RETHINK PRIORITIES

Vaccine delivery

Timelines and drivers of delay in low- and middle-income countries

Global Health and Development Department

December 2023 • Report

AUTHORS

Greer Gosnell — Senior Researcher II, Rethink Priorities

Erin Braid — Research Assistant, Rethink Priorities

MANAGER

Melanie Basnak — Senior Research Manager, Rethink Priorities

Vaccine delivery: Timelines and drivers of delay in low- and middle-income countries

Greer Gosnell — Senior Researcher II, Rethink Priorities
Erin Braid — Research Assistant, Rethink Priorities
Melanie Basnak — Senior Research Manager, Rethink Priorities

Suggested citation: Gosnell, G., Braid, E., & Basnak, M. 2023. Vaccine delivery: Timelines and drivers of delay in low- and middle-income countries. Rethink Priorities.
[https://rethinkpriorities.org/publications/vaccine-delivery]

Global Health and Development at Rethink Priorities

The Global Health and Development Department of Rethink Priorities is a multidisciplinary research and consulting group that seeks to disseminate actionable insights and drive positive change in the fields of global health, international development, and climate change.
https://rethinkpriorities.org/global-health-and-development

For all queries, please contact ghd@rethinkpriorities.org.

We thank Open Philanthropy for commissioning and funding this research report. The views expressed herein are not necessarily endorsed by Open Philanthropy.

RETHINK PRIORITIES
530 Divisadero St. PMB #796
San Francisco, California 94117
United States of America

About Rethink Priorities
Rethink Priorities is a research and implementation group that identifies pressing opportunities to make the world better. We act upon these opportunities by developing and implementing strategies, projects, and solutions to key issues. We do this work in close partnership with foundations and impact-focused nonprofits.
www.rethinkpriorities.org

Contents

Editorial note

This report was produced by Rethink Priorities during February and March 2023. The project was commissioned and supported by Open Philanthropy, which does not necessarily endorse our conclusions.

For this report, we investigated the global rollout of six classes of vaccines across the past 70 years, with a special focus on any delays between a vaccine's initial availability in high-income countries and its widespread availability in low- and middle-income countries. For each vaccine, we have described the rollout process, highlighted key factors contributing to delays, and created timelines of certain milestones to enable comparisons across vaccines. See below for more about our research approach.

We have tried to flag major sources of uncertainty in the report, and are open to revising our views based on new information or further research.

Executive summary

Universal introduction of vaccines in low- and middle-income countries (LMICs) has tended to lag behind introductions in high-income countries (HICs). While affordability appears to have been a large source of delay in some cases, the establishment of Gavi appears to have largely alleviated this bottleneck for countries eligible to receive support. Gavi is a global public-private partnership that supports vaccine delivery in LMICs through a variety of initiatives. Gavi support for financing vaccine supplies, developing combination vaccines, and/or coordinating vaccine delivery campaigns appears to have been instrumental in catalyzing the national introduction of vaccines for each of several diseases we consider, including polio, measles, Hib disease, rotavirus, pneumococcal disease, typhoid, and human papilloma virus (HPV). While scrutinizing specific Gavi programs and approaches was outside the scope of this report, the experts we consulted generally agreed that the affordability of vaccines should no longer be a significant barrier to their introduction in LMICs.

While delays between vaccine introduction milestones appear to be shrinking with time, there remain opportunities for improving efficiency and experiences throughout the process. Possible interventions suggested by our research include:

- Improving (accessibility of) evidence on disease burden in LMICs
- Generating robust clinical evidence of effectiveness in LMICs concurrently with evidence generation in HICs
- Designing vaccines to improve uptake and compliance in LMICs (e.g., more multivalent vaccines)
- Improving demand forecasting and implementing market shaping interventions (e.g., long-term or future procurement arrangements, stakeholder coordination, and development of vaccine criteria for manufacturers) to ensure sufficient supply
- Building capacity in LMICs (e.g., adaptability to administer to different age groups)

Experts in vaccine delivery confirmed that the above interventions are worthy of attention, and each expert highlighted the importance of context. In other words, not all solutions will work nor bottlenecks exist for each vaccine or each country, and unique solutions and bottlenecks will arise in different contexts. Several experts therefore encouraged increased involvement of national and subnational/local-level stakeholders to increase understanding of context-specific opportunities (e.g., integration with existing programs and priorities) and constraints (e.g., vaccine culture or crowded vaccine schedules) and improve accountability. Experts also emphasized the need to develop more opportunities for stakeholder learning, particularly for countries to learn from each other and from their own domestic non-health sectors.

Research approach

This research aims to understand whether and at which point(s) there are time gaps between milestones in the process from vaccine development to vaccine delivery in low- and middle-income countries (LMICs). We classify countries as LMICs if they are, or eventually become, eligible for Gavi support.[1] Similarly, "high-income countries" (HICs) are those that do not eventually become eligible for Gavi support.

[1] Note that Gavi eligibility (currently defined by Gross National Income less than or equal to $1730; see more about Gavi eligibility here) does not perfectly overlap with World Bank definitions of countries characterized by "low" and "lower-middle" income levels. While all low-income countries (GNI below $1086) — are eligible for Gavi support, not all middle-income countries (GNI between $1086 and $4255) are eligible (World Bank, 2023). Our definition of LMIC for the purpose of this report refers to currently Gavi-eligible countries.

The approach we take is to identify the years in which particular milestones were reached for eight vaccines for which VIEW-hub contains data (we exclude Covid-19 vaccines). Open Philanthropy identified the milestones on which we primarily focus:

- Initiation date of first Phase 3 trial
- Date of interim data release from Ph3
- Date of final publication of Ph3
- Date of first approval in a HIC (or by EMA)
- Date of 3rd approval in HIC (or by EMA)
- Date of first WHO prequalification
- Date of first Gavi-eligible country introduction
- Date of Gavi support (if relevant)
- Date of >10M sales in LMICs
- Date of 10th Gavi-eligible country introduction

Note: The early history of the polio, measles, and Hib vaccines dates back to the 1950s-1980s, so some of the information we identified may be less accurate given the more limited data and resources (e.g., ClinicalTrials.gov was not established until 2000, and UNICEF procurement data generally does not precede 1996). Therefore, the precise year of the first Phase 3 clinical trials and their publication, as well as the year when sales thresholds were met, is based on our best guess.

We created a spreadsheet to visualize and compare these timelines, which largely overlap with the written timelines in the following sections of this draft. In many cases, we came across additional milestones that we felt were worth noting, or there were several vaccines for a particular disease and including all information in the written timeline would have made them difficult to follow, so there may be minor discrepancies across the written and visual timelines. For each vaccine, we include what we perceive to be the top causes of delays to LMIC introduction, the written timeline, and a narrative storyline that provides more detail.

To better inform and provide context around our desk research, we conducted interviews with experts within some of the major organizational players involved in vaccine delivery to LMICs. Specifically, we spoke with International Vaccine Access Center (IVAC), Farzana Muhib and Bill Hausdorff at PATH, Lora Shimp at John Snow, Inc. (JSI), and another expert who is not named in this report.

Inactivated polio vaccines

Top causes of delay were alternatives being preferred for use in endemic countries and supply issues

1. Existence of a cheaper, more communally protective, but individually riskier polio vaccine, which was preferred for use in endemic countries.
2. Supply constraints. UNICEF paused planned distributions for two years due to insufficient supply.

Timeline: 1954-2019

1954: Large-scale field trials of the inactivated polio vaccine (IPV) (Francis, 1955)
1955: IPV licensed in the United States (WHO, 2023)

2005: Imovax Polio receives WHO prequalification (WHO, 2023)
2012: WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommends that all countries include at least one dose of IPV in their routine immunization programs (WHO, 2013)
2013: The World Health Assembly aims for all countries to include at least one routine dose of IPV by 2015 (WHO, 2013)
2013: Gavi offers support for IPV introduction (Gavi, 2013)
2014: First Gavi-supported introduction of IPV (Nepal; Gavi, 2018)
2014: ~10 million doses procured through UNICEF (Lewis et al., 2017; UNICEF, 2019)
2019: All countries include IPV in their routine immunization programs (VIEW-hub, 2023)

IPV has been used since the 1950s, but was not considered a global public health priority until 2013; after that, despite supply issues, all countries introduced IPV by 2019

Historical background

Famously, the inactivated polio vaccine (IPV) was developed by Jonas Salk in the early 1950s and tested in a large randomized controlled trial in 1954 (Francis, 1955). Following this trial, the vaccine was quickly licensed in 1955 and subsequently widely used in the United States (WHO, 2023).

In 1958 and 1959, a second polio vaccine, the oral polio vaccine (OPV) containing live attenuated virus, was tested in large trials in the Soviet Union and Czechoslovakia. For decades thereafter, **OPV was the preferred vaccine for polio reduction and elimination efforts, especially in LMICs, because it is cheaper than IPV, easier to administer, and more effective at preventing onward transmission** of the virus (Bandyopadhyay et al., 2015).

However, the live virus in OPV can itself occasionally cause paralytic disease. Furthermore, it can mutate, regain the transmissibility and virulence of the wild poliovirus, and begin to circulate, especially in communities with low vaccination rates (Bandyopadhyay et al., 2015). Therefore, **a complete eradication of polio most likely requires a transition from OPV to IPV**.

Global introduction of IPV

As HICs have eliminated polio, they have transitioned from OPV to IPV. For example, Italy began phasing out OPV in 1999, and moved to an IPV-only vaccine schedule after the WHO officially declared that the European region was polio-free in 2002 (Mele et al., 2002). Globally, OPV vaccination campaigns and other measures have been effective in reducing the incidence of polio. **As the absolute number of polio cases has declined, the proportion of polio cases attributable to OPV has increased and even become a majority**, with 2012 being the first year in which there were more cases of paralytic polio caused by OPV than caused by wild polioviruses (Sutter et al., 2014).

