Routine childhood immunization (diphtheria, pertussis, tetanus, polio, BCG, measles, hepatitis B, Hib, rubella)

Authors: Makvandi-Nejad S, Kaur G, Ahmed S, Watkins D, Coates MM, Økland JM, Haaland ØA, Johansson KA

Description of condition and intervention

Immunization has been proven to be one of the most effective interventions available to protect mass populations against subsequent life-threatening infectious diseases, consequently, control and eliminate this group of diseases. Vaccination does not require any major lifestyle alterations. Many of the currently available vaccines require multiple administrations for optimal effectiveness, either to elicit adequate primary immune response or to boost response that wears off over time. It is estimated that one out of seven death among young children could be preventable in case of vaccines with 100% efficacy and 100% immunization (WHO 2020).

Prior to introduction of a vaccination programme into a national health program, as a preventive intervention, three key issues are required to be considered. 1) Whether the target disease is a public health priority, the magnitude of the disease burden in the country and the existence and effectiveness of other strategies for preventing and controlling the disease; 2) the second issue is the vaccine in question. This includes the vaccine's safety, efficacy, economic and financial attributes (i.e., cost, affordability, and cost-effectiveness), and whether the country can expect a reliable supply of the vaccine; 3) finally, the capacity of the immunization programme and underlying health system to successfully introduce the vaccine and be able to continue to provide and deliver the vaccine supply. This includes fiscal impact and financial sustainability (WHO,2014). Therefore, it is crucial to identify the challenges associated with implementation of such programme in LMICs compared to HICs. Many of the vaccine preventable deaths are usually due to the failure to obtain the vaccine in timely manner because of financial constrains or lack of access to the vaccine (Bundy et al) .

Childhood immunization series are referred to a scheme of vaccinations, administrated between the ages of 0-18 years (Summarised in Supplementary Table 1) (Source: CDC).

International guidelines for immunization (Source:CDC)

Vaccine	Treated population	Age group	Treated fraction
BCG	Total	0	1

HepB			
HepB_inj1	Total	0	1
HepB_inj2	Total	1-2 mos	1
HepB_inj3	Total	6-15 mos	1

RV			
RV_inj1	Total	2 mos	1
RV_inj2	Total	4 mos	1

DTP			
DTP_inj1	Total	2 mos	1
DTP_inj2	Total	4 mos	1
DTP_inj3	Total	6 mos	1
DTP_inj4	Total	15 mos	1
DTP_inj5	Total	4-6 yrs	1

Hib			
Hib_inj1	Total	2 mos	1
Hib_inj2	Total	4 mos	1
Hib_inj3	Total	12-15 mos	1

PCV			
PCV_inj1	Total	2 mos	1
PCV_inj2	Total	4 mos	1
PCV_inj3	Total	6 mos	1
PCV_inj4	Total	12-15 mos	1

IPV			
IPV_inj1	Total	2 mos	1
IPV_inj2	Total	4 mos	1
IPV_inj3	Total	6-15 mos	1
IPV_inj4	Total	18 mos	1
IPV_inj5	Total	4-6 yrs	1

MMR			
MMR_inj1	Total	9-15 mos	1
MMR_inj2	Total	4-6 yrs	1

MenA_conj			
MenA_conj_inj1	Total	9-12 mos	1

Intervention attributes

Type of interventions

Preventive

Delivery platform

Vaccine administered to infants and young children can be delivered in community-based primary health care, while adolescent vaccines are mainly delivered by public health units (PHUs) such as health centers and school-based immunization programs.

Equity

In addition to considerations like cost-effectiveness and health systems factors, dimensions of equity can be relevant for priority setting. The opportunity for a long and healthy life varies according to the severity of a health condition that individuals might have, so there are inequities in individuals' opportunities for long and healthy lives based on the health conditions they face. Metrics used to estimate the severity of illness at an individual level can be used to help prioritize those with less opportunity for lifetime health. FairChoices: DCP Analytics Tool uses Health adjusted age of death (HAAD), which is a metric that estimates the number of years lived from birth to death, discounting years lived with disability. A high HAAD thus represents a disease less severe in terms of lifetime health loss, while a low HAAD represents a disease that is severe on average, causing early death or a long period of severe disability. It is also possible to estimate the distribution of HAAD across individuals with a health condition. FairChoices shows for each intervention an average HAAD value of the conditions that are affected by respective interventions that have health effects. Additionally, a plot shows HAAD values for around 290 conditions (Johansson KA et al 2020).

Time dependence

Moderate level of urgency and treatment outcomes will not be highly affected by some days of delay.

