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Methodology for key projections in the Gavi 2021-2025 Investment Opportunity

The Gavi 2021-2025 Investment Opportunity presents projections of the number of children we expect countries to immunise with Gavi support and the associated health and economic impacts. This technical appendix summarizes the methodology used to derive these projections and other key pieces of evidence.

Underlying assumptions and forecasts

There are two key components underlying the impact projections. The first is how we define the support Gavi provides to countries. The second is the set of assumptions that are used to produce forecasts of future immunization coverage for vaccines in the Gavi portfolio. The following section describes these in more detail.

Gavi support

Like other institutional investment cases in the health space, Gavi takes a contribution perspective to reflect the impact of immunization activities undertaken by countries with the support of the Alliance. Nevertheless, historically and for this investment case, Gavi "support" is defined narrowly to only count the impact of the new vaccines that Gavi has helped each country introduce and scale-up, as opposed to counting the total impact of all immunization activity across Gavi-supported countries.[1]

Effectively, Gavi counts the impact of vaccinations for which it provides direct financial support or catalytic support. The former includes financing to countries for new vaccines regardless of country transition phase and co-financing requirements, while the latter is counted during the five-year period immediately following a country's transition out of Gavi direct support for a particular vaccine, and is limited to the following cases:

- Countries that introduce a vaccine with Gavi support and continue to finance routine delivery after Gavi support concludes,
- Countries that finance routine delivery of a vaccine on their own after Gavi finances the launch of the vaccine through a catch-up campaign,
- Countries that have access to Gavi-negotiated lower prices even though self-financing the vaccine (e.g., PCV and HPV).

In the 2021-2025 period, approximately 90% of future deaths averted are expected to come through direct support.

[1] Gavi "support" excludes the impact of vaccines that Gavi funds but did not help a country introduce, for example first dose of measles component of the measles-rubella vaccine.

The 2021-2025 Investment Opportunity impact projections includes supported vaccines delivered through routine systems and campaigns, including those currently in the Gavi portfolio and the 6 new vaccines approved by the Gavi Board in November 2018 under the vaccine investment strategy (VIS), as follows: pentavalent, yellow fever, inactive polio (IPV), pneumococcal (PCV), rotavirus, measles second dose, measles-rubella, human papillomavirus (HPV), meningitis A (Men A), Japanese encephalitis (JE), typhoid conjugate vaccine (TCV), diphtheria, tetanus, pertussis-containing (DTP) boosters, hepatitis B birth dose, preventive cholera, rabies post-exposure prophylaxis, meningitis multivalent conjugate, and if available, respiratory syncytial virus (RSV).

Vaccine coverage forecasts

Future coverage of vaccines in the Gavi portfolio is based on analyses that are linked to Gavi's financial forecasts. These projections – known as the operational forecast (OP) – forecast dose requirements for countries based on their historical trend of consumption of existing vaccines. This forecast of dose requirements is translated into the number of people immunized and is updated on an annual basis. Gavi forecasts assume likely dates of vaccine introduction based on non-binding expressions of interest from eligible countries, applications to Gavi for vaccine support, intended introductions as reported to the World Health Organization (WHO) and assessment of country capacity to introduce a specific vaccine in a specific time frame. Following introduction, coverage of new vaccines are typically assumed to reach coverage of a reference vaccine (e.g., DTP3) within two to three years or longer for large countries, after which coverage is assumed to increase 1 percent per year up until a maximum of 90% or 95% depending on the vaccine.[2]

The future number of individuals expected to be immunized with different vaccines in the Investment Opportunity is based on Gavi's latest operational forecast ("OP16"), released in November 2018.[3] Since Gavi ultimately reports on progress on increasing routine immunization coverage using WHO/UNICEF National Immunisation Coverage estimates (WUENIC), the routine immunization rates in the OP16 were adjusted so that the implied coverage in 2018 is consistent with historical coverage in 2017 as reported in the July 2018 update of WUENIC. No adjustment was made for future campaigns or new introductions.

Due to higher uncertainty and more recent information, two vaccine programs' OP16 forecasts were updated since November 2018 for the Investment Opportunity:

[2] Lee, Lisa A., et al. "The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance." Vaccine 31 (2013): B61-B72.
[3] The latest aggregate vaccine volume forecast ("Base Demand Forecast" v16) is publicly available at: https://www.gavi.org/library/gavi-documents/supply-procurement/gavi-base-demand-forecast/

- HPV: Considering the recent HPV vaccine supply shortages, the OP16 HPV forecast was updated in April 2019 to reflect the latest information available on various supply and programmatic scenarios.
- TCV: As typhoid containing vaccine is a new Gavi program,[4] the information on country demand is preliminary and evolving continuously. The OP16 forecast assumptions were updated for the Investment Opportunity based on early OP17 assumptions to reflect the current (July 2019) view on uptake of the vaccine.