Both IPV and OPV were originally developed in trivalent forms, protecting against all three serotypes (i.e. strains) of the wild poliovirus. There was particular urgency around transitioning away from OPV containing poliovirus type 2, because type 2 was eradicated in the wild in 1999; all type 2 cases after that year were vaccine-derived. Furthermore, over 90% of the circulating vaccine-derived polioviruses were type 2 (WHO, 2013). In 2011, the WHO was "contemplating" a switch from the trivalent OPV (containing types 1, 2, and 3) to a bivalent OPV (containing types 1 and 3). However, this switch would leave vaccinees vulnerable to any lingering

vaccine-derived type 2 polioviruses in circulation. To mitigate this risk, SAGE recommended in November 2012 that all countries still using OPV introduce at least one dose of trivalent IPV in their routine immunization program, before making the switch from trivalent OPV to bivalent OPV (WHO, 2013).

The Polio Eradication & Endgame Strategic Plan 2013-2018, endorsed by the World Health Assembly in May 2013, **called for the introduction of at least one dose of IPV in every country by 2015, and for all use of trivalent OPV to be ended by 2016 (p. 52). In November 2013, Gavi announced that it would offer support for the introduction of IPV** into routine immunization programs. Furthermore, due to "the global health priority of polio eradication," Gavi waived the usual co-financing requirements in the case of IPV. In September 2014, Nepal became the first country to introduce IPV with Gavi support (Gavi, 2023).

Some international funding was also made available for IPV introduction in middle-income countries that were not Gavi-eligible. The Polio Oversight Board, which oversees the World Health Assembly's polio eradication efforts, allocated $45 million for this purpose in June 2014, though ultimately only $16 million was disbursed. (For more about this program, see Blankenhorn et al., 2017.)

Supply constraints have slowed adoption in some countries. **Between 2014 and 2018, due to technical issues scaling up vaccine production, only about half the doses that manufacturers contractually agreed to supply to UNICEF were actually delivered** (UNICEF, 2019), **and unforecasted demand for IPV use in campaigns (as opposed to routine vaccination programs) caused further strain on the limited supply** (Lewis et al., 2017). In March 2016, facing a global shortage of IPV, the Polio Oversight Board decided to pause or delay IPV procurement through UNICEF for 35 lower-risk countries. In 2018, availability of IPV increased, and UNICEF was able to resume supplying the 35 deprioritized countries (UNICEF, 2019).

As of April 2019, when Mongolia and Zimbabwe introduced IPV, all countries now include IPV in their routine vaccination programs (VIEW-hub, 2023).

Measles-containing vaccines

Top causes of delay were cost and limited urgency

1. Delay in the case of measles (dose 2) and measles-rubella appears to have been primarily related to cost and limited urgency to adopt, given the relatively rapid increase in universal introductions following Gavi support.

Timeline: 1963-2018

- Measles (dose 2) vaccine in black
- Measles- and rubella-containing vaccine in gray

1960: Large-scale trials of first measles vaccine, and their publication (WHO, 2023)[2]

[2] "Enders and his team tested their measles vaccine on small groups of children from 1958 to 1960, before beginning trials on thousands of children in New York City and Nigeria. In 1961 it was hailed as 100% effective and the first measles vaccine was licensed for public use in 1963" (WHO, 2023). The earliest start

1963: Licensure of two measles vaccines (Conis, 2019, p. 119), including *Rubeovax* by Merck and *Pfizer-Vax Measles-K* by Pfizer (Hendriks and Blume, 2013)[3]
1963: First universal introduction in a HIC (Iran; VIEW-hub, 2023)
1969: First "Phase 3" clinical trial begins (best guess; Fahlgren, 1988, p. 132, Table 3)[4]
1969: First universal introduction in a HIC (United States; VIEW-hub, 2023)
1970: Third universal introduction in a HIC (France, Monaco; VIEW-hub, 2023)
1971: Third universal introduction in a HIC (Bosnia and Herzegovina; VIEW-hub, 2023)
1971: First Phase 3 trial publication (Stokes et al., 1971)
1971: Licensure of first MR and MMR vaccines (Merck MMR and M-R-Vax; Immunize.org, 2021)
1974: Establishment of WHO's Expanded Program on Immunization (EPI), with measles among the first targeted diseases (WHO, 2023); MMR often used under EPI (Immunize.org, 2021)
1981: First universal introduction in a LMIC (Lesotho; VIEW-hub, 2023)
1980s and early 1990s: Over 1 million and over 10m sales, presumably[5]
1993: First measles WHO prequalification (1, 2, and 5 doses, Serum Institute of India) (WHO, 2023)
1995: First universal introduction in an LMIC (Lebanon; VIEW-hub, 2023)
2000: First MR WHO prequalification (2, 5, and 10 doses, Serum Institute of India; WHO, 2023)
2001: Establishment of the Measles and Rubella Partnership
2003: MMR WHO prequalification (1, 2, and 5 doses, Serum Institute of India; WHO, 2023)

---

date of a Phase 3 trial that comes up in a search on ClinicalTrials.gov containing "measles" is in 1998, well after the initiation of measles immunization campaigns around the globe.
Additionally, "Enders wanted to encourage other investigators and made the strain freely available. Very soon numerous other researchers (including Anton Schwarz at American Home Products and Maurice Hilleman at Merck) were also working at attenuating it further" (Hendriks and Blume, 2013).

[3] "In 1963, both an inactivated ("killed") and a live, attenuated (Edmonston B strain) measles vaccine were licensed for use in the United States. The inactivated vaccine was withdrawn in 1967 because it did not protect well against measles. The original Edmonston B vaccine was withdrawn in 1975 because of a relatively high frequency of fever and rash in recipients. A live, further attenuated (Schwarz strain) vaccine was first introduced in 1965, but also is no longer used in the United States. Another live, further attenuated strain (Edmonston-Enders strain) vaccine was licensed in 1968. These further attenuated vaccines caused fewer reactions than the original Edmonston B vaccine. In 1971, measles vaccine was licensed as a combined measles, mumps, and rubella (MMR) vaccine. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed" (CDC, 2021).

[4] Our research has indicated that Phase 3 trials generally include 300-3000 participants. Since MMR was licensed in 1971, we considered studies from Table 3 (Fahlgren, 1988, p. 132) published on or before this date and selected the only trial that contained more than 300 subjects. We assume the trial was conducted in 1969, given the product's licensure in that year.

[5] WHO coverage data for Lesotho and Lebanon only date back to 1999, so the sales estimation approach we use in the spreadsheet tab "Sales Estimates" (primarily to estimate sales for the pneumococcal vaccine) is unavailable here. Market Information for Access to Vaccines (MI4A) data for measles only dates back to 2005, and UNICEF sources (e.g., see Figure 2 here and Figure 3 on p. 4 here) provide procurement information dating back to 1996-2000; UNICEF procured >50 million doses in 1996 alone, suggesting that the date of interest is many years earlier. A resource from 1993 suggests that 131 million doses of the measles vaccines were procured by the WHO and the Pan American Health Organization, and an additional 30 million were procured outside of North America, Europe, and Japan in the 1990s (see Mitchell et al., 1993, Table 4-1), which additionally leads us to believe that sales in LMICs exceeded 1 million and 10 million several years earlier. However, the only LMICs to universally introduce the measles vaccine were Lesotho (1981), Kyrgyzstan (1986), and Tajikistan (1986), and our BOTEC for the 1980s alone suggests the 1 million sales threshold was surpassed in LMICs countries, though not the 10 million sales threshold.

2004: Gavi support for measles (dose 2) begins (Jaupart et al., 2019)
2009: 10th universal introduction in a LMIC (Pakistan; VIEW-hub, 2023)
2012: Initiation of Gavi support for MR[6] (Gavi, 2018)
2013: 10th universal introduction in an LMIC (Senegal; VIEW-hub, 2023)
2016: First region to be declared free of endemic measles by independent expert body (Region of the Americas; WHO, 2023)
2017: Initiation of Gavi support under new measles and rubella strategy (Gavi, 2018)[7]
2018: Revocation of above declaration[8] (WHO, 2023)

The most important factor in encouraging universal introduction of MCVs in LMICs appears to have been Gavi support in the 2000s (dose 2) and 2010s (measles-rubella)

A clarificatory note: The distinction that VIEW-Hub and others make between measles dose 2 (MCV2) and measles and rubella (MR) vaccines is due to the recommendation that those who receive the MR or MMR vaccine as their first dose of a measles-containing vaccine (MCV) receive a second dose, given that 15% of children "don't develop protective immunity [to measles] after their first dose" (WHO, 2023). MCV1 and MCV2 therefore refer to the first and second doses of any measles-containing vaccine (i.e. monovalent, MR, or MMR).

A measles outbreak in Boston in 1954 led doctors in the US to isolate a culture and cultivate the virus, from which they developed the earliest measles vaccine. Small-scale trials from 1958-1960 were sufficiently promising to scale trials up into the thousands of children (from New York City and Nigeria). **By 1961, doctors declared 100% effectiveness, and licensure followed in 1963** (WHO, 2023). Iran became the first HIC to universally introduce the measles vaccine in the same year (VIEW-hub, 2023).

However, **universal introduction in other HICs did not come until almost a decade later due to the need for additional research on live vs. inactivated vaccines** (particularly on tradeoffs between side effects and the duration of protection; Hendriks and Blume, 2013, p. 1394). **Additionally, in HICs, measles did not pose a major threat to children's health** and was viewed as a normal part of childhood development, so there was little urgency (and even reluctance from parents due to the "ever-increasing number of immunizing injections") to introduce the

[6] "In order to have a long-term impact on both measles and rubella control, we have invested more than US$ 600 million in large-scale measles-rubella catch-up campaigns since 2012. This catalytic support requires countries to introduce MR vaccines into their routine system after a campaign. Gavi also supports measles and measles-rubella follow-up campaigns to address immunity gaps in the population and help build population immunity" (Gavi, 2018).
[7] "2017 marked the first year of Gavi-supported measles vaccine introductions and campaigns under our new measles and rubella strategy. The bulk of our support for measles vaccine is allocated towards the combined measles-rubella (MR) vaccine, which also provides protection against congenital rubella syndrome" (Gavi, 2018).
[8] A social and political crisis in one country in the Americas led to gaps in vaccination schedules and slow responses. Measles outbreak and (eventually contained) spread led the WHO regional office (Pan American Health Organization, or PAHO) to engage in capacity building to bolster immunization and response speed.

vaccine or set target coverage levels (Hendriks and Blume, 2013, p. 1395).[9] Another early setback occurred in the **late 1990s, when The Lancet published a paper linking the measles vaccine to autism**. Coupled with the spread of misinformation by vaccine skeptics in HICs, coverage in many HICs dropped. Over ten years later, the British General Medical Council declared the study fraudulent and it was retracted.