Population in need of interventions

Treated population: Children in the age-group 0 to 14 years, both genders receive the intervention, based upon the immunization schedule as shown in table 1. The treated fraction is assumed 100% for this intervention.

Affected population: The population in the age group between 0 to 59 years benefit from different vaccines received at different timepoints as per immunization schedule.

Vaccine	Affected population	Age group	Affected fraction	Comments
BCG	Total	0-14	1	-
HepB	Total	0-14	1	80–90% of infants infected during the 1st year and 30–50% of children infected <6 years old develop chronic infections 30–50% of children infected before the age of 6 years develop chronic infections.
RV	Total	3 mos-3 yrs	1	-
DTP	Total	<5 yrs	1	-
Hib	Total	<2 years old	1	-
PCV	Total	<18 mos	1	-
IPV	Total	<5 years	1	-
MMR	Total	Measle:< 5 yrs Mumps: 5-9 yrs Rubella	1	-
MenA_conj	Total	Infants and Children	1	-

Disease states addressed

Diphtheria, whooping cough, tetanus; acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, liver cancer due to hepatitis B; lower respiratory infections, meningitis; tuberculosis; measles, mumps, rubella; polio; meningitis, lower respiratory infections; and diarrheal diseases are the conditions addressed by diphtheria, pertussis, tetanus vaccine; hepatitis B vaccine; HiB vaccine; BCG vaccine; measles, mumps, rubella vaccine; polio; and pneumococcal vaccine respectively.

Intervention effect and safety

Higgins et al. 2016 have evaluated the efficacy of BCG and standard titre measles containing vaccines (MCV) in a systematic review, including assessment of risk of bias, and meta-analyses of similar studies. Many of these studies were observational and few were clinical trials. They reported that BCG and MCV vaccines are associated with all-cause mortality reduction. The relative risks for BCG vaccine were estimated to be 0.70 (95% confidence interval 0.49 to 1.01) from five clinical trials and 0.47 (0.32 to 0.69) from nine observational studies at high risk of bias. For MCV, the relative risk was 0.74 (0.51 to 1.07) from four clinical trials and 0.51 (0.42 to 0.63) from 18 observational studies at high risk of bias. In a randomised, double-blinded trial in 1083 volunteers, close to 100% efficacy rate was observed when the participants received all three doses of HepB

vaccine (Szmuness et al., 1981). The efficacy of the RV vaccine depends on the mortality rate. Clark et al. in 20196 showed that in a low mortality setting (15 observation), RV vaccines for infant schedule was about 98% with a two-week follow up of final dose of vaccination and 94% after 12 months. In medium-mortality settings (11 observations), the equivalent estimates were 82% after two weeks follow up and 77% after 12 months. Finally, in settings with high mortality (24 observations), it was estimated to be 66% after two weeks of follow up and only 44% after 12 months. In three cohort studies with 3104 total participants, vaccination with one does of MMR vaccine showed to be 95% effective in preventing clinical measles among preschool children. Furthermore, one or two doses of MMR vaccine were respectively 92% and 95% effective in preventing secondary measles cases (Demicheli et al., 2012). In one study from in India, 100% % seroprotection was detected for diphtheria, tetanus, HepB and Hib following the primary immunization and for pertussis the efficacy was 95.4%-96.1% (Bairwa et al., 2012). In another phase III clinical study, 226 healthy Indian infants were immunized with a DTaP-IPV//PRP~T vaccine (PentaximTM; containing Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus and Hib). Seroprotection rates for diphtheria and tetanus were 99.1% and 99%-100% for polio. The vaccine response rates to pertussis antigens and Hib were 93.7% and 85.7%, respectively (Dutta et al., 2009). In a systematic review and meta analyses the efficacy of meningococcal C conjugate vaccine were evaluated. The effectiveness of polysaccharide vaccines was 65% – 83.7% (different age groups), while the effectiveness of the conjugate vaccines was 66% – 100%. Incidence decline of laboratory-confirmed meningococcal disease for the conjugate vaccine ranged from 77% – 100% among different ages groups (De Oliveira et al., 2017). In a systematic review the efficacy of pneumococcal conjugate vaccine was evaluated to be 63% to 74% for all serotypes (Pavia et al., 2009). In summary, the effect sizes taken from the published literature for various vaccines are mentioned below:

Vaccine	Mortality reduction	Disability reduction	Incident reduction	Prevalence reduction	Comments
BCG	0	0	0.19	0.19	-
HepB	0	0	0.95	0.95	-
RV	0	0	0.8	0.8	-
DTP	0	0	0.8/0.99/0.85	0.8/0.99/0.85	Diphtheria/Tetanus/Pertussis
Hib	0	0	0.75	0.75	-
PCV	0.64	0	0	0	-
IPV	0	?	?	?	-
MMR	0	0	0.997	0.997	-
Meningococcal conjugate	0	0	0.7	0	-

Table 1: Effect and safety of routine childhood vaccines

What happens?	No intervention	With intervention	Certainty of evidence
Prevalence (RRR*) with BCG vaccine Tuberculosis	0.9		
Prevalence (RRR) with HepB vaccine Acute hepatitis B Cirrhosis & other chronic diseases due to hepatitis B Liver cancer	0.8 0.9 0.9		
Prevalence (RRR) with rotavirus vaccine			

Diarrheal disease	0.68	
Prevalence (RRR) with DTP vaccine Diphtheria Whooping cough Tetanus	 0.8 0.99 0.85	
Prevalence (RRR) with Hib vaccine Lower respiratory infections Meningitis	 0.11 0.11	
Prevalence (RRR) with Pneumococcal vaccine Lower respiratory infections	 0.265	
Prevalence (RRR) with oral/IPV vaccine Polio	 1	
Prevalence (RRR) with MMR vaccine Measles Mumps Rubella	 1 1 0.85	

*(RRR) Relative risk reduction

Model assumptions

Table 2: Summary of model parameters and values used in FairChoices – DCP Analytical Tool

Category	DTP	Hepatitis B	HiB	BCG	Rotavirus	Pneumococcal	MMR	Polio
Intervention	Routine childhood vaccines							
Cost calculation								
Treated population	All births							
Gender	Both							
Age	Births							
Treated fraction	1							
Effect calculation								
Affected population	Those with condition							
Affected fraction age	0 to 5 years	0 to 59 years	0 to 5 years	0 to 14 years	0 to 5 years	0 to 5 years	0 to 59 years	0 to 5 years
Affected gender	Both							
Affected fraction condition	1							
Comparison	No vaccine							
Prevalence Reduction (RRR)	Diphtheria: 0.8	Acute hepatitis B: 0.8 Cirrhosis & other	Lower respiratory infections: 0.11	Tuberculosis: 0.9	Diarrheal disease: 0.68	Lower respiratory infections: 0.265	Measles:1 Mumps:1 Rubella:0.85	Polio:1

	Whooping cough: 0.99 Tetanus: 0.85	chronic diseases due to hepatitis B: 0.9 Liver cancer: 0.9	Meningitis: 0.11					

*Relative risk reduction (RRR) estimated as 1-relative risk (RR)

Intervention Cost

Intervention cost (currency & year)	Pentavalent vaccine	BCG	Rotavirus	Pneumococcal	MMR	Polio
	0.207 USD (2019)	0.00935 USD (2019)	1.425 USD (2019)	7.76 USD (2019)	0.1736 USD (2019)	0.0135 USD (2019)

Source: UNICEF prices

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Appendix

Literature Review for effectiveness & safety

This literature search is an example of a structured, focused review of literature and guidelines with level 1 of quality. Level 1: intervention inputs taken from DCP3 or generated in an ad hoc manner (e.g., quick google search found one study of cervical cancer screening cost-effectiveness that was used to create an effectiveness parameter for that intervention).

Level of evidence of efficacy studies:

1. low (expert opinions, case series, reports, low-quality case control studies)
2. moderate (high quality case control studies, low quality cohort studies)
3. high (high quality cohort studies, individual RCTs)
4. very high (multiple RCTs, metaanalysis, systematic review, clinical practice guidelines)

Appendix 1: Supplementary Materials

Table 1. Childhood immunization series (Adapted from CDC, ref)

Vaccine (Birth to 15 months	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos
HepB	1st dose	2nd dose			3rd dose			
Rotavirus (RV)			1st dose	2nd dose	1			
Diphtheria, tetanus, pertussis (DTP)			1st dose	2nd dose	3rd dose			4th dose
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	2		3rd or 4th dose[3]	
Pneumococcal conjugate (PCV)			1st dose	2nd dose	3rd dose		3rd dose	
Inactivated poliovirus (IPV)			1st dose	2nd dose	3rd dose			
Influenza (IIV)					Annual vaccination 1 or 2 doses			
Measles, mumps, rubella (MMR)					3	1st dose		
Varicella								1st dose
Hep A					4			2 dose series
Meningococcal (MenACWY-D: ≥9 mos; MenACWY-CRM: ≥2 mos)			5					

Vaccine (18 mos-18 yrs)	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
HepB	3rd dose								
Diphtheria, tetanus, pertussis	4th dose			5th dose					
Inactivated poliovirus (IPV)	3rd dose			4th dose					
						Annual vaccination 1 or 2 doses			
Influenza (IIV)	Annual vaccination 1-2 doses					Annual vaccination 1 dose			
Measles, mumps, rubella (MMR)				2nd dose					
Varicella				2nd dose					

[1]**Rotavirus vaccination**

It starts at the minimum age of 6 weeks. There are two different types of this vaccine:
Rotarix: 2-dose series at 2 and 4 months
RotaTeq: 3-dose series at 2, 4, and 6 months
If any dose in the series is either RotaTeq or unknown, default to 3-dose series.

[2]**Haemophilus influenzae type b vaccination**

It starts at the minimum age of 6 weeks

ActHIB, Hiberix, or Pentacel: 4-dose series at 2, 4, 6, 12–15 months
PedvaxHIB: 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before 12 months and dose 2 before 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **Unvaccinated at 15–**59 months: 1 dose
- Previously unvaccinated children age 60 months or older who are not considered high risk do not require catch-up vaccination.
- For other catch-up guidance, see Table 2.

[3]**Measles, mumps, and rubella vaccination**

It starts at the minimum age of 12 months for routine vaccination

Routine vaccination

2-dose series at 12–15 months, 4–6 years

Dose 2 may be administered as early as 4 weeks after dose 1.

Catch-up vaccination

Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart

- The maximum age for use of MMRV is 12 years.

[4]**Hepatitis A vaccination**

It starts at the minimum age of 12 months for routine vaccination

Routine vaccination

2-dose series (minimum interval: 6 months) beginning at age 12 months

Catch-up vaccination

Unvaccinated persons through 18 years should complete a 2-dose series (minimum interval: 6 months);
Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
Adolescents 18 years and older may receive the combined HepA and HepB vaccine, Twinrix®, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).

[5]**Meningococcal serogroup** A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra])

Routine vaccination

2-dose series at 11–12 years, 16 years

Catch-up vaccination

Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
Age 16–18 years: 1 dose

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
2011–20								
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)
2021–30								
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)
2011–30								
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.

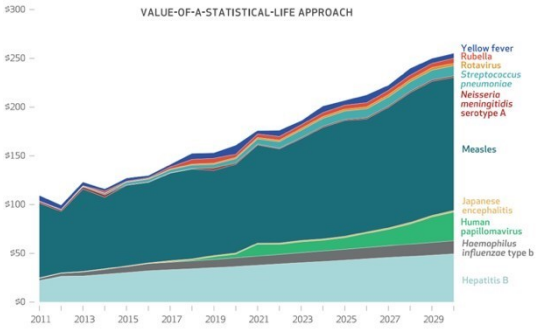
Table 2. Childhood vaccine series and their targeted infectious diseases

Vaccine	GBD nosology	GBD level	Comment
BCG	Tuberculosis	3	-
HepB	Hepatitis B	3/4	-
RV	Diarrheal diseases	3/4	Rotavirus
DTP	Diphtheria, tetanus, Whooping cough	3/4	Diphtheria, tetanus, pertussis

Hib	H influenzae type B meningitis	3/4	Haemophilus influenzae type b
PCV	Meningitis	3/4	Pneumococcal conjugate
IPV	Polio	3/4	Inactivated poliovirus
Influenza (IIV)	Upper respiratory tract infection	3/4	Sometimes lower respiratory tract
MMR	Measles, mumps, rubella	3/4	-
Meningococcal conjugate	Meningococcal meningitis	3/4	-

EXHIBIT 4

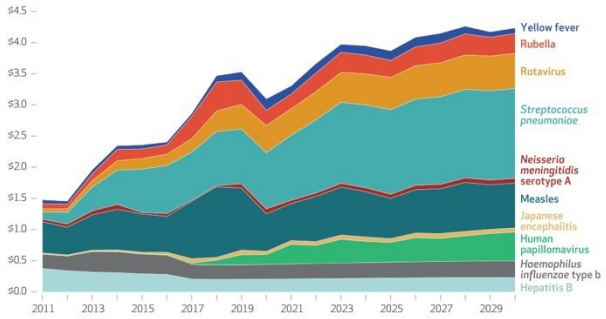
Total economic benefits derived using a value-of-a-statistical-life approach (in billions) for ninety-four low- and middle-income countries, by pathogen, 2011–30



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.

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.

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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)
2021–30								
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)
2011–30								
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.