In addition to using Gavi forecasts, sensitivity analyses that relied on coverage forecasts provided by the University of Washington Institute for Health Metrics and Evaluation (IHME) were conducted for vaccine programs where IHME forecasts were available.[5]

Number reached with Gavi-support: 300 million in 2021-2025 and 1.1 billion by 2025 [Endnote 11]

The number reached corresponds to Gavi's strategy indicator of unique children immunised,[6] and refers to the total number of children vaccinated with the last recommended dose of any Gavi-supported vaccine delivered through routine systems, corrected on a country-by-country basis so that children receiving multiple vaccines are not double-counted. The indicator is calculated as the count of children immunized with the Gavi-supported vaccine achieving the highest projected coverage in a country each year (usually pentavalent vaccine) summed across all countries. Because of the focus on routine programs, the number immunised through campaigns and other supplementary immunisation activities are excluded. Sensitivity analyses incorporating IHME coverage forecasts where available led to similar projections of the number of unique children immunized (approximately 2% lower in 2025 as compared to Gavi's internal forecasts).

Health systems touchpoints catalyzed: 1.4 billion in 2021-2025 [Endnote 17]

This indicator represents a count of the distinct health system contacts that a child has when vaccinated with Gavi-supported vaccines through routine systems, aggregated across all children immunised each year. In order to compute this number, we first specify 4 groups of vaccines that would be on the same schedules:

[4] Gavi opened a new funding window in late 2017, with the first applications submitted in early 2018, and introductions starting in 2019. Additional information available on the Gavi website at: https://www.gavi.org/support/nvs/typhoid/

[5] IHME vaccine forecasts were available for the following vaccines: Haemophilus influenzae type b (Hib), Measles 1st and 2nd dose (MCV1 and MCV2) and rotavirus. The forecasts were obtained through personal communications and were used by IHME as one of the inputs to forecast life expectancy and cause-specific mortality in 195 countries. Additional information available from: Foreman, Kyle J., et al. "Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories." The Lancet 392.10159 (2018): 2052-2090.

[6] Gavi Strategy 2016-2020 Indicator Definitions, https://www.gavi.org/results/measuring/2016-2020-indicators/

(1) pentavalent, PCV and rotavirus vaccines for which a full course of vaccinations requires 3 health system visits, (2) measles and measles-rubella which require 2 visits, (3) HPV which requires 2 visits, and where relevant, (4) yellow fever which requires 1 visit. We then count the number of contact points with the health system required to complete the vaccination series for children immunised with the Gavi-supported vaccine achieving the highest projected coverage in each vaccine group in a country each year and sum up the results across countries. Because we are interested in touchpoints with the health system, campaigns and other supplementary immunisation activities are excluded.

Of note, the Investment Opportunity states the following: *Each year, routine immunisation programmes in these [Gavi-supported] countries deliver over 750 million doses of vaccines to over 65 million children* (p. 13).[7] This number is different from the above and is an indicator of the increased complexity for health systems to deliver a large number of vaccines through routine systems. It refers to the total number of administered doses across all vaccines used to immunise children in 2017 in Gavi 68 countries through routine systems,[8] summed across countries. The following vaccines are included in the calculation: hepatitis B birth dose, Bacillus Calmette–Guérin (BCG), measles and measles-rubella, JE, Men A, yellow fever, polio, IPV, pentavalent, PCV, HPV and rotavirus. The country-specific number of children immunised with a complete course of each vaccine was computed using the WUENIC July 2018 estimates of vaccine coverage multiplied by UN population estimates of the relevant target population. The number of administered doses per completed vaccine course was based on the WHO recommended vaccine schedule.

Health impact: 7-8 million future deaths averted in 2021-2025, 22 million by 2025 [Endnote 11]

Gavi relies on academic disease modelling groups to estimate health impact figures, with previous peer reviewed publications outlining the approach.[9] In 2017 the coordination of these modeling groups and the aggregation of impact estimates shifted from the Gavi Secretariat to the Vaccine Impact Modelling Consortium (VIMC), which is led by a secretariat based at Imperial College London. The primary aim of the consortium is to coordinate vaccine impact modelling efforts and to deliver a more efficient and transparent approach to generating disease burden and vaccine impact estimates. In addition, the Consortium works on aggregating the estimates across a portfolio of ten vaccine-preventable diseases and further advancing the

[7] This paragraph provides more details to the explanation in endnote 23 of the main document.
[8] Gavi eligible countries at the beginning of the 4.0 strategy period
[9] See for example:
Lee, Lisa A., et al. 2013
Ozawa, Sachiko, et al. "Return on investment from childhood immunization in low-and middle-income countries, 2011–20." Health Affairs 35.2 (2016): 199-207.
Ozawa, Sachiko, et al. “Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001–2020.” Bulletin of the World Health Organization 95 (2017): 629-638 /

research agenda in the field of vaccine impact modelling. Gavi provides half of its annual funding, with the other half provided by the Bill and Melinda Gates Foundation (BMGF), and it is guided by an independent Scientific Advisory Board with representatives from WHO, UNICEF, UNFPA, Wellcome Trust, Princeton University and the Johns Hopkins School of Public Health.

Background on VIMC models

The VIMC Secretariat coordinates the work of 18 academic research groups with each group estimating the impact of a specific vaccine based on a counterfactual in which no vaccines are administered.[10] Inputs and outputs are standardized by the VIMC Secretariat to ensure comparability across the disease models. Full model runs are conducted every two years with the latest version of the models (last full model run in November 2017), and interim updates are conducted bi-annually, coinciding with the updates to the WUENIC coverage estimates and the Gavi operational forecast.

To date and to ensure consistency with past reporting and targets for the 2016-2020 strategy period, Gavi reports on impact based on estimates from one "focal" model per disease. Over the past two years, the VIMC has expanded the breadth of modeling activity to the extent that there are now at least 2 different models per disease,[11] which is important for accounting for uncertainty in estimated impact due to model differences. The ranges of total impact that are presented in the Investment Opportunity draw on estimates from the focal models that have been used historically for Gavi reporting, as well as the estimates from the latest model averages that are now computed by the VIMC to incorporate the additional information obtained from having multiple models per disease. These methods are described in detail in a VIMC working paper[12] and will be published in an academic journal.

The impact models that are included in the VIMC are listed in the following table, with more information available on the VIMC website[13] and the supplementary material of the working paper.[14]

[10] For vaccines with multiple delivery strategies (e.g., measles), the counterfactual is calculated as the incremental impact of each delivery strategy. For details see the "Technical description of impact estimation methods and VIMC impact estimates" on the VIMC website at https://www.vaccineimpact.org/resources/

[11] The VIMC recently added a second yellow fever model, but the results from the second model were not available at the time of the development of the Investment Opportunity

[12] Li, Xiang., et al, "Estimating the health impact of vaccination against 10 pathogens in 98 low- and middle-income countries". Pending publication in late 2019, a pre-print version can be accessed here: https://medrxiv.org/cgi/content/short/19004358v1

[13] https://www.vaccineimpact.org/

[14] Pending publication, the model descriptions from the supplementary materials are available on https://www.medrxiv.org/content/10.1101/19004358v1.supplementary-material

Table 1 Modelling groups and model types included in VIMC

Pathogen/vaccine	Lead institution for model	Model type
Hepatitis B (HepB)	Center for Disease Analysis	dynamic
	Imperial College London	dynamic
	Independent (model developed by Goldstein et al. 2005[15])*	static
Human papillomavirus (HPV)	Harvard School of Public Health*	static
	London School of Hygiene and Tropical Medicine (LSHTM)	static
Haemophilus influenzae type B (Hib)	Johns Hopkins University*	static
	LSHTM	static
Japanese encephalitis (JE)	Oxford University*	dynamic
	University of Notre Dame	dynamic
Measles (measles)	LSHTM	dynamic
	Pennsylvania State University*	dynamic
Neisseria meningitidis serogroup A (MenA)	University of Cambridge	dynamic
	Kaiser Permanente Washington*	dynamic
Streptococcus pneumoniae (PCV)	Johns Hopkins University*	static
	LSHTM	static
Rotavirus (rota)	Johns Hopkins University*	static
	LSHTM	static
Rubella (rubella)	Johns Hopkins University	dynamic
	Public Health England*	dynamic
Yellow fever (YF)	Imperial College London*	static

*Focal models: models used historically to report on Gavi impact

Health impact projections in the Investment Opportunity

The future deaths averted presented in the Investment Opportunity are calculated relative to the timing of the intervention and reflect the long-term impact of vaccination.[16] This is done by assigning model-based estimates of future deaths

[15] Goldstein, Susan T., et al. "A mathematical model to estimate global hepatitis B disease burden and vaccination impact." International journal of epidemiology 34.6 (2005): 1329-1339.

[16] The VIMC Secretariat aggregates the results generated by modeling groups using 3 different approaches. The first provides the cross-sectional view of impact in a particular calendar year, the second provides the long-term impact of vaccines by looking at the total number of future deaths averted over the lifetime of annual vaccinated birth cohorts, and the third provides an intervention view, by summing the future impact across all vaccinated cohorts attributed to the year vaccination occurred. The lifetime cohort and intervention views produce fairly similar results as both capture the

averted back to the year in which vaccines were administered. This approach links financing and vaccine delivery to impact irrespective of the timing of benefits and helps to put all vaccines on a comparable level even though effects vary by age (e.g., the benefits of measles containing vaccine occur soon after vaccination, whereas the benefits of hepatitis B and HPV vaccines are realized decades later). More details on this approach to calculating impact, and comparison to alternative approaches considering cross-sectional impact and impact over the lifetime of a vaccinated cohort, are presented in a VIMC technical note, available on the VIMC website at https://www.vaccineimpact.org/resources/.

The impact estimates in the Investment Opportunity were computed directly from the January 2019 VIMC interim update (201710-201810 touchstone), which incorporates the 2018 update of WUENIC and Gavi's OP16, with some exceptions, as follows:

- HPV: Projections of future deaths averted from HPV vaccination were generated from updated Gavi April 2019 forecasts of HPV vaccine introductions and coverage levels, reflecting new supply and programmatic scenarios. The number of girls expected to be vaccinated based on these updated forecasts were multiplied against the VIMC country specific impact ratios (i.e., deaths averted per person immunised) from each HPV model to obtain projected deaths averted. In the Investment Opportunity (Figure 4, p. 12), the base case is presented, along with lower and higher bounds to reflect uncertainty in future supply. The original OP16 based estimate is also reported (p.11) when discussing the potential impact under a non-supply-constrained scenario.
- Yellow fever: Because the VIMC currently only has one yellow fever model, we used two different versions of the model – the 2015 and 2017 versions (respectively the 201510-201810 and 201710-201810 touchstones)— to account for potential uncertainty due to model specifications. The earlier version of the model was used as the 'focal' model and the 201710-201810 model, which incorporates new assumptions around case fatality rates, was used as the alternative.
- TCV: Since the VIMC has not yet incorporated a typhoid model, future deaths averted were estimated based on the average impact rate of 0.7 deaths per 1,000 immunised, an estimate generated by the Yale School of Public Health in 2017 to inform Gavi's considerations on opening a TCV funding window.[17] This impact rate was multiplied by the estimated number immunised under different demand scenarios in the July 2019 updated forecast. In the Investment Opportunity (Figure 4, p.12), the base case is presented along with lower and higher bounds to reflect uncertainty in uptake.

impacts of vaccines with delayed impact, namely hepatitis B and HPV vaccine. The VIMC technical note available at https://www.vaccineimpact.org/resources/ describes these three approaches and presents a comparable set of results to illustrate their similarities and differences.

[17] Typhoid conjugate vaccine support window- Annex B
https://www.gavi.org/about/governance/gavi-board/minutes/2017/29-nov/

- VIS vaccines: Impact estimates are based on the VIS 2018 investment case presented to the Gavi Board in November 2018.[18] In the Investment Opportunity, the estimates are presented as a range with low and high values representing the lower and upper ranges of potential health impact outcomes of each VIS candidate (Table 2). The range reflects the use of multiple disease impact models per vaccine, and considers only the baseline scenario for demand, burden of disease, vaccine efficacy and other parameters.

Table 2 Estimated future deaths averted from Gavi supported VIS vaccines, 2021-2025*

Vaccine	Deaths averted
DTP booster	6,900
Hepatitis B birth dose	11,300 - 56,000
OCV	8,100- 13,600
Rabies post-exposure prophylaxis	5,800
Meningitis	10,200 – 17,300
RSV	700 – 3,400
Total	43,400 – 90,400

Based on analysis conducted for the November 2018 VIS Board Decision. Ranges reflect only the base-case scenario estimated using different models per disease
*Rounded down for presentation, unrounded totals are 43,423 – 90,493

To arrive at the overall projection of 7-8 million future deaths averted by countries with the help of Gavi support in 2021-2025, we conducted multiple analyses with the aim of getting to a range of likely total impact. The analyses included using impact estimates from multiple models for the same disease and using alternative coverage forecasts. We focused on the vaccines in the current VIMC modeling portfolio, as these will account for the bulk of the impact in the next strategy period.[19]

For continuity and comparability with previous strategy periods, we started with focal model estimates. We then looked at the results from model averages (similar to what the VIMC presents in its working paper) as well as from the mix of models generating the lowest and highest estimates to understand the bounds of potential total impact in the next strategy period. For model averages, we approximated lower and upper

[18] Vaccine investment Strategy – Annex B - VIS 2018 candidates cost, impact and case for investment
https://www.gavi.org/about/governance/gavi-board/minutes/2018/28-nov/
[19] We estimate between 140,000 to 310,000 future deaths averted from VIS and Typhoid in the next strategy period, less than 5 percent of the total.

uncertainty bounds applying the ratio of deaths averted to the 95% confidence intervals bounds calculated by the VIMC in their upcoming academic paper.[20]

As shown by the disease-specific vaccine impact rates (Table 3) there is wide variation in the estimates due to model differences. Point estimates (Table 4) using focal models and the model averages yield ~ 7 and ~8 million future deaths averted respectively, with total impact potentially ranging somewhere between ~5 and ~10 million looking at the models that generate the lowest and highest impact estimates for each disease.

Table 3 Deaths averted per 1,000 fully vaccinated persons (FVPs)

Vaccine/ Pathogen	Focal model	Model averages	Model minimum	Model maximum
PCV	2.7	2.2 (1.0 - 4.0)	1.8	2.7
Rota	0.7	0.8 (0.5 - 1.1)	0.7	0.9
Pentavalent HepB	10.1	15.0 (11.7 18.3)	7.2	24.1
Pentavalent Hib	3.6	2.7 (1.1 - 4.0)	1.8	3.6
Measles and rubella Measles	4.2	4.2 (0.0 - 9.7)	3.6	4.8
Measles and rubella Rubella	0.2	0.2*	0.1	0.2
YF	3.5	5.2 (1.5 - 9.9)	3.5	5.2
MenA	1.3	0.8 (0.3 - 1.5)	0.4	1.3
HPV	17.6	18.1 (12.7 - 20.4)	17.1	19.1
JE	0.4	0.5 (0.0 - 21.9)	0.4	0.6

*uncertainty bounds around model averages not available

[20] The confidence intervals in the VIMC paper were calculated for both the estimates calculated from the cross-sectional view and over lifetime of vaccinated birth cohorts. We used the latter to estimate the bounds around the point estimates from the model averages shown here, which are calculated with respect to the year vaccination occurs.

Table 4 Estimates of future deaths averted with Gavi support 2021-2025*

Vaccine/ pathogen	Focal model	Model averages	Model minimum	Model maximum
PCV	700k	550k (250k - 1m)	470k	700k
Rota	150k	150k (100k-250k)	150k	190k
Pentavalent HepB	2.1m	3.1m (2.4m - 3.8m)	1.5m	5m
Pentavalent Hib	750k	550k (200k - 850k)	350k	750k
Measles and rubella Measles	1.4m	1.4m (15k - 3.3m)	1.2m	1.6m
Measles and rubella Rubella	76k	50k**	30k	100k
YF	700k	1m (250k- 2m)	700k	1m
MenA	100k	71k (25k-100k)	30k	100k
HPV	950k	1m (700k - 1.1m)	950k	1m
JE	5,000	7k (200 - 300k)	5k	9k
Total	~7m	~8 m	~5 m	~10m

*Numbers rounded down for presentation – based on the unrounded numbers, the totals are 7.07m for the focal model, 8.16m for model averages, 5.51m for model minimum and 10.39m for model maximum
** uncertainty bounds not available

To test the sensitivity of our results to the OP assumptions, we used IHME coverage forecasts where available for routine programs instead of the OP16-based forecast, and calculated deaths averted using the focal and model averages by multiplying country-antigen level impact ratios with the IHME expected number immunised. The IHME-based coverage forecasts yielded future deaths averted projections that were 3 to 7 percent lower at the portfolio level as compared to OP-based forecasts.
More details on impact projections are available in the VIMC working paper mentioned above, which presents results from 2000-2030 based on cross-sectional and lifetime cohort approaches for aggregating vaccine impact using model averages for 10 pathogens in 98 low- and middle-income countries as well as in Gavi

eligible countries (Gavi 73). For the latter, it considers both Gavi and non-Gavi supported programmes. As such, the estimates in the paper are larger than those presented here, especially for measles as the Gavi investment opportunity estimates exclude the impact from the first dose of the measles vaccine. The VIMC paper also uses a previous version of the Gavi operational forecast (OP15) and does not incorporate the more recent updates to forecasted coverage.

Economic benefits generated through Gavi-support: 80-100 billion in 2021-2025 [Endnote 14]

Similarly to the health impacts, estimates of economic benefits generated by Gavi-supported immunizations are computed by an external academic institution, the Decade of Vaccine Economics (DOVE) research group, housed at the International Vaccine Access Center (IVAC) at Johns Hopkins University. DOVE aims to generate economic evidence on vaccine impact in LMICs, focusing on building economic models to estimate the cost of illness, return-on-investment, and the cost of financing vaccine programs. It is funded by the BMGF and is guided by a Steering Committee comprised of BMGF, Gavi Secretariat, WHO, UNICEF, World Bank, IHME, PAHO, and the Harvard School of Public Health.

DOVE-cost of illness (DOVE-COI) models[21] serve as the primary method for estimating economic benefits. The models calculate the value of averting short and long-term costs associated with the diseases that Gavi-supported vaccines protect against and use estimates of cases and deaths from the VIMC focal models (201710-201810 touchstone with yellow fever estimates coming from the 201510-201810 touchstone). The results reflect the incremental impact of Gavi-funded vaccinations based on the coverage estimates from OP16.

The short and long-term costs measured by the COI models include: (1) acute treatment costs associated with a specified illness; (2) transportation costs associated with a specified illness; (3) caretaker wages lost because of a child's illness; (4) productivity losses that occur due to premature death; and (5) productivity losses due to disability. The detailed methodology on how each of these costs are computed and data sources are available on the Immunization Economics website at http://immunizationeconomics.org/dove-roi.

[21] Ozawa, S. et al. "Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001–2020." Bull World Health Organ. 2017 Sep 1; 95(9): 629–638
Ozawa, S., et al. "Return on investment from childhood immunization in low-and middle-income countries, 2011–20." Health Affairs 35.2 (2016): 199-207.
Stack, M., et al. "Estimated economic benefits during the 'decade of vaccines' include treatment savings, gains in labor productivity." Health affairs 30.6 (2011): 1021-1028.

The human capital approach was used to determine the economic impact of lost productivity due to disability and death. This approach uses the discounted lifetime earnings of an individual in full health as an approximation of the economic value of their life. Since productivity loss due to deaths averted constituted the largest portion of the economic benefits (>90 percent), sensitivity analyses around the assumption of the value of productivity were conducted. In the DOVE-COI models, GDP per capita is used as an analogue for the economic contribution of affected individuals in each year and assumes that individuals are economically productive between ages 15 and 6422 and that labor participation is 100%. The main analysis assumes constant value of productivity, using the 2018 value of GDP per capita. Sensitivity analyses incorporated a growth rate for GDP per capita as a proxy for the increasing value of labor productivity. This assumption doubles the estimates of economic benefits, which suggests that the main estimates of economic benefits from Gavi-supported vaccinations are conservative. In addition, it is important to note that the DOVE estimate include 10 antigens and exclude the newer and planned vaccines in the Gavi portfolio, such as TCV and VIS vaccines.

Other key data in the investment case

Vaccine preventable deaths in children 2000- 2017 [Endnote 4]

We computed the percentage decline in vaccine preventable deaths (VPDs) from 2000 to 2017 in under-five-year-olds based on existing burden of disease estimates. The focus of the analysis was on 10 vaccine preventable causes of death, which included: measles, diphtheria, tetanus, pertussis, hepatitis B, Haemophilus influenzae type b, pneumococcal disease, rotavirus diarrhoea, meningococcal meningitis, and yellow fever. We aggregated the estimated annual number of under-five deaths for each cause across countries to obtain global totals, and then computed the percentage decline from 2000 to 2017.

No organization produces specific mortality estimates for all 10 of these causes of death, so we relied on two main sources of estimates. The first set of estimates come from the World Health Organization and Johns Hopkins University. The second set of estimates come from the Institute for Health Metrics and Evaluation at the University of Washington, which publishes the Global Burden of Disease study each year. As we had two main sources of burden estimates, we computed one series of total VPD deaths based on WHO/Johns Hopkins estimates, filling in values for missing diseases where necessary with estimates from IHME, and we computed a second series of VPD deaths based on IHME estimates, filling in values for missing diseases where necessary with estimates from WHO/Johns Hopkins. While slightly overlapping, having two sets of estimates has the advantage of providing

[22] OECD definition of the working age population

some indication of the uncertainty due to different estimates approaches. The following table describes the sources we used by cause.

Table 5 Sources for vaccine preventable causes of death in under-five-year-old children[23]

	WHO based estimates	IHME based estimates
Measles	WHO	GBD 2017
Diphtheria	WHO	GBD 2017
Tetanus	WHO	GBD 2017
Pertussis	WHO	GBD 2017
Hepatitis B	GBD 2017	GBD 2017
Haemophilus influenzae type b	Johns Hopkins	Johns Hopkins
Pneumococcal	Johns Hopkins	Johns Hopkins
Rotavirus	WHO	GBD 2017
Meningococcal meningitis	GBD2017	GBD 2017
Yellow fever	WHO	GBD 2017

The WHO-based estimates and the IHME-based estimates are similar in terms of the total number of under-five VPD deaths. The WHO-based series suggests 630,000 children died of VPDs in 2017 as compared to 2.2 million in 2000 (71% decline), and the IHME-based series suggests 670,000 children died of VPDs in 2017 as compared to 2.1 million in 2000 (68% decline). The estimated time trends are provided in the following graphs, for both the WHO-based estimates and the IHME-based estimates.

[23] More detailed source information is as follows:
WHO estimates for measles and tetanus:
https://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html
WHO estimates for diphtheria and yellow fever:
https://www.who.int/healthinfo/global_burden_disease/estimates/en/WHO estimates for pertussis:
https://www.who.int/healthinfo/global_burden_disease/estimates_child_cod_2000_2015/en/
WHO estimates for rotavirus:
https://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/.
Johns Hopkins estimates for pneumococcal and Hib:
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30247-X/fulltext
IHME GBD 2017 study:
http://ghdx.healthdata.org/gbd-2017

Figure 1 WHO-based estimates of under-five VPD deaths

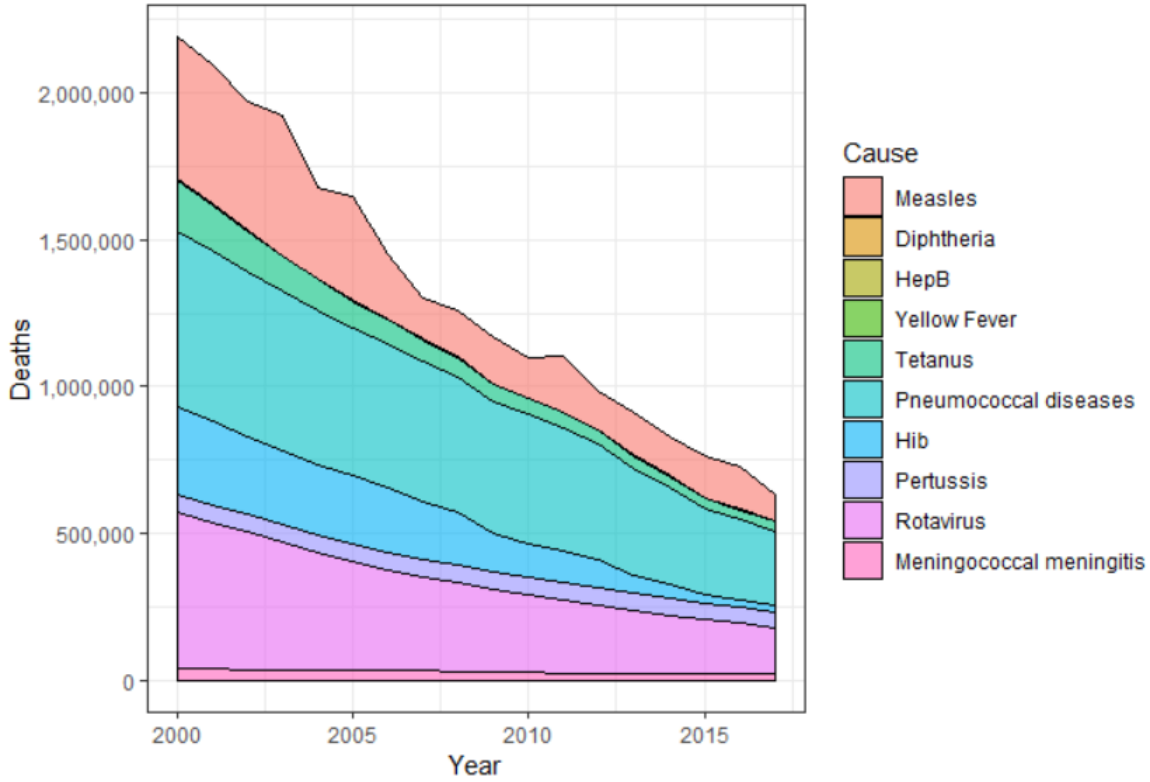
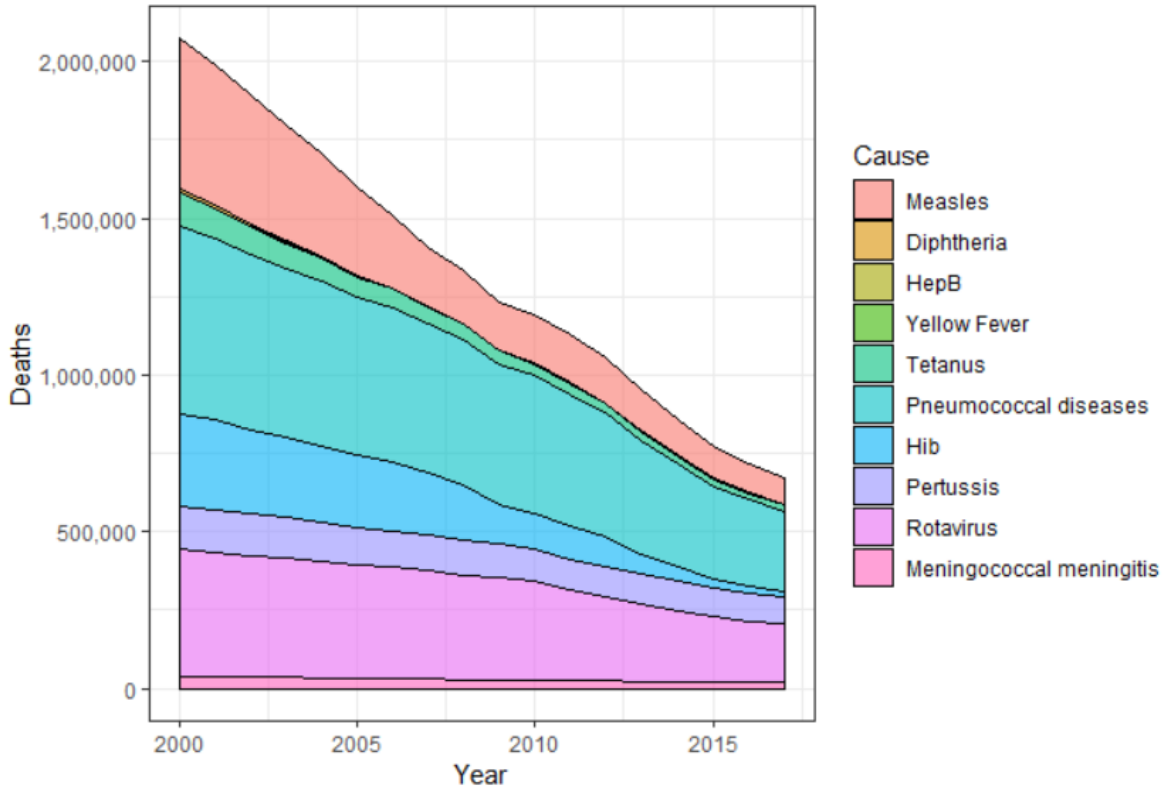


Figure 2 IHME-based estimates of under-five VPD deaths.



Proportion of zero-dose children living below the poverty line [Endnote 8]

The percentage of children living below the poverty line in Gavi-supported countries was estimated by Fraym, a geospatial data consultancy firm specializing on Africa.[24] Their findings suggest that two out of three zero-dose children live below the poverty line.

To generate the estimate, Fraym harmonized data from a variety of sources in order to create a database that includes both vaccination and poverty indicators. Childhood vaccination data were obtained from the most recent large-scale household surveys including UNICEF's Multiple Indicator Cluster Surveys (MICS), USAID's Demographic and Health Surveys (DHS) and AIDS Indicator Surveys (AIS), and the World Bank's Living Standards Measurement Studies (LSMS) (Table 6). Poverty headcount data was collected from the World Bank database using two indicators: the poverty headcount ratio at national poverty lines[25] and the international poverty headcount ratio at $1.90 a day (2011 PPP),[26] which are compiled from household survey data and official government documents. Population data on the number of surviving infants was taken from the UN Population Division's World Population Prospects. The focus of the analysis was on 19 large countries that will receive Gavi support throughout 2021-2025, which are listed in Table 6.

Table 6 List of surveys used for the analysis

Country	Year	Survey
Afghanistan	2015	DHS
Bangladesh	2014	DHS
Benin	2018	DHS
Burundi	2017	DHS
Chad	2015	DHS
Congo (Democratic Republic of the)	2014	DHS
Ethiopia	2016	DHS
Kenya	2014	DHS
Malawi	2016	DHS
Mozambique	2015	AIS
Nepal	2016	DHS
Niger	2014	LSMS
Nigeria	2013	MIC
Pakistan	2018	DHS
Rwanda	2015	DHS
Senegal	2016	DHS
Tanzania (United Republic of)	2016	DHS
Uganda	2016	DHS
Zambia	2014	DHS

[24] Additional information on Fraym is available on their website at: https://fraym.io/

[25] "Poverty Headcount Ratio at National Poverty Lines (% of Population)." World Bank Data, World Bank, https://data.worldbank.org/indicator/SI.POV.NAHC.

[26] "Poverty headcount ratio at $1.90 a day (2011 PPP) (% of population)." World Bank Data, World Bank, https://data.worldbank.org/indicator/SI.POV.DDAY.

For this analysis, children were considered to be “zero-dose” if they had not received any dose of the diphtheria, tetanus and pertussis (DTP) containing vaccine by the time they were two years old.

To harmonize the poverty and immunization coverage data, Fraym mapped the distribution of wealth indexes computed from DHS, MICS, or AIS surveys to the distribution of consumption-based poverty obtained from the World Bank poverty headcount data.[27] The analysis identified household consumption amounts at different poverty headcount percentile thresholds, and then used the percentiles in the wealth index and associated them with this consumption amount. For example, if 27 percent of the Ethiopian population lives on less than $1.90 per day, then the poorest 27 percent in the DHS wealth index would be considered as living below $1.90 per day. Through this method, it was possible to translate household survey wealth indices into dollars per day consumption, the latter being more comparable across countries and providing a measure of absolute as opposed to relative poverty levels. This approach assumes that two different measures of poverty (asset index and total consumption) identify the same households as poor. While this assumption may not be ideal, it enables an estimate of poverty levels that can be linked to immunization coverage. For each country, this translation process was applied to both the poverty headcount ratio at national poverty lines and the international poverty headcount ratio at $1.90 a day.

For each country, the harmonized household survey data were used to calculate the percentage of DTP zero-dose children who live under the poverty line. These statistics were combined with estimates of the number of surviving infants to calculate the total number of zero-dose children, as well as the overall proportion of DTP zero-dose children who live under the poverty line. Both national and international ($1.90 per day) poverty lines were considered, and the final estimate was similar (in aggregate across countries) using either definition.

[27] The wealth index is an asset-based composite measure calculated using a Principal Component Analysis. For more information on the construction of the wealth index, see the following: https://www.dhsprogram.com/programming/wealth%20index/Steps_to_constructing_the_new_DHS_Wealth_Index.pdf