<sup>25</sup> (see appendix 8)<sup>12</sup> to estimate averted treatment costs, transportation costs, lost caregiver wages, and productivity loss due to disability and death. We assumed that all costs were constant over time and discounted from the year of impact to the year of vaccination at 3 percent per year.

We estimated treatment costs averted by multiplying cases by care-seeking rates,<sup>26</sup> per visit or per diem health facility costs,<sup>27</sup> and length-of-stay.<sup>28–33</sup> Additional medication diagnostic costs were conservatively estimated to be 25–50 percent of the facility fees.<sup>34</sup> Transportation costs were estimated by multiplying the cost per round trip to a health care facility<sup>35</sup> by the number of care-seeking cases and visits per case. We assumed that caregivers would have the lowest opportunity cost of time to take children to a health facility for vaccination, so we used minimum wage<sup>36,37</sup> to estimate their productivity loss.

The human capital approach<sup>38</sup> was employed to estimate productivity loss averted. Gross domestic product (GDP) per capita in 2018<sup>31</sup> was used to approximate an individual's annual economic contribution to society. We estimated productivity loss for the working-age population (ages 15–64) and assumed that labor-force participation was 100 percent, to include the substantial informal sector in low- and middle-income countries, where approximately 70 percent<sup>39</sup> of workers are informal and are excluded from official labor-force participation rates. To account for childhood mortality from other causes, childhood cases and deaths were multiplied by the probability of survival to fifteen years.<sup>13</sup> Productivity loss due to disability was estimated by multiplying the discounted duration of disability by disability weights from the Global Burden of Disease study<sup>40</sup> and GDP per capita.<sup>41</sup>

► **VALUE-OF-A-STATISTICAL-LIFE APPROACH:** The value-of-a-statistical-life approach is derived

through aggregating individuals' willingness to pay for a small mortality risk reduction for an entire population to estimate the value of saving one life.<sup>11</sup> For transparency and reproducibility, we applied methods outlined in the *Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development*.<sup>11</sup> Because of the paucity of direct value-of-a-statistical-life estimates from low- and middle-income countries,<sup>42</sup> we applied the value-transfer approach to extrapolate the value of a statistical life from the US to all low- and middle-income countries in the model. The value-transfer approach adjusts for differences in income by using a multiplier of the ratio of GDP per capita in the target and reference countries raised to an income elasticity (see appendix 4).<sup>12</sup> We used a US value of a statistical life of 160 times GDP per capita<sup>11</sup> (\$10,002,805 in 2018) and an income elasticity of 1.5.<sup>42</sup> For thirty-one low-income countries, this method yielded estimates below the value of future earnings, which is unreasonably low because willingness-to-pay likely includes both monetary and nonmonetary aspects of life. Thus, we imputed twenty times GDP per capita as a minimum value of a statistical life, or approximately the value of future earnings for a person of the median age.<sup>11</sup> Because deaths averted occur years after vaccination, the value of a statistical life was estimated for the year of death, using projected GDP per capita growth.<sup>43</sup> The resulting value-of-a-statistical-life values were multiplied by the corresponding number of deaths averted.

**RETURN ON INVESTMENT** ROI is the ratio of net benefits (benefits minus costs) to costs. Estimates of economic benefits and costs were aligned by country, pathogen, delivery strategy, and year. A small number (2 percent) of data points for costs did not have corresponding estimates of cases and deaths averted, so these costs were excluded.

**SENSITIVITY ANALYSIS** Probabilistic sensitivity analysis and one-way sensitivity analysis were each conducted separately for immunization program costs and economic benefits. We simultaneously varied four parameters for immunization program costs: delivery costs for routine activities and supplemental immunization activities, incremental delivery costs for new vaccine introduction, and vaccine price change per year. Uncertainty ranges for each delivery cost type were determined using the distribution of all relevant data points. Vaccine price change per year varied by  $\pm 15$  percent. Five parameters were varied for economic benefits: treatment costs, transportation costs, cases and deaths averted, and GDP per capita. Ranges and distributions were based on the modelwide distribution of point estimates, with additional data for trans-

portation and treatment costs extracted from a systematic review.<sup>34</sup> Uncertainty ranges for cases and deaths were derived from a Vaccine Impact Modelling Consortium publication.<sup>25</sup> A Monte Carlo simulation was performed with ten thousand bootstrap replications to construct a 95 percent uncertainty range. Uncertainty ranges for the ROI estimates were modeled using results of the probabilistic sensitivity analysis performed on the economic benefits and costing models. One-way sensitivity analysis was performed to assess the impact of individual parameters on the ROI.

**LIMITATIONS** This analysis had several limitations. First, these models built on health impact estimates provided by the Vaccine Impact Modelling Consortium, and any limitations inherent in the health impact models (that is, homogenous disease risk and vaccine coverage rates at the national level for most pathogens, uncertainty in demographic estimates, and gaps in empirical data) also apply to the costing and benefits models.<sup>25</sup> Second, to align with cost estimates, the value-of-a-statistical-life-based economic benefits were estimated using US dollars instead of purchasing power parity exchange rates. This approach generated a conservative estimate of value-of-a-statistical-life benefits, as it does not adjust for living standards in low- and middle-income countries. Third, these estimates are intended for use at the aggregate international level, as they do not capture the subnational variation that would be necessary for evidence-based decision making at the country level. Our results reflect the expected ROI from immunization programs against ten pathogens if funding and coverage goals were achieved as outlined in the Gavi operational forecast. Exogenous factors may have affected model parameters, such as vaccine introduction years, number of doses, and price. Nonetheless, our study leveraged the most up-to-date and newly available data sources and methodologies to provide insights on economic returns from immunization programs in low- and middle-income countries.

## Study Results

**IMMUNIZATION PROGRAM COSTS** Total immunization program costs for ten pathogens increase from \$25.2 billion in the first decade (2011–20) to \$39.9 billion in the second decade (2021–30) for ninety-four low- and middle-income countries (exhibit 1). The total costs approximately average out to \$24.6 per surviving infant in the first decade and \$41.2 per surviving infant in the second decade (data not shown), which is within the range estimated by empirical studies.<sup>44</sup> For Gavi countries, the costs increase from \$21.7 bil-

lion between 2011 and 2020 to \$36.2 billion between 2021 and 2030 (exhibit 1). Exhibit 2 shows the overall increasing trend for total costs.

Over the course of two decades, vaccine costs account for 53.6 percent (95% confidence interval: 40.9, 61.8) of the total immunization program costs in ninety-four low- and middle-income countries and 51.9 percent (95% CI: 41.5, 64.0) in Gavi countries. Immunization delivery costs account for 46.4 percent (95% CI: 38.2, 59.1) and 48.1 percent (95% CI: 36.0, 58.5) of total immunization program costs, respectively (data not shown). The proportion of the total costs of newer vaccines (*S. pneumoniae*, human papillomavirus, and rotavirus) relative to the total vaccine portfolio increases over time. The results from one-way sensitivity analysis showed that uncertainty in total immunization program costs is primarily driven by country-specific routine immunization delivery cost per dose (see appendix 9).<sup>12</sup>

**ECONOMIC BENEFITS** Using the cost-of-illness method, we estimated that vaccines against ten pathogens averted \$681.9 billion of economic burden in ninety-four low- and middle-income countries between 2011 and 2020 (exhibit 1). Most of the benefit would accrue in the seventy-three Gavi-eligible countries, with \$639.1 billion averted during this decade (see appendix 10).<sup>12</sup> The models predicted that an increase in coverage and the introduction of new vaccines would lead to even greater economic benefits from 2021 to 2030. The cost-of-illness method yielded estimates of \$828.5 billion and \$781.6 billion in all ninety-four countries and the seventy-three Gavi countries, respectively (see appendix 10).<sup>12</sup> Productivity loss due to death and disability accounts for more than 98.9 percent of the economic benefits of vaccines, with treatment costs, transportation costs, and caretaker wages together making up 1.1 percent of economic benefits over the model time horizon (see appendix 10).<sup>12</sup>

The value-of-a-statistical-life approach, as expected, generated larger estimates of the economic benefits. From 2011 to 2020, \$1,311.6 billion of economic benefits were accrued in ninety-four countries and \$1,204.0 billion in Gavi countries (exhibit 1). In the second decade the value-of-a-statistical-life method forecasted larger economic benefits of \$2,125.1 billion in ninety-four countries and \$1,977.8 billion in Gavi countries. Exhibits 3 and 4 show cost-of-illness and value-of-a-statistical-life benefits, respectively, by pathogen.

Across both methods, the pathogen driving the results was measles. Across all countries and years included in the analysis, vaccination against measles accounted for 76.4 percent and

**EXHIBIT 1**

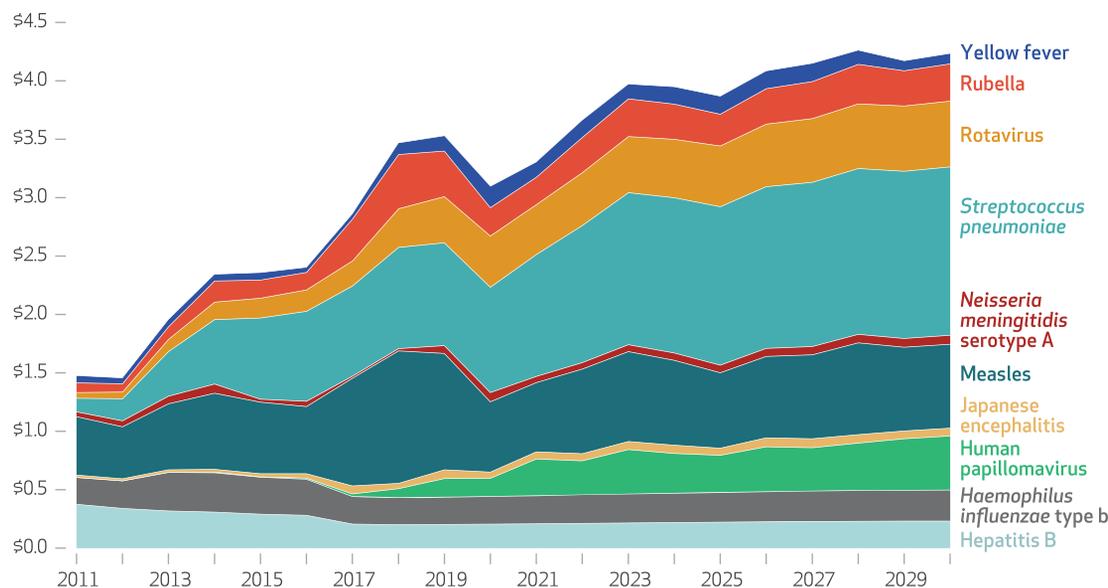
**Economic benefits and immunization program costs (in billions of dollars) and return on investment (ROI) for seventy-three Gavi-supported countries and ninety-four low- and middle-income countries, by decade and analytic approach, 2011-30**

	Gavi countries (n = 73)				Total countries (n = 94)			
	Cost-of-illness approach		Value-of-a-statistical-life approach		Cost-of-illness approach		Value-of-a-statistical-life approach	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
<b>2011-20</b>								
Benefits	\$639.1	(\$280.3-\$1,127.9)	\$1,204.0	(\$556.1-\$2,027.0)	\$681.9	(\$300.0-\$1,202.5)	\$1,311.6	(\$607.0-\$2,203.4)
Costs	\$21.7	(\$18.0-\$27.5)	\$21.7	(\$18.0-\$27.5)	\$25.2	(\$21.1-\$31.3)	\$25.2	(\$21.1-\$31.3)
Net benefits	\$617.5	(\$259.3-\$1,108.0)	\$1,182.3	(\$534.0-\$2,004.5)	\$656.7	(\$276.1-\$1,175.6)	\$1,286.4	(\$583.0-\$2,174.3)
ROI	28.5	(11.5-53.0)	54.6	(23.6-96.7)	26.1	(10.7-48.4)	51.0	(22.5-90.1)
<b>2021-30</b>								
Benefits	\$781.6	(\$351.8-\$1,356.3)	\$1,977.8	(\$937.0-\$3,230.4)	\$828.5	(\$373.8-\$1,439.3)	\$2,125.1	(\$1,007.3-\$3,462.4)
Costs	\$36.2	(\$30.0-\$48.1)	\$36.2	(\$30.0-\$48.1)	\$39.9	(\$33.2-\$51.9)	\$39.9	(\$33.2-\$51.9)
Net benefits	\$745.4	(\$316.8-\$1,321.1)	\$1,941.7	(\$901.7-\$3,188.4)	\$788.6	(\$334.5-\$1,397.7)	\$2,085.1	(\$970.0-\$3,415.3)
ROI	20.6	(8.3-38.0)	53.7	(23.3-92.9)	19.8	(8.1-37.0)	52.2	(23.3-91.0)
<b>2011-30</b>								
Benefits	\$1,420.8	(\$631.9-\$2,485.6)	\$3,181.8	(\$1,493.6-\$5,253.9)	\$1,510.4	(\$674.3-\$2,643.2)	\$3,436.7	(\$1,615.8-\$5,657.2)
Costs	\$57.8	(\$48.2-\$74.7)	\$57.8	(\$48.2-\$74.7)	\$65.1	(\$54.5-\$82.5)	\$65.1	(\$54.5-\$82.5)
Net benefits	\$1,362.9	(\$575.4-\$2,428.9)	\$3,123.9	(\$1,433.4-\$5,194.6)	\$1,445.3	(\$611.1-\$2,577.4)	\$3,371.5	(\$1,550.3-\$5,590.7)
ROI	23.6	(9.5-43.4)	54.0	(23.4-94.1)	22.2	(9.1-41.5)	51.8	(23.1-90.5)

**SOURCES** Authors' analysis of model parameters provided by the Vaccine Impact Modelling Consortium (see note 25 in text), with parameters for treatment costs, transportation cost, lost caregiver wages, productivity loss, and value of a statistical life from multiple sources (see notes 25-39 in text); and authors' analysis of immunization program costs primarily based on population data from the United Nations *World Population Prospects: The 2017 Revision* (see note 13 in text) and vaccine coverage data provided by the Vaccine Impact Modelling Consortium, based on Gavi's operational forecast, version 16 (see note 14 in text), with parameters for vaccine prices and immunization delivery costs from multiple sources (see notes 14-24 in text). **NOTES** ROI estimates are rounded to one decimal point. Costs, benefits, and net benefits are expressed in billions of 2018 US dollars and rounded to one decimal point. Net benefits = (Benefits) - (Costs). ROI = (Benefits - Costs)/(Costs) = (Net benefits)/(Costs). CI is confidence interval.

**EXHIBIT 2**

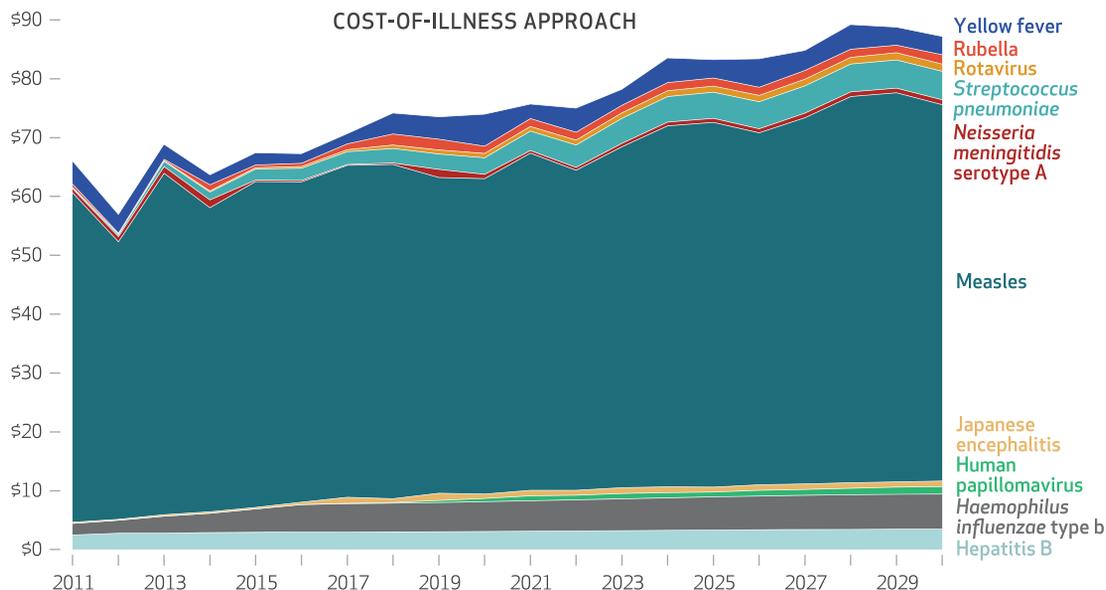
**Total immunization program costs (in billions) for ninety-four low- and middle-income countries, by pathogen, 2011-30**



**SOURCE** Authors' analysis of immunization program costs based on population data from the United Nations *World Population Prospects: The 2017 Revision* (see note 13 in text) and vaccine coverage data provided by the Vaccine Impact Modelling Consortium, based on Gavi's operational forecast, version 16 (see note 14 in text), with parameters for vaccine prices and immunization delivery costs from multiple sources (see notes 16-24 in text). **NOTE** Immunization program costs are expressed in billions of 2018 US dollars.

EXHIBIT 3

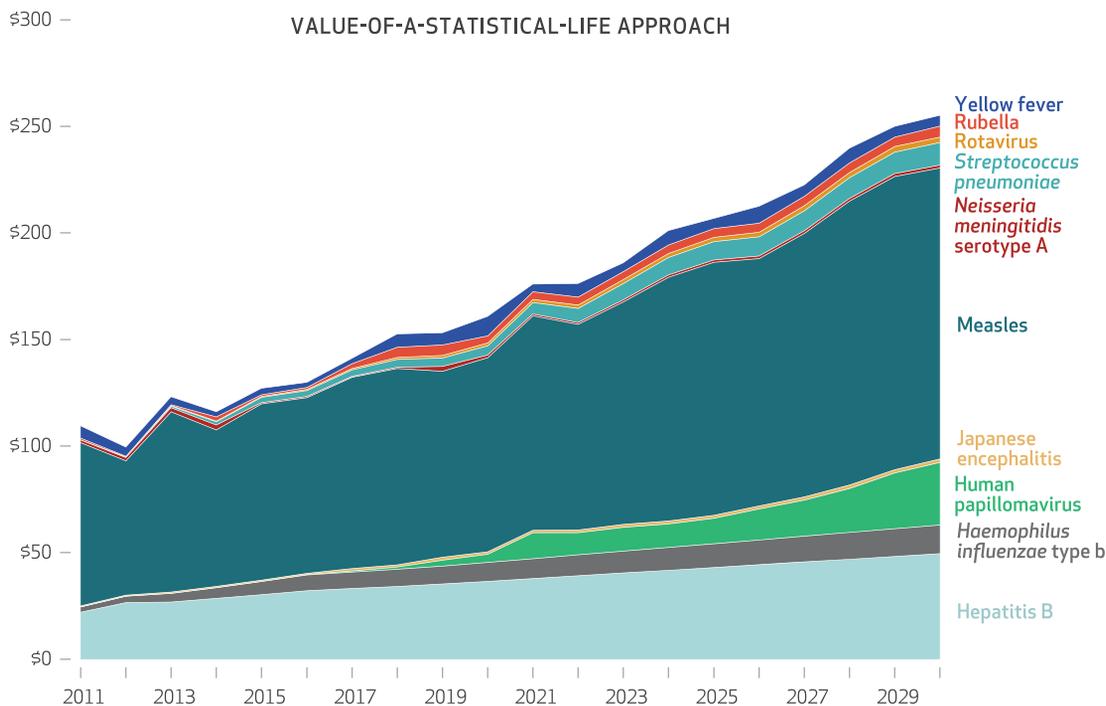
Total economic benefits derived using a cost-of-illness approach (in billions) for ninety-four low- and middle-income countries, by pathogen, 2011-30



**SOURCE** Authors' analysis of economic benefits based on estimates of cases and deaths averted provided by the Vaccine Impact Modelling Consortium (see note 25 in text), with parameters for treatment costs, transportation cost, lost caregiver wages, productivity loss, and value of a statistical life from multiple sources (see notes 26-41 in text). **NOTE** Economic benefits are expressed in billions of 2018 US dollars.

EXHIBIT 4

Total economic benefits derived using a value-of-a-statistical-life approach (in billions) for ninety-four low- and middle-income countries, by pathogen, 2011-30



**SOURCE** Authors' analysis of economic benefits based on estimates of cases and deaths averted provided by the Vaccine Impact Modelling Consortium (see note 25 in text) and parameters extracted from notes 41-43 in text. **NOTE** Economic benefits are expressed in billions of 2018 US dollars.

58.5 percent of economic benefits, using the cost-of-illness and value-of-a-statistical-life approaches, respectively (exhibits 3 and 4). One-way sensitivity analysis showed that GDP per capita and the number of cases and deaths averted were the largest drivers of uncertainty in economic benefits (see appendix 9).<sup>12</sup>

**RETURN ON INVESTMENT** The ROI from immunization programs across two decades is 22.2 using the cost-of-illness approach and 51.8 using the value-of-a-statistical-life approach for the ninety-four low- and middle-income countries (exhibit 1). For Gavi countries, the ROI is 23.6 and 54.0 using the cost-of-illness and value-of-a-statistical-life approaches, respectively. Exhibit 5 shows the economic benefits, costs, and ROI for the period 2011–30.

A decade-by-decade breakdown shows that the ROI using the cost-of-illness approach was 26.1 for ninety-four low- and middle-income countries and 28.5 for Gavi countries in the first decade, which decreased to 19.8 for ninety-four low- and middle-income countries and 20.6 for Gavi countries in the second decade (exhibit 1). The one-way sensitivity analysis showed that the largest drivers of uncertainty in ROI using the cost-of-illness approach are GDP per capita and health impact, followed by ROI delivery cost,

vaccine price change per year, supplemental immunization activity delivery cost, inpatient costs, incremental delivery cost for new vaccine introduction, transportation costs, and outpatient costs (see appendix 9).<sup>12</sup>

For ninety-four countries, ROI using the value-of-a-statistical-life approach remains relatively constant, totaling 51.0 for the first decade and 52.2 in the second decade (exhibit 1). For Gavi countries, it was 54.6 and 53.7 in the first and second decades, respectively. For the value-of-a-statistical-life approach, GDP per capita and health impact are also the largest drivers of uncertainty, followed by routine immunization delivery cost, vaccine price change, supplemental immunization activity delivery cost, and new vaccine introduction (see appendix 9).<sup>12</sup>

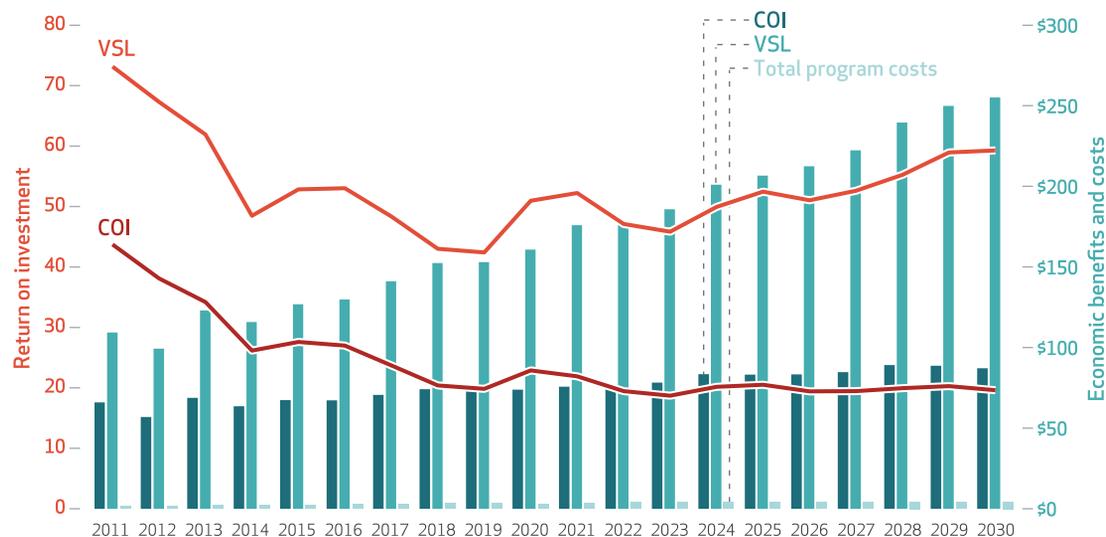
The net benefit reflects the scale of impact of immunization. For ninety-four countries from 2011 to 2030, the net benefit of vaccine programs is \$1,445.3 billion and \$3,371.5 billion, using the cost-of-illness and value-of-a-statistical-life methods, respectively (exhibit 1).

## Discussion

The upward trend in total immunization program costs is explained by changes over time in

### EXHIBIT 5

**Return on investment (ratio of net benefits to costs) and economic benefits and immunization program costs (in billions) for ninety-four low- and middle-income countries, 2011–30**



**SOURCES** Authors' analysis of economic benefits based on estimates of cases and deaths averted provided by the Vaccine Impact Modelling Consortium (see note 25 in text), with parameters for treatment costs, transportation cost, lost caregiver wages, productivity loss, and value of a statistical life from multiple sources (see notes 26–41 in text); and authors' analysis of immunization program costs primarily based on population data from the United Nations *World Population Prospects: The 2017 Revision* (see note 13 in text) and vaccine coverage data provided by the Vaccine Impact Modelling Consortium, based on Gavi's operational forecast, version 16 (see note 14 in text), with parameters for vaccine prices and immunization delivery costs from multiple sources (see notes 16–24 in text).

**NOTES** Immunization program costs and economic benefits are expressed in billions of 2018 US dollars. COI is cost-of-illness approach. VSL is value-of-a-statistical-life approach.

the number of doses, vaccine prices, and additional delivery costs for new vaccines. The projection method from Gavi's operational forecast leads to an increasing number of routine doses for all vaccines over the time horizon as a result of population growth and increasing coverage. In addition, it is projected that more countries will introduce newer vaccines (for example, for human papillomavirus, *S. pneumoniae*, and rotavirus) in the second decade. These vaccines are more expensive than other existing vaccines and require start-up and introduction costs, increasing total vaccine costs over time.

Similarly, the models predict that total economic benefits from vaccination will increase over the time horizon as a result of increases in coverage and new vaccine introduction. As more cases and deaths are averted from 2021 to 2030, larger total economic benefits will be realized. Measles-containing vaccines account for most of the economic benefits in both decades, in part because measles transmission and the case fatality rate are high in the absence of vaccination.

ROI reflects the average economic benefit realized per dollar invested in immunization programs. Using the cost-of-illness approach to estimate economic benefits, the economic benefits reflect averted treatment costs, earned caregiver wages, and contributions to labor productivity. Using the value-of-a-statistical-life approach, the ROI reflects a social return on investment, as it captures the intangible value placed on life that is not typically monetized using the cost-of-illness approach. Despite increases in economic benefits over time using both methods, there are disparate trends in ROI depending on the approach used to estimate economic benefits. Using the cost-of-illness approach, the ROI decreases in the second decade because economic benefits do not increase proportionally to costs, as some newer vaccines yield lower average benefits per dose compared to older vaccines. For example, the human papillomavirus vaccine has a limited impact on productivity loss because of the late onset of human papillomavirus-related cervical cancer and the assumption that the working population consists only of people ages fifteen to sixty-four. The decreasing trend in ROI calculated with the cost-of-illness approach is also apparent when applying a growth rate to the annual value of productivity (GDP per capita) (see appendix 11).<sup>12</sup>

The value-of-a-statistical-life approach examines the broader economic benefits of vaccination irrespective of productivity-related benefits. Using the standard value-of-a-statistical-life approach, the economic benefits of death averted are not adjusted for age at death (that is, the

averted death of a child and that of an adult are assumed to be valued equally by society). However, economic benefits derived using the value-of-a-statistical-life approach are based on the ratio of GDP per capita in the target country to that in the US in the year of impact, resulting in an increasing social value of lives saved as income in developing countries increases relative to the US. The cost-of-illness method weights vaccines that combat diseases with high child fatality rates, such as measles, more heavily than the value-of-a-statistical-life approach. Given these differences, ROI using a cost-of-illness approach decreases over the course of two decades, whereas ROI using a value-of-a-statistical-life approach remains relatively constant during the same period. Although neither approach shows an increase in ROI in the second decade, a sub-analysis of the incremental increase in investment beyond 2020 showed a positive ROI (see appendix 12).<sup>12</sup>

This study focuses on the same set of pathogens and countries targeted by Ozawa and colleagues;<sup>6</sup> however, the difference in definitions of model components, data inputs and sources, and underlying methodologies warrants caution for directly comparing the ROI estimates for the period 2011–20 from two studies. For economic benefits, in addition to updating data for wages and facility costs, our approach to estimating productivity loss is more conservative, and the value-transfer method for estimating the value of a statistical life is distinct from the full-income approach used by Ozawa and colleagues<sup>6</sup> (see appendix 13).<sup>12</sup> For immunization program costs, the major difference lies in the definition, data sources, and imputation method for immunization delivery cost, as well as key assumptions about the relationship between delivery cost per dose and vaccine coverage rate (see appendix 14).<sup>12</sup>

Nevertheless, we were able to conduct a comparison between two studies for years (2011–17) for which historical vaccine price data were available. For example, we found that the historical average weighted vaccine prices for *S. pneumoniae*, human papillomavirus, and rotavirus vaccines were, on average, 18 percent lower than the projected average weighted prices (data not shown). The pentavalent vaccine price alone decreased by 19 percent, on average, between 2011 and 2017, driven by a 57 percent decrease in 2017 resulting from a new vaccine supply agreement between UNICEF and manufacturers.<sup>45</sup> The reduction in new vaccine prices signifies the global immunization community's successful efforts to increase the affordability of new vaccines,<sup>46</sup> which should be further promoted in future decades while maintaining a competitive market

landscape. Furthermore, our analysis shows that the actual introduction of newer vaccines was slower than in earlier projections for the Decade of Vaccines. The delays in introduction may have been driven by exogenous factors such as vaccine supply constraints and implementation barriers, suggesting the need for a broader focus on market shaping and health systems functioning to improve vaccine access.

## Policy Implications

The global ROI estimates from this study will inform country policy makers and decision makers in funding agencies and contribute to resource mobilization efforts for immunization programs to reach the goals set by the global community as part of Immunization Agenda 2030<sup>9</sup> and Gavi's new five-year strategy.<sup>47</sup> Our future research will focus on country-specific ROI estimates that could be used to inform resource allocation decisions at the country level.

Potential users of ROI estimates could use either the cost-of-illness approach or the value-of-a-statistical-life approach according to their policy questions of interest. Insights from the ROI using the cost-of-illness approach will inform

decisions that require consideration of the budgetary and macroeconomic aspects of immunization. In contrast, the value-of-a-statistical-life approach captures broader economic benefits of immunization beyond those attributable to wages and averted costs. This study applied a standardized method for the value-of-a-statistical-life approach that will increase comparability to ROI estimates for other interventions and facilitate the prioritization of health- and social-sector investments.

## Conclusion

The results of this study demonstrate the upward trend of total economic benefits from immunization using the cost-of-illness and value-of-a-statistical-life approaches and immunization program costs from 2011 to 2030. Two analytical methods confirmed the expected continued high ROI from immunization programs in the next decade despite the disparate trends in ROI over time resulting from the differences in valuing economic benefits. Sustained investment and commitment to increasing access to vaccines will be vital to attaining the projected ROI in the coming decade. ■

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