Following the licensure of an improved measles vaccine in 1968 (Edmonston-Enders) and of the mumps (1967) and rubella (1969) vaccines, the three were combined (sometimes also with varicella) into one vaccine. While VIEW-Hub claims the first universal introduction of the MR vaccine took place in the US in 1969, other sources suggest it was not developed and licensed until 1971 (Smithsonian, 2023; Immunize.org, 2021). **In 1974, building on the rapid eradication of smallpox, the WHO's Expanded Program on Immunization** (now the Essential Program on Immunization) **turned its focus to immunizing all children against several additional diseases, including measles**, and MMR was often delivered under this program.[10]

In 1981, Lesotho (a small country landlocked in South Africa) became the first LMIC to universally introduce a measles vaccine. Kyrgyzstan and Tajikistan became the second and third LMICs to do so in 1986, twelve and seven years (respectively) before the **measles vaccine's WHO prequalification in 1993**, when the Syrian Arab Republic became the fourth. Following introduction in Lebanon in 1995, almost ten additional years passed before adoption by additional LMICs (Afghanistan and Yemen in 2004), which occurred three years after the founding of the Measles & Rubella Partnership (M&RP) in 2001 and one year after the first MMR WHO prequalification in 2003. M&RP is a partnership of several stakeholders (American Red Cross, the Bill & Melinda Gates Foundation, Gavi, the United Nations Foundation, the U.S. Centers for Disease Control and Prevention (CDC), UNICEF, and the WHO) to eradicate measles by helping countries to plan, fund, and implement measles vaccine delivery.

It was not until the early 2010s, following the introduction of Gavi campaigns[11] for measles and eventually measles-rubella under The Measles (& Rubella) Initiative — which Gavi financially supported and the International Finance Facility for Immunisation facilitated (IFFIm, 2007) — that many LMICs began to introduce these vaccines into their national

[9] Conis (2019) provides an overview of obstacles to universal introduction in the US, which we summarize here. The earliest setbacks stemmed from low motivation to vaccinate, misinformation campaigns, racial and socioeconomic divides (largely due to administration by private practice physicians serving primarily "young middle- and upper-class white families", p. 119), poor record keeping, lax enforcement of compulsory immunization laws, and improper vaccine storage in the late 1970s. Ultimately, persuasive publicity (e.g., involving celebrities, journalists, and local health departments), the spread of compulsory immunization laws due to a compelling demonstration of their effectiveness in Texarkana, and a combined vaccine that limited the number of contacts required helped bring coverage of schoolchildren to 96%. A swell of value-driven skepticism and misinformation led to setbacks in the early 1990s, but Measles is often considered to have been eliminated when President Clinton initiated an entitlement program (Vaccines for Children) in 1993 that offered vaccines to children who had historically lacked access — Native American, Alaska Native, uninsured (for vaccines), and Medicaid (p. 121). Berg and Blume (2020) discuss reasons for the ten-year delay between introduction in the US compared to Denmark and the Netherlands, which we have not read since it is somewhat outside of the scope of this research.

[10] "The word "expanded" referred to the addition of measles and poliomyelitis to the vaccines then being used in the immunization program" (Bland & Clements, 1998).

[11] "A measles campaign is a coordinated effort of health workers, volunteers, and communities to ensure that within a short period of time vaccination teams reach every child. Partners also support related activities including training, safe-injection practices and disease surveillance. The campaigns are carried out for several days for children under 15 years of age. Follow-up campaigns occur three to four years after the initial mass campaigns for children under five years of age who were born since the first mass campaign." (UN Foundation, 2002)

immunization programs. In fact, 20 LMICs universally introduced MCV2 between 2012 and 2015 (VIEW-hub, 2023). Thus, WHO prequalification appears to have had limited influence on universal introduction in LMICs.

It appears that the biggest driver of LMIC measles vaccine introductions was simply Gavi support and campaigns. According to Jaupart et al., 2019, "Gavi began supporting MCV2 (second dose) measles vaccinations specifically in 2004 and MCV1 in 2012."[12] The authors find that Gavi eligibility increased protection against measles by 10.5 percentage points after 2004 (95% CI 6-15 percentage points; see Table 1 for their range of estimates across a series of robustness checks). **However, according to VIEW-hub data, no Gavi-eligible countries universally introduced MCV2 between 2004 and 2008. Muhib (PATH) believes this gap is attributable to the lack of a "group that made it their focus to ensure countries had the evidence they needed to introduce the vaccine" and the requirement of an additional visit for vaccine administration**. She also said that 2008 was a critical year in Gavi's development (for instance, it refined its application processes).

Hib vaccines

Top causes of delay were costs, limited awareness of the disease burden, and the lag in LMIC trials

1. High costs, deriving from patent restrictions, lack of supply-side competition, and delays in multivalent vaccine development.
2. Uncertainty about disease burden.
3. Limited communication and awareness in LMICs.
4. Lag between HIC field trials and LMIC field trials, though difficult to assess the counterfactual (as costs would have remained a barrier to LMIC adoption).

Timeline: 1984-2010

1984-1988: First field trials in Alaska and Finland[13] (Heath, 1998, Table 1; CDC, 1991)
1987: First publication of a clinical study (Heath, 1998, Table 1; Eskola et al., 1987)
1987: Licensure of the Hib conjugate vaccine in the U.S. (CDC, 2021)
1989: First universal introduction in a HIC (Iceland; VIEW-hub, 2023)
1990: Third (and fifth) universal introductions (Finland, Germany, Switzerland, and the United States; VIEW-hub, 2023)
1993: Phase 3 trial initiation in The Gambia (Mulholland et al., 1999)

[12] "The earlier Gavi-supported second dose vaccine is used as an opportunity to administer a first dose for children who are not already vaccinated. However, Gavi's funding of general immunisation system support and supply chain strengthening took effect from the start, and Gavi channelled non-country-specific funding for measles vaccination programmes via several partner organisations."
[13] Most trials on ClinicalTrials.gov were initiated in 1999 or later, so earlier trials that led to licenses for older vaccines are not included in their database. While we can be sure that the trials in their database are Phase 3, such classification is usually not specified for earlier trials. Downloading the ClinicalTrials.gov data, sorting by Start Date, and identifying the first trial (and the first trial with results) suggests these dates should be Jan99-Mar00, GSK, "Immunogenicity and Reactogenicity of DTPa-HBV-IPV/Hib, Compared to DTPa-HBV-IPV and Hib Administered Separately" (with results: Dec03-Feb07, GSK, "Safety of DTPa-IPV/Hib & DTPa-HBV-IPV/Hib, Followed by DTPa-IPV/Hib Vaccine in Infants Who Received Hepatitis B Vaccine"). However, given our research indicates that several relevant studies are not in the ClinicalTrials.gov database, we rely more heavily on the literature to identify relevant studies.

1997: First universal introduction in an LMIC (The Gambia[14]), due to manufacturer donation (Gavi, 2011); by end of this year, 27 HICs had adopted (VIEW-hub, 2023)
1998: First WHO prequalification for Hib vaccine (monovalent ActHIB vaccine; WHO, 2023)
1998: Universal introduction in half of HICs (Gavi, 2011)
2000: Initiation of Gavi support for Hib (Gavi, 2011)
2001: Over 1m and over 10m pentavalent vaccines procured (UNICEF, 2017, Figure 1, p. 2)[15]
2004: 10th universal introduction in LMICs (Lithuania; VIEW-hub, 2023)[16]
2005: Gavi Board grant (four years, $37 million) for Hib Initiative[17] (Gavi, 2011)
2006: WHO SAGE global recommendation for Hib vaccine inclusion in national immunization programs (Gavi, 2011; Morris et al., 2008, p. 441)
2007: Gavi approval of $537 million for critical vaccine programs, with $370 million going toward Hib immunization (40% increase in country eligibility; Gavi, 2007)
2008: Universal introduction of Hib in half of LMICs (Gavi, 2011)
2009: Universal introduction in almost all Gavi-eligible countries (Gavi, 2011)
2010: WHO prequalification for multivalent Hib conjugate vaccine (WHO, 2023)

Early Hib conjugate vaccines were developed using evidence in HICs and ultimately integrated into a more financially viable multivalent vaccine, which became the Hib vaccine of choice in LMICs after a successful Phase 3 trial in The Gambia—followed by Gavi support—enabled their procurement

The PRP-D Hib vaccine was the first conjugate vaccine to be developed and licensed to prevent *Haemophilus influenzae* type b infection. Subsequent development of PRP-T (conjugated to tetanus toxoid), PRP-OMP (conjugated to meningococcal outer membrane protein), and PRP-CRM (conjugated to CRM_{197}) proved more efficient than PRP-D (conjugated to diphtheria toxoid), which ultimately led to the withdrawal of PRP-D from the market (Van Den Biggelaar and Pomat, 2013, p. 2527).

Initial Hib conjugate vaccine trials in 1984-1988 had proven the efficacy of the Hib conjugate vaccines in North America and Europe in the prevention of Hib meningitis, though Hib pneumonia is more relevant globally, and particularly for developing countries. Such **differences in epidemiological context,**[18] **combined with other generalizability concerns** that stemmed from the disparate findings across Finnish and Alaskan native populations in the late 1980s, **provided justification for a Phase 3 trial in The Gambia** in 1993. The decision to undertake the trial rested with the trial's Steering Committee, which included representatives from both The Gambian government and representatives from major international public health organizations (Mulholland et al., 1999, p. 750).

[14] "...large efficacy trial of a Haemophilus influenzae type B (HIB) conjugate vaccine conducted in the western part of The Gambia (Mulholland et al., 1997)" (Leach et al., 1999).
[15] Before 2000, The Gambia was the only LMIC adopter (having adopted in 1997), and they received their vaccines on donation. The UNICEF source only goes back to 2001, but given that the first Gavi-eligible country adopted in 2001, we ruled out that >1m sales in Gavi-eligible countries had been reached in 2000.
[16] Note this date conflicts with that in CDC (2008) (Figure at bottom), which suggests 10+ Gavi-eligible countries had access to the Hib vaccine by 2002.
[17] The focus of the initiative was data collection and dissemination, research, and advocacy to encourage adoption. Initiative participants included the Bloomberg School of Medicine (Johns Hopkins), the CDC, and the London School of Hygiene and Tropical Medicine.
[18] For instance, the interaction between vaccine efficacy and prevalent issues in Africa such as malnutrition, malaria, and high incidence of pneumonia could not be studied in the European and North American contexts (Mulholland et al., 1999, p. 750).

This trial was seemingly crucial in speeding up Hib vaccine delivery timelines, as it demonstrated a higher-than-expected attribution of pneumonia to Hib in this context, and **WHO recommendations were largely based on this trial** (Mulholland et al., 1999). In 1997, seventeen months following the trial's end date, **The Gambia became the first LMIC to universally introduce the Hib[19] vaccine, thanks to vaccine donations** from the manufacturer in exchange for an agreement from UNICEF to procure a particular quantity of DTP vaccines from them.

According to Gavi, **other LICs initially lacked access to the Hib vaccine due to prohibitively high costs**. Hib conjugate vaccine prices were about twice those of multivalent MMR vaccines and averaged $3.15/dose (as opposed to $1.4/dose for other vaccines under WHO's Expanded Program on Immunization; Zarei et al., 2016, p. 6). With only one manufacturer supplying UNICEF, **lack of competition caused prices to remain high for years**.

The introduction of Gavi in 2000 made financial support for the Hib vaccine available, though concerns about costs remained and were compounded by **"limited awareness and communication about the disease" and "uncertainty about Hib disease burden"** (Gavi, 2011), in part due to the difficulty in diagnosing Hib pneumonia (Mulholland et al., 1999). **Gavi's support for combining the Hib vaccine with the diphtheria-tetanus-pertussis (DTP3) and hepatitis B vaccines—creating one pentavalent vaccine[20]—reduced costs[21] and increased uptake in a major way** (Hausdorff and Muhib, PATH), and our understanding is that the DTPHb vaccine is the primary, and very likely the sole, vaccine that has been distributed through Gavi (all Gavi-eligible countries have now introduced the pentavalent vaccine; Gavi, 2023).[22] Given the importance of Gavi and its partners in lowering costs and increasing access to the pentavalent vaccine, we dive deeper into the stakeholders involved and the market shaping approaches used in a separate subsection below.

Additionally, **Gavi's Hib Initiative encouraged adoption through capacity and awareness building** (CDC, 2008). According to Muhib (PATH), this initiative and the introduction of the pentavalent vaccine were crucial given countries' limited understanding of the Hib disease burden at the time.

In addition to the availability of the multivalent vaccine, another factor considered by Zarei et al. (2016) to have been crucial to introduction in North and South America is product vialing, which one expert also mentioned in our interview. Both **multivalence and vialing "affect the vaccine wastage level, cost, reconstitution necessity, space of cold chain, and education events for medical employees"** (p. 6).

---

[19] The Gambia introduced the PRP-T Hib vaccine (Chandran et al., 2008).

[20] While Hib is often administered as a polyvalent vaccine—which are intended to improve compliance by reducing the number of injections and visits—with diphtheria, tetanus, and pertussis, Van Den Biggelaar and Pomat (2013) suggest that a conjugate vaccine including pneumococcal could improve uptake and compliance (p. 2527).

[21] "Combining five different vaccines in a single vial, pentavalent vaccine brings cost savings in terms of equipment, delivery and disposal programmes" (Gavi, 2022).

[22] For example, Wikipedia states that "In 2012, UNICEF and the World Health Organization issued and recommended a joint statement to the Immunization Division, Ministry of Health and Family Welfare, Government of India and other developing nations in separate documents about the use of pentavalent vaccines to protect against five of the leading causes of vaccine-preventable death in children. By 2013, pentavalent vaccines accounted for 100% of the DTP-containing vaccines procured by UNICEF, which supplies vaccines to a large proportion of the world's children. In 2014, South Sudan became the last of the 73 GAVI-supported countries to introduce the five-in-one vaccine." Note, however, that Wikipedia states that the first WHO prequalification for the pentavalent vaccine was in 2006, and our research suggests it was 2010.

Another barrier to early adoption in developing countries was their inability to access patented information on how to manufacture the vaccines throughout the 1990s. In 1998, the National Institute for Public Health and the Environment/Netherlands Vaccine Institute conjured a scheme wherein they would "develop commercially viable and scalable Hib conjugate vaccine production, without patent violation, by employing technology transmissible to manufacturers in developing countries," helping to overcome this bottleneck and ensure vaccine manufacturers had sustainable access to inexpensive supply of the combined vaccine (Zarei et al., 2016, p. 6).[23]

While the lag in field trial implementation (start date of 1984 in Finland, compared to start date of 1997 in The Gambia) is large, cost and lack of urgency seemingly represent additional key drivers of delay. Given Gavi's immediate support for Hib upon the organization's establishment in 2000, **it seems plausible that an organization like Gavi could have been founded prior to 2000 if Hib (and other vaccine) trials in developing countries had been undertaken at the same time as the early trials in HICs.** In the case of Hib, **both the establishment of Gavi and the existence of a relevant clinical trial were crucial to vaccine delivery in LMICs in the early 2000s**.

As of March 2023, China — which is no longer Gavi-eligible, and which is now a Gavi donor — is the only country that has not introduced Hib (VIEW-hub, 2023).

Gavi's support helped lower prices (from $3.60-$3.63 to $0.78-$1.29 per dose) and increase immunization, with more than 661 million children being immunized with the pentavalent vaccine in the 73 Gavi-supported countries

The Hib vaccine has existed since the early 1990s, but take-up of the vaccine was very slow, with only one LIC having introduced it by 2000. Sources suggest that slow uptake was due to limited awareness of the burden associated with Hib and also to high vaccine costs (Gavi, 2018). To boost the low uptake of Hib (and also HepB) vaccines, Gavi started offering the pentavalent vaccine in 2001, which had added benefits of lowering shipping costs and environmental impact, as well as accelerating protection and requiring fewer doses for immunization against the same conditions.

Initially, due to little competition, the Gavi market price for Hib combination vaccines did not decrease. Enter the Developing Countries Vaccine Manufacturers' Network (DCVMN), an alliance of vaccine manufacturers from LMICs that aims to offer an affordable and consistent supply of vaccines, which set a strategic priority of increasing access to Hib- and HepB-containing DTP combination vaccines by getting more manufacturers to produce it (Jadhav et al., 2008). The Netherlands Vaccine Institute developed a patent-free process to produce conjugate vaccines against Hib, and transferred the technology to DCVMN members, leading to more manufacturers entering the market for the pentavalent vaccine. Over the 2005-2010 period, manufacturers increased from one to five. This triggered a reduction in prices from ~$3.6 per dose in 2005 to $3.2-2.25 per dose in 2010 (Malhame et al., 2019).

[23] Two years later, the establishment of the Developing Countries Vaccine Manufacturers Network (DCVMN) kicked off an alliance that "provides data and professional education plans, development of technology, inspiring transfer of technologies, advanced research and development, and community teaching regarding the accessibility of secure, cheap, and effective vaccines" (Zarei et al., 2016, p. 6). Its member manufacturers produce a number of vaccines, including Hib vaccines.

Gavi's initial model (for pentavalent, but also other vaccines) sought to influence vaccine availability and prices by providing funding, improving demand, and using centralized procurement. After a 2010 evaluation suggested that their efforts were improving the demand[24] but still needed to improve supply, Gavi drafted a new Supply and Procurement Strategy. As with most market-shaping approaches, this strategy involved the coordination between various stakeholders: Gavi Secretariat served a coordinating role, UNICEF and PAHO managed most of the procurement, supply, and distribution, the WHO developed product standards, and manufacturers supplied vaccines, while the Bill and Melinda Gates Foundation (BMGF) provided financial and technical support to some manufacturers (Malhame et al., 2019).

Initial market shaping interventions included the publication of a Strategic Demand Forecast by the Gavi Secretariat, the publication of price and product data by UNICEF, long-term procurement arrangements with suppliers, and technical assistance to National Regulatory Authorities and manufacturers by the WHO (Malhame et al., 2019). During subsequent years (2011-2015), the latter type of intervention accelerated, and PATH (with funding from BMGF) provided technical assistance to several manufacturers. BMGF also executed a risk-sharing agreement that brought an additional manufacturer into the space and increased supply, while lowering the vaccine price by about a third. It is estimated that this agreement led to $150 million in savings for Gavi over the four years it lasted. UNICEF executed a tender for supply in the 2013-2016 period, with a cost of $1.15-$2.95 per dose. In 2015, The Government of India executed a tender of their own, with an annual demand of 90 million doses and lower prices than those available to UNICEF at the time. In 2016, UNICEF developed a procurement strategy resulting in a phased tender, including agreements to procure 150 million doses annually at $0.6-$1.4 per dose, which was expected (in 2019) to result in savings of over $350 million for Gavi-funded procurement (Malhame et al., 2019).

The **price of the pentavalent vaccine** varies depending on presentation and manufacturer, but — seemingly thanks to the efforts mentioned above — **has decreased from $3.60-$3.63 in 2006 to $0.78-$1.29 per dose in 2023** (UNICEF, 2022). Gavi claims that by the end of 2021, **more than 661 million children had been immunized with the pentavalent vaccine** with their support (Gavi, 2023). Other estimates suggest that from 2001 to 2020, the Hib and HepB components of the pentavalent vaccine averted 10 million deaths and 390 million DALYs, while also generating more than $250 billion in economic and social value in the 73 countries where the pentavalent vaccine was supported by Gavi (Malhame et al., 2019).

Rotavirus vaccines

Top causes of delay were a vaccine recall and geographically inappropriate trials

1. Recall of first generation vaccine. Eight years between US approval of the first rotavirus vaccine and US approval of a vaccine in use today.
2. Geographically inappropriate trials. Three years between first national rollouts and WHO recommendation for the countries with the highest burden.

Timeline: 1989-2018

1989-1991: First Phase 3 trial of rotavirus vaccines (Bernstein et al., 1995)

[24] With demand increasing from less than 50 million to about 100 million doses in the 2005-2010 period.

1998: Licensure of RotaShield in the US (Kapikian, 2011, p. 297)
1999: Withdrawal of RotaShield by manufacturer (Kapikian, 2011, p. 297)
2001-2004: First Phase 3 trial of RotaTeq (Vesikari et al., 2006)
2003-2004: First Phase 3 trial of Rotarix (Ruiz-Palacios et al., 2006)
2006: Licensure of Rotarix in the EU (EMA, 2023)
2006: Licensure of RotaTeq in the US (FDA, 2006)
2006: First universal introductions in the United States, Austria, Luxembourg, Panama, El Salvador, Nicaragua, and Brazil (VIEW-hub, 2023)
2007: WHO recommendation of routine rotavirus vaccination in Europe, the US, Latin America (WHO, 2007)
2007: Initiation of Gavi support in Europe and Latin America (Gavi, 2018)
2008: WHO prequalification of RotaTeq (Burke et al., 2019)
2009: WHO prequalification of Rotarix (Burke et al., 2019)
2009: WHO recommendation of routine rotavirus vaccination worldwide (WHO, 2009)
2009: Initiation of Gavi support for rotavirus vaccines worldwide (Gavi, 2018)
2011: Procurement of over 1 million doses through UNICEF (UNICEF, 2014)
2012: Procurement of over 10 million doses through UNICEF (UNICEF, 2014, p. 2, Figure 3)
2018: WHO prequalification for Rotavac and ROTASIIL (Burke et al., 2019)

First-generation rotavirus vaccines were withdrawn; second-generation vaccines were initially tested only in Europe and the Americas, and were not globally recommended until post-approval studies elsewhere

First generation

Clinical trials of the first rotavirus vaccine candidates took place in the late 1980s and throughout the 1990s, in the US, Finland, Peru, Brazil, and Venezuela (Pérez-Schael et al., 1997). In 1998, the first rotavirus vaccine, RotaShield from Wyeth, was approved and rolled out in the US. However, a vaccine surveillance program raised concerns that RotaShield was causing intussusception (a kind of bowel obstruction) in one out of every ~10,000 infants vaccinated. **In 1999, less than a year after its introduction, Wyeth discontinued RotaShield**. It was never used at scale outside the US.

Second generation

The two main rotavirus vaccines in use today are RotaTeq, from Merck, and Rotarix, from GlaxoSmithKline (GSK). Both are oral, live attenuated vaccines, and they have similar efficacy and safety profiles, though Rotarix is monovalent and RotaTeq is pentavalent. The two vaccines were developed in parallel: the first Phase 3 trial of RotaTeq was conducted between 2001-2004, and in 2006 it was approved by the FDA; the **first Phase 3 trial of Rotarix was conducted between 2003-2004, and in 2006 it was approved by the European Medicines Agency.**

Due to the need to rule out rare adverse events like intussusception, these Phase 3 trials were very large. The first Phase 3 trial of Rotarix (Ruiz-Palacios et al. 2006) enrolled more than 63,000 infants across 11 Latin American countries and Finland; the first Phase 3 trial of RotaTeq, Vesikari et al. (2006), enrolled more than 68,000 infants across the United States, Taiwan, five countries in Europe, and four countries in Latin America. **Based on the results of these trials, seven countries added rotavirus vaccines to their national vaccination programs in 2006**: the United States, Austria, Luxembourg, Panama, El Salvador, Nicaragua, and Brazil. In 2007, Australia, Mexico, Ecuador, and Belgium followed suit.

By 2007, the WHO "strongly" recommended that rotavirus vaccines be included in national programs in "regions where vaccine efficacy data suggest a significant public health impact and where appropriate infrastructure and financing mechanisms are available," noting that "[t]o date, the clinical efficacy of rotavirus vaccines has been demonstrated mainly in the United States, Europe and Latin America."

Over the following few years, GSK and Merck ran follow-up Phase 3 trials in Asia and Africa, with GSK testing Rotarix in Malawi and South Africa, and Merck testing RotaTeq in Ghana, Kenya, Mali, Bangladesh, and Vietnam (WHO, 2009). In general, these trials found that the vaccines had lower efficacy in countries with higher child mortality rates. For example, the trial in Malawi found that vaccination prevented ~50% of cases of severe rotavirus gastroenteritis, and in South Africa vaccination prevented ~75% of cases, while in the United States and other low-child-mortality countries, vaccine efficacy was estimated at 85-95% (WHO, 2009). However, since the incidence of severe rotavirus gastroenteritis was higher at baseline in the countries with higher child mortality, **the vaccines actually averted more cases in those countries, despite the lower efficacy** (e.g., an estimated 3.9 cases averted per 100 vaccinees in Malawi, compared to 2.5 cases averted per 100 vaccinees in South Africa). Overall, the **WHO concluded in 2009 that rotavirus vaccines should be included in national vaccination programs worldwide.**

Following this recommendation, Gavi offered support for rotavirus vaccines worldwide (Gavi, 2018). In 2011, the first Gavi-supported country, Sudan, added rotavirus vaccines to its national program. As of 2022, 123 countries, 42 Gavi-supported, have routine rotavirus vaccinations (VIEW-hub, 2023).

Third generation

In 2018, two new rotavirus vaccines received WHO prequalification: Rotavac, from Bharat Biotech, and ROTASIIL, from the Serum Institute of India. These vaccines were phased into use in India between 2016 and 2019 (Burke et al., 2019), and are now also used in the DRC, Burkina Faso, and Kyrgyzstan (ROTASIIL); Benin, Ghana, and Timor-Leste (Rotavac).

Pneumococcal vaccines

Top causes of delay were efficacy (serotype coverage) and supply constraints

1. The top cause of delay for LMICs specifically appears to have been concerns around efficacy/serotype coverage of early vaccines in the 2000s.
2. Some relatively brief (≤1 year) country-level delays in the early 2010s arose from supply constraints.

Timeline: 1995-2011

1995-1998: First Phase 3 trial of pneumococcal vaccines (FDA, 2011, p. 3)[25]

[25] "Efficacy was assessed in a randomized, double-blinded clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either Prevnar® or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-15 months of age" (FDA, 2011, p. 3).

2000: Universal introduction of Prevnar (PCV7[26]) in the US (CDC, 2023; FDA, 2011 p. 2; VIEW-hub, 2023)
2002: Universal introduction in Canada (VIEW-hub, 2023)
2003: Funding ($30m) from GAVI to Johns Hopkins Bloomberg School of Public Health $30m for PneumoADIP ("Accelerated Development and Introduction Plan")[27]
2005: Universal introduction in three additional HICs (Australia, Luxembourg, Qatar, and Italy; VIEW-hub, 2023)
2007: WHO recommendation of PCV7 for all infants and children (WHO, 2007)
2008: Universal introduction of PCV7 in 26 WHO member states (18 from 2007-08), 24 of which are HICs (CDC, 2008)
2009: WHO prequalification of GSK's Synflorix (WHO, 2023)
2009: Gavi-supported introduction in Rwanda and The Gambia (Gavi, 2009)[28]
2009: Launch of Gavi's Pneumococcal Advance Market Commitment (AMC) (ended in 2020; Gavi, 2023)
2010: Licensure of PCV13 in US (CDC, 2022)
2010: First Gavi AMC-supported introduction in Nicaragua in December 2010, with new countries introducing over several following months (Gavi, 2020)
2010: Over one million sales in LMICs (see "Sales estimates" sheet here)[29]
2011: EMA approves Prev(e)nar (EMA, 2011)
2011: Tenth universal introduction in LMIC (IVAC, 2013, p. 11; VIEW-hub, 2023)

Pneumococcal vaccines took 14 years from start of the first Phase 3 trial to first introduction in two LMICs, while the time lapse was only 2-3 years for higher-valent variants developed over a decade later to reach 10+ LMICs, highlighting the importance of meeting target product profiles early

Phase 3 trials for pneumococcal vaccines date back to the mid-1990s, initially targeting seven serotypes. These **heptavalent pneumococcal conjugated vaccines (PCV7)[30] were approved and rolled out in the United States by 2000**, and it was not for another 2-5 years that other HICs began to introduce the vaccine universally. In 2005, the Center for Global Development (CGDev) published a report exploring the feasibility of advance market commitments in vaccine deployment (CGDev, 2005), which kicked off global conversations around such a commitment (Gavi, 2020). According to the CDC, **PCV7's high cost limited introduction globally in these early years of development**, though 90 of 193 WHO member states had licensed PCV7 by 2008. **Gavi made funding available in 2006**, and in 2008, 11 Gavi-eligible

[26] The initial pneumococcal conjugate vaccine targeted seven serotypes, though PCV13, PCV15, and PCV20 later became available (along with PPSV23, a polysaccharide vaccine; CDC, 2022).
[27] "In 2003, the GAVI Alliance created the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) to work with GAVI-eligible countries to provide evidence of disease burden and vaccine effectiveness, to support evidence-driven policy-making, and to ensure a sustainable, affordable supply of vaccine. The decision of the GAVI Alliance in 2006 to support introduction of PCV in eligible countries was based on evidence generated by PneumoADIP and WHO." (CDC, 2008)
[28] Note that the "universal introduction actual date" in Rwanda is listed as September 20, 2011 on VIEW-Hub, whereas Gambia's is August 19, 2009 (click on the country in the map to see this date). India introduced the pneumococcal vaccine in 2016-17.
[29] We estimate >1 million sales from countries that adopted the vaccine without Gavi support (i.e. The Gambia and Rwanda) in 2010, though Gavi-supported countries surpassed 1 million sales the following year with Kenya's adoption alone.
[30] Note that there are two classes of pneumococcal vaccine at present, including "one based on polysaccharides and the other based on polysaccharides conjugated to a carrier protein" (WHO, 2023). From our reading of the literature, the latter is the WHO-prequalified class that has been rolled out in LMICs to date, so we ignore polysaccharide vaccines in this research.

countries submitted applications, eight of which were approved (CDC, 2008).[31] In 2009, Rwanda and The Gambia became the first LMICs to introduce a pneumococcal vaccine — Pfizer's PCV7 vaccine (Prevnar 7) — on a national scale, though by then, higher-valent vaccines were in the pipeline and no additional LMICs ultimately introduced a PCV7 vaccine.

The first completed Phase 3 trial we identified[32] for the higher-valent PCV10 started in January 2006 and completed after one year, with related publications emerging in 2009 (ClinicalTrials.gov, 2023). **One month after Phase 3 trial completion (in February 2007), five HICs and the Gates Foundation committed $1.5 billion to launch an advance market commitment (AMC) for the pneumococcal vaccine**. Around 2008, Phase 3 trials for PCV13 began, with initial publications around 2010 (e.g., see Bryant et al., 2010, Yeh et al. 2010), the same year the FDA licensed PCV13 in the US (CDC, 2022). **It was not until 2009 that Gavi established its AMC, despite an independent committee of experts having recommended pneumococcal disease as their preferred candidate for the first AMC pilot in February 2006** (Gavi, 2020).[33] Since this AMC was the first of its kind, it required several convenings of experts and working groups to make decisions on its functioning and various parameters (Gavi, 2020), and presumably significant backend work to operationalize it. Given lower setup costs, we would expect that this three-year delay would be shortened for future vaccine AMCs.

Our research suggests that The Gambia and Rwanda were the only LMICs to introduce PCV7 while subsequent countries introduced higher-valent vaccines. In fact, Bill Hausdorff (PATH) mentioned that Gavi's **"outlining what serotypes a PCV must contain to be considered of global value was an important signal to developers as to what vaccines to invest in."** In 2010, the AMC had facilitated one million doses of Pfizer's PCV13 vaccine, and by the next year the number of pneumococcal vaccines procured had reached more than 10 million vaccines (Pfizer's PCV13 and GSK's PCV10; UNICEF, 2020, p. 6-7, Figure 3 and Table 3).

Accordingly, Luthra et al. (2021) suggest that **concerns about efficacy and/or serotype coverage led to delays in pneumococcal vaccine introductions in LMICs**,[34] so that "achieving the desired [target product profile] can potentially accelerate [new vaccine introduction] timelines"

[31] These eight include Rwanda and The Gambia — which both introduced PCV7 in 2009 — as well as the Central African Republic, the Democratic Republic of Congo, Guyana, Honduras, Kenya, and Nicaragua). We did not come across information on the three countries that were not approved.

[32] We did not find narrative sources about the first Phase 3 trials for PCV10 vaccines, so we downloaded all of the Phase 3 trials containing "PCV10" on ClinicalTrials.gov into a .csv file, sorted by start date, and identified the earliest trial where the "Study Results" column indicated "Has results", which was a GSK trial from January 2006 - January 2007.

[33] Two technical working groups convened in Rome (September 2006) and London (November 2006) seven and nine months following this expert recommendation. By February 2007, five HICs and the Gates Foundation had committed $1.5 billion to launch the AMC. Three months later (in May 2007) a call for applications to serve on the AMC's Independent Assessment Committee (IAC) was opened, and selections were made six months later (November 2007). Meanwhile, economic expert groups and IAC member trainings were being held from August 2007-November 2008. In June 2009, 3.5 years after the independent expert committee's initial recommendation, the AMC became operational; within 3-4 months, manufacturers' participation was secured, and manufacturers made their first long-term commitments 5-6 months later. Another six months later, in December 2010, the first LMIC that had not yet adopted (Nicaragua) rolled out pneumococcal vaccines under the AMC's terms, which had been extended to Rwanda and The Gambia under a grandfathering agreement in June 2010, one year after the signing of the AMC legal agreements (Gavi, 2020).

[34] "Additional barriers to uptake of these vaccines may relate to concerns about the product itself including efficacy, and/or serotype coverage, as was the case for PCV7 versus PCV10/PCV13 …" (p. 8). Esposito et al. (2010) suggest the concern is related to increases in serotypes not included in PCV7: "Despite its advantages, the widespread use of PCV7 has been accompanied by a small but statistically significant increase in the incidence of pneumococcal disease due to nonvaccine serotypes in both children and adults, leading to a slightly lower-than-expected vaccination efficacy" (p. 1017).

(p. 8). While one expert was unconcerned about serotype coverage as a bottleneck going forward, Hausdorff (PATH) highlighted that immunization schedules are extremely crowded and combinations are "much more likely to catalyze introduction."

Luthra et al. (2021) also suggest that **completion of multiple "global-level milestones" before or simultaneous to product licensure — as well as WHO prequalification following soon after licensure — can lead to more rapid introduction in LMICs**. They claim that the concurrence of WHO PQ[35] and licensure in the case of the 10- and 13-valent pneumococcal vaccines (PCV10 and PCV13) led to faster introduction. However, experts at PATH said that the pneumococcal vaccine is an anomaly in this sense, and experts generally confirmed that this order of events may only occur in emergencies.

Supply availability also appears to have caused delays for some countries in the early 2010s: "Two countries postponed introduction from 2013 to 2014 due to supply availability and two additional countries chose to delay their 2013 introductions to 2014 to allow sufficient time for introduction preparations following the mid 2013 confirmation of available PCV supply" (UNICEF, 2013, p. 5). To address the issue, new AMC contracts were drawn up to increase supply,[36] albeit with tail prices decreased by 10 cents (from $3.50 to $3.40 per dose) from 2014 onward. Part of the reason for within-country supply shortfall is related to countries' "catch-up activities," whereby countries supplied PCV to children under age one rather than only surviving infants, the latter of which informs quantities approved under the AMC. In these cases, UNICEF brought forward future deliveries to avoid national stockouts (UNICEF, 2013, p. 5).

Typhoid conjugate vaccines

Top causes of delay were neglect of the first candidate and low takeup by countries

1. Lack of commercial followup on the first candidate vaccine. Roughly 16 years between evidence of efficacy for the first typhoid conjugate vaccine (TCV) and evidence of efficacy for a TCV in use today.
2. Slow adoption on the country level. Only seven adopting countries in the five years since global recommendation and Gavi funding.

Timeline: 1998-2019

1998-2000: First Phase 3 trial of a typhoid vaccine (Lin et al., 2001)
2005: Development of Typbar-TCV begins (Bharat Biotech, 2013)

[35] They mention not only WHO PQ but also SAGE recommendations, though in the case of pneumococcal, SAGE did not issue a recommendation until 2019, when it recommended PCV10 and PCV13 for children under age five (WHO, 2019).
[36] Initially, Pfizer donated PCV7 to UNICEF. Pfizer's initial AMC contract in 2010 stipulated supply of 30 million doses annually from 2013 to 2021, and its second contract added an additional 18 million annually from 2014 onward. A subsequent contract further increased the quantity supplied by 26 million annual doses from 2016, so that 74 million annual doses were contracted by 2016. Similarly, GSK was initially contracted to supply 30 million doses a year from 2012, and an additional contract for 18 million (24 million) doses took effect from 2014 (2015), leading to overall annual supply of 72 million doses by 2015. From 2009 to 2013, manufacturers had contracts with UNICEF to produce an aggregate supply of 1.46 billion doses by 2024, with an annual supply of 146 million doses by 2016 (73% of the AMC annual target). This information is only current as of 2013 (UNICEF, 2013, p. 4-5), and we have not spent time searching for more recent related information.

2008: Licensure of Peda Typh in India (Sahastrabuddhe and Saluja, 2019)
2011-2012: Phase 3 trial of Typbar-TCV in India (Mohan et al., 2015)
2013: Launch of Typbar-TCV in India (Bharat Biotech, 2013)
2015-2016: Human challenge trial of Typbar-TCV (Jin et al., 2017)
2017: SAGE recommendation of typhoid conjugate vaccines (WHO, 2018)
2017: WHO prequalification of Typbar-TCV (WHO, 2021)
2018: Gavi funding for TCV becomes available (Gavi, 2023)
2019: Pakistan becomes the first country to add TCV to its national vaccination program (VIEW-hub, 2023)
2019: Over 10 (20+) million doses procured through Gavi (UNICEF, 2022).

After an early candidate with proven efficacy was never commercialized, and commercialized vaccines lacked proof of efficacy, a human challenge trial solidified expert consensus, but takeup has still been slow

Before the development of typhoid conjugate vaccines, there were earlier generations of typhoid vaccines available, such as the Vi polysaccharide vaccine, which has been licensed in the US since 1994 (Sahastrabuddhe and Saluja, 2019). These vaccines were considered safe and effective, but their protection lasted only a few years, and they were not suitable for young children. Typhoid conjugate vaccines, which provoke a stronger immune response by combining a typhoid antigen (such as Vi polysaccharide) with a stronger antigen, have been developed to address these issues.

In the 1990s, the US NIH developed and tested the first typhoid conjugate vaccine, which combined Vi polysaccharide with recombinant *Pseudomonas aeruginosa* exotoxin; Vi-rEPA for short. **Vi-rEPA was tested in a large randomized controlled trial conducted from 1998 to 2000, enrolling 11,000 children ages 2-5 in Vietnam** (Lin et al., 2001). The vaccine was found to have about 90% efficacy and was hailed as an exciting advance (Guerrant and Kosek, 2001). A followup study later found that Vi-rEPA was safe and immunogenic in infants as young as two months (Thiem et al., 2011). **However, no commercial Vi-rEPA product was ever made, and the vaccine has never been used at scale.** The NIH has since transferred ownership of the technology to China's Lanzhou Institute of Biological Products, and PATH has provided some technical assistance toward creating a candidate vaccine (Gavi, 2020), but no further progress has been made.

In conversation, Bill Hausdorff of PATH suggested that the initial demonstration of efficacy being limited to children two years and older was a barrier to further progress and uptake, because routine immunization programs typically only reach children in their first year of life.

In the 2000s, Bio-Med, an Indian vaccine company, developed a typhoid conjugate vaccine under the brand name Peda Typh. Peda Typh combines Vi polysaccharide with tetanus toxoid protein; Vi-TT for short. Peda Typh was licensed in India in 2008 (Sahastrabuddhe and Saluja, 2019). Its efficacy has been evaluated in one cluster-randomized trial of 900 children (Mitra et al., 2016). **The WHO recommendations on typhoid vaccines do not consider Peda Typh due to the limited evidence** (WHO, 2018).

Meanwhile, Bharat Biotech, another Indian biotech company, had been manufacturing Vi polysaccharide vaccines under the brand name Typbar. Starting in 2005, they also developed a Vi-TT typhoid conjugate vaccine, which they called Typbar-TCV. A Phase 3 trial comparing

Typbar-TCV to Typbar was conducted between 2011 and 2012, finding that Typbar-TCV provoked a better immune response and was safe for children as young as six months (Mohan et al., 2015). Typbar-TCV was launched in India in 2013 (Bharat Biotech, 2013).

Internationally, Bharat's Phase 3 trial was not considered a sufficient demonstration of Typbar-TCV's efficacy, since it focused on safety and immunogenicity rather than clinical disease endpoints. **To provide evidence of efficacy, researchers in the UK conducted a human challenge trial[37] of Typbar-TCV, which was funded by the Gates Foundation and the European Commission** (Jin et al., 2017). The trial was conducted from 2015 to 2016, and found that vaccination reduced typhoid infections by about 50% in a human challenge trial setting. Relying on this result, a meeting of SAGE in October 2017 concluded that "[a]mong the available typhoid vaccines, TCV is preferred at all ages in view of its improved immunological properties, suitability for use in younger children and expected longer duration of protection" (WHO, 2018). Typbar-TCV received WHO prequalification in December 2017 (WHO, 2021).

Gavi expressed interest in funding typhoid vaccination as early as 2008, but decided not to offer funding at that time due to the lack of a suitable vaccine (Gavi, 2023). **Following the WHO's recommendation and prequalification of Typbar-TCV in 2017, Gavi made funding available for TCV in 2018.** In 2019, Pakistan became the first country to add TCV to its national vaccination program. About 22 million doses of Typbar-TCV were procured through Gavi in 2019, up from less than 1 million in 2018 (UNICEF, 2022).

As of 2023, a total of seven countries have introduced TCV: Pakistan, Liberia, Zimbabwe, Bhutan, China, Nepal, and Samoa (VIEW-hub, 2023). **UNICEF attributes the slow global uptake of TCV to "countries' competing health priorities, limited capacity to define local typhoid epidemiology and lack of commitment to typhoid control in endemic countries"** (UNICEF, 2022). **Notably, India has not added any typhoid vaccine to its national program, though it has developed a sizable private market in TCV**; between 2013 and 2019 an estimated 11 million doses of Typbar-TCV were sold in India (Reddy et al., 2022).

A second typhoid conjugate vaccine was WHO-prequalified in 2020. It is a combination of Vi and CRM_{197}, developed by GSK Vaccines Institute for Global Health (Sahastrabuddhe and Saluja, 2019) and manufactured by Biological E under the brand name TYPHIBEV (WHO, 2021). In 2022, UNICEF awarded contracts for ~24 million TCV doses to Biological E, while Bharat Biotech was awarded contracts for ~16 million doses (UNICEF, 2022).

HPV vaccines

Top causes of delay were high costs and insufficient supply

1. Prohibitive costs. The initial vaccine costs were ~$100-$120 per dose, with a full course needing 2-3 doses depending on the vaccine.
2. Insufficient supply. Surging global demand and supply shortages in 2016 led Gavi to lower their target from 40 million to 14 million girls covered by 2020 (Gavi, 2018).[38]

[37] Human challenge trials are studies that "involve the deliberate exposure of human volunteers to infectious agents" (WHO, 2017, p. 578).
[38] Note that we have not researched what the actual coverage achieved in 2020 was, so they might have managed to reach more than 14 million girls.

Timeline: 2001-2019

2001-2007: First Phase 3 trial for quadrivalent vaccine (Schiller et al., 2012; ClinicalTrials.gov, 2023)[39]
2004-2006: First Phase 3 trial for bivalent vaccine (ClinicalTrials.gov, 2023)
2006: Licensure of the quadrivalent vaccine for females aged 9-26 in US (Bryan et al., 2016)
2006: First four universal introductions in HICs (France, Monaco, Switzerland, US; VIEW-hub, 2023)[40]
2007: Publication of first Phase 3 trial for quadrivalent vaccine (Schiller et al., 2012)
2007: Publication of interim analysis of first Phase 3 trial for bivalent vaccine (Paavonen et al., 2007)
2007-2010: First Phase 3 trial for nonavalent vaccine (ClinicalTrials.gov, 2023)
2009: First WHO prequalification of quadrivalent vaccine (Gardasil by Merck Vaccines; WHO, 2023)
2009: First WHO prequalification of bivalent vaccine (Cervarix by GlaxoSmithKline Biologicals SA; WHO, 2023)
2009: Publication of first Phase 3 trial for bivalent vaccine (Paavonen et al., 2009)
2009: Licensure of the bivalent vaccine for females age 10-25 in US (Bryan et al., 2016)
2009: Licensure of the quadrivalent vaccine for males age 9-26 in US (Bryan et al., 2016)
2011: First universal introduction in a LMIC (Rwanda; VIEW-hub, 2023)[41]
2011: Initiation of Gavi funding for HPV (Hanson et al., 2015)[42]
2014: Over one million sales in LMICs (UNICEF, 2020, Figure 5, p. 6)[43]
2014-2015: Licensure of nonavalent vaccine for females and males age 9-26 in US (Bryan et al., 2016)
2015: Publication of first Phase 3 trial for nonavalent vaccine (Joura et al., 2015)
2015: Second universal introduction in an LMIC (Uganda; VIEW-hub, 2023)
2018: First WHO prequalification of nonavalent vaccine (Gardasil 9 by Merck Vaccines; WHO, 2023)
2019: 10th universal introduction in an LMIC (The Gambia, VIEW-hub, 2023)
2019: Over 10 million sales in LMICs (UNICEF, 2020, Figure 5, p. 6)

[39] We are using the year listed as 'Actual Primary Completion Date' in CT.gov as the last year of the trial, since it seems more likely to be the relevant year given that publication of the trial results occurred after that year but before the year of 'Actual Study Completion Date.'
[40] VIEW-hub lists introductions in France, Monaco, Switzerland and the US as starting in 2006. Markowitz et al. (2012), who look at the story of the vaccine five years after its introduction, mention the introduction in the US and Austria happening in 2006, and then in the next countries to implement it happening in 2007 (Markowitz et al., 2012).
[41] Even though ViewHub indicates introduction in 2011, Gavi mentioned in 2013 that it would start supporting HPV vaccines for nation-wide use in Rwanda in 2014, so it is unclear what the coverage rate was, if any, in Rwanda prior to 2014 (Gavi, 2013).
[42] "In November 2011, the Gavi Board opened a funding window to provide support to countries interested in introducing HPV vaccination" (Hanson et al., 2015).
[43] It seems like Gavi supports the supply of both the Bivalent and Tetravalent vaccines, so both of the sales milestones likely come from a combination of both vaccines (UNICEF, 2020, Table 2, p. 8).

Despite high effectiveness from the main vaccines, initial introduction of the HPV vaccine was slow in LMICs due to high costs, but seems to be improving with Gavi's support

Development story

In the early 2000s, two large Phase 3 trials (FUTURE I and FUTURE II, with trial sites in Europe, across America, and in Asia Pacific) evaluated a quadrivalent HPV vaccine (Schiller et al., 2012). This vaccine, commercialized by Merck as Gardasil, is designed to protect against HPV16 and HPV18, the two types responsible for 70% of cervical cancer, and HPV6 and HPV11, which are responsible for ~90% of external genital warts in men and women. In the mid 2000s, the Costa Rica HPV Vaccine Trial Phase 3 trial in Costa Rica evaluated the bivalent vaccine (Schiller et al., 2012). This vaccine, commercialized by GSK as Cervarix, is designed to protect against the main HPV types associated with cancer, HPV 16 and HPV18. Both vaccines demonstrated great efficacy in the prevention of clinical precursors of cervical cancer (Bryan et al., 2016).

The quadrivalent and bivalent vaccines were licensed in 2006 and 2009, respectively.

Even though these vaccines protect against the main HPV types causing cervical cancer, the attributable protection is 70%. To enhance this to 85%, Merck developed a nonavalent HPV vaccine including the five next most common types responsible for cancer, with Phase 3 trials conducted from 2007-2010. In 2014, this vaccine, commercialized as Gardasil 9, was licensed (Bryan et al., 2016, ClinicalTrials.gov, 2023).

Introduction to LMICs and causes of delay

In 2009, both the quadrivalent and bivalent vaccines received WHO prequalification, and WHO recommended HPV vaccination 'for countries where cervical cancer is a public health priority and where the introduction of the vaccine is feasible and financially sustainable' (Jumaan et al., 2013).

By the beginning of 2012, the quadrivalent and bivalent vaccines had been licensed in over 100 countries, and incorporated into national vaccination programs of at least 39 countries (Markowitz et al., 2012). However, most of those were HICs, **and only two LMICs**, Bhutan and Rwanda,[44] **had introduced it, mainly due to prohibitive costs** (~$100-$120/dose). At the time, there were ~528,000 new cases of cervical cancer worldwide annually, with 9 out of 10 associated deaths occurring in LMICs (Hanson et al., 2015).

In 2011, the price of the vaccine was lowered significantly through the Pan American Health Organization's Revolving Fund, reaching a cost of $14/dose, which represented a big reduction but was still costly for many LMICs (Markowitz et al., 2012). That same year, **Gavi started offering support for the introduction of the HPV vaccine to eligible countries and managed to secure access to the vaccine for $4.5-$4.6 per dose** (Gavi, 2013, Gavi, 2018), receiving applications from 15 countries in the first year alone (Gavi, 2013). This support was initially conditional on successful demonstration of feasibility: Gavi would support countries in implementing a pilot version of the vaccination program to gain experience delivering a vaccine to adolescents, and to evaluate the feasibility of a national program (Hanson et al., 2015). Gavi fully covered the costs of vaccine supply and procurement for this program, and

[44] Bhutan and Rwanda were able to include HPV in their National immunization programs after receiving the support of donation programs in 2010 and 2011, respectively.

provided a cash grant to support most of the operational costs. For subsequent national introductions, Gavi required countries to co-finance the vaccine cost based on their Gross National Income per capita. In 2016, Gavi removed the demonstration requirement (Gavi, 2018).

In the ten years that followed Gavi's initial support, 27 countries, including 19 countries in sub-Saharan Africa, introduced HPV vaccination programs, with ten more planning to do so (Gavi, 2022).

The main reason for the delay of introduction of the HPV vaccine in LMICs appears to have been high costs. Other factors include insufficient supply to meet increasing demand (Gavi, 2018) **and lack of data documenting disease burden** (Jumaan et al., 2013).

Following introductions, some of the most commonly cited factors that have affected the vaccine's delivery are concerns about vaccine safety (mostly due to misinformation and negative rumors), limited experience delivering vaccines to adolescents, worries from religious communities[45] (Hanson et al., 2015, Markowitz et al., 2012, Jumaan et al., 2013), and difficulties in meeting the vaccination schedule of two or three doses. Luckily, the last hurdle may soon be removed, given SAGE's news indicating that a single dose of the vaccine is comparable to two or three doses in providing protection (Gavi, 2022).

Implications and discussion

Visual timeline

We focus on vaccines that received WHO prequalification prior to at least one universal introduction in a LMIC, since WHO prequalification is necessary for UNICEF procurement of vaccines (Muhib).[46]

We first review the time lapse between initiation of the first large-scale (Phase 3, where identifiable) trial and its publication. This time gap has lengthened over time, from about one year in the 1950s to 5-7 years for the most recent HPV vaccine. The gap is 2-5 years for vaccines where the original Ph3 trials started between 1980 and 2000. This increase is perhaps suggestive of increasingly stringent (and perhaps bureaucratic) clinical trial and publication requirements, as well as more care taken in the conduct of science.

While the time lapsed between first and tenth LMIC introductions appeared to have all but disappeared for vaccines whose timelines begin in the 2000s, HPV presents an anomaly. Gavi support preceded first LMIC adoption in the case of Rotarix (rotavirus), Synflorix and Prevnar 13 (pneumococcal), and Typbar-TCV (typhoid), and within 0-2 years, 10 LMICs had adopted. For these pneumococcal and typhoid vaccines, ten million sales were reached in the same year of the first LMIC introduction (it was two years later for the rotavirus vaccine). For HPV, the timeline was much slower, which we attribute to reasons mentioned in our discussion of HPV, including lack of awareness of the disease burden, the difficulty of introducing a vaccine for adolescents (as opposed to infants), and the existence of other vaccine donors who supported early introduction in particular LMICs pre-Gavi support. We see a similar lapse of time for Hib

[45] Noting concerns about the vaccine being a 'license to have premarital sex' (Jumaan et al., 2013).
[46] We identified one case where our timeline is inconsistent with this ordering: LMIC introductions occurred prior to WHO prequalification for the pentavalent vaccine.

(seven years), also in part due to a manufacturer donation in The Gambia following the successful Phase 3 trial conducted there.

Bottlenecks in the vaccine delivery process

We asked experts a general question about the bottlenecks they perceived in the vaccine delivery process, and additionally asked them to comment on the importance of several potential bottlenecks that Open Philanthropy and our team had identified.

As a caveat, **all experts emphasized that actual bottlenecks are highly context-specific**. One expert warned against trying to make generalizations across vaccines and across countries. They highlighted differences in cold chain availability, political will, levels of vaccine acceptance, HR and vaccine delivery capacity, electricity supply, funding, vaccine availability, and leadership consistency at the national level, with "even more layers" at the subnational level (where such a distinction exists). Muhib (PATH) and Shimp (JSI) also emphasized the importance of context. Thus, a deep understanding of context may be important for identifying promising funding opportunities.

Vaccine originator companies in HICs not prioritizing LMICs

When asked about vaccine originator companies being primarily located in HICs and not prioritizing LMIC access, experts somewhat diverged in their perceptions of importance. One expert said it was important to encourage manufacturing in LMICs, while Shimp (JSI) emphasized the role of trust in established manufacturers, which tend to be based in HICs. The first expert acknowledged the complexity of building trust and encouraged investment to do so, including improvements to global regulatory capacity, agreements with supply regions, safety protocols, and tracking and response capacity. They mentioned the importance of demand predictability in this context, since manufacturers often cannot be flexible in which vaccine they are producing. Shimp mentioned that increasing manufacturing in LMICs will be a long process that takes time and investment, and that it might be expedient in the short term to start with technology transfer for steps like vialing the vaccine.

Bill Hausdorff (PATH) suggested more involvement of national governments, as well as groups of national experts who provide recommendations to policymakers and immunization program managers, which are called National Immunization Technical Advisory Groups (NITAGs). "**A major bottleneck has been underestimating the need to ensure vaccines being developed fit the desires and needs of NITAGs and [Ministries of Health], not just in the choice of target but also in the formulation of the vaccine**," he said. He provided an interesting example where a typhoid vaccine for two-year-old Vietnamese children did not materialize due to the lack of delivery system for that age group, and 17 years passed before they were able to introduce a typhoid vaccine for infants.

Clinical evidence from HICs irrelevant to LMIC contexts

Experts generally agreed that the generalizability of clinical evidence used for approvals in HICs to LMIC contexts is an issue. They mentioned that there may be both medical and contextual reasons that clinical evidence in LMICs is important, for instance if there are different strains of the virus in LMIC contexts than in HICs.

Shimp (JSI) said that LMICs are generally happy to introduce a vaccine that has proven effective in other LMICs, noting a correlation between the level of acceptance and the similarity of that country to their own. Muhib (PATH) also alluded to a preference for evidence

in one's own country, "especially if they have strong research organizations," for instance in countries like Bangladesh. She suggested that "at a minimum, trials should be conducted in the region, or in non-HIC markets," and that multinational corporations are increasingly conducting these more LMIC-applicable trials. **Another expert pointed out that logistical concerns may also be overcome if clinical trials are suited to LMIC contexts** (e.g., size of vial, delivery costs, necessary features of national programs, need for cold chain space, etc.).

Low prioritization of vaccine delivery by LMIC governments

One expert strongly agreed that LMIC prioritization of vaccines is an important factor. As with all other considerations, **prioritization varies by country**, where some have stronger health structures and more systematic processes for incorporating new vaccines (e.g., Shimp (JSI) mentioned that Cambodia had already prioritized their list of anticipated new vaccine introductions based on disease burden, cost, and other considerations when JSI began conversations with them as part of the RAVIN rotavirus vaccine support project). **The expert suggested a need for integration of vaccination with "whatever the country's priority is"** (e.g., education, antenatal care) so that vaccines can be administered at those touch points. For instance, in the US, compulsory vaccination for schooling had a large impact on coverage (see Conis, 2019).

Hausdorff and Muhib (PATH) agreed that this concern depends on a number of country- and vaccine-specific factors, as countries face a plethora of healthcare needs and **adding another standalone injection may simply be too difficult given crowded vaccine schedules**. To increase countries' prioritization of vaccine delivery, Muhib said, there is a **need for "data on disease burden in their countries, the health economic data – cost of illness and cost of introduction, and the expected impact of the vaccine on disease and deaths."**

For instance, in the near term, Muhib expects respiratory syncytial virus (RSV) vaccines to become available to pregnant women in HICs given broad awareness of RSV in newborns and efficient delivery systems. Since LMICs often lack awareness (and therefore demand) and delivery capacity, she expects a delay in such availability in LMICs: "The health systems of these countries are usually overwhelmed and poorly resourced," she said, so "without clear demonstration of impact or an imminent threat … it is difficult for LMICs to introduce new vaccines."

A solution that Muhib suggested to improve countries' vaccine introductions is to **develop more "combination vaccines that would ideally be administered in as few doses as possible."** Hausdorff (PATH) similarly suggested that "combinations are much more likely to catalyze introduction, as was clearly seen with Hib vaccines back in the early 2000s." **Shimp cautioned that, while beneficial, multivalent vaccines are generally prohibitively expensive for LMICs** and that "Gavi is not co-financing these."[47] When asked about why they are more costly, she mentioned production difficulty, limited numbers of manufacturers who can recoup R&D costs through higher income markets, and more elaborate quality assurance processes.

Slow or unclear policy recommendations from global or national bodies

When asked about the importance of slow or unclear policy recommendations from global bodies and/or national bodies, Shimp's (JSI) immediate response was that this issue is "really

[47] In our research, we found that the Hib pentavalent vaccine helped lower costs. However, Shimp pointed out that it took several years and intensive support from Hib Initiative to get the pentavalent vaccine covered by Gavi and the price lowered, and that for HPV9 and other newer vaccines, it may be several years before we see competition among manufacturers and eventually lower prices.

important." She said that **NITAGs are usually convened when there's a specific decision to be made**; for example, when a new vaccine becomes available from Gavi. However, **she would favor more regular technical and interagency coordination meetings** and earlier decision making, rather than "someone having to push for each meeting" (usually Gavi or WHO advisors to the country, though she said the WHO is understaffed on this front).

Hausdorff (PATH) believes this issue was clearly apparent in the case of RTS,S, the only WHO-prequalified malaria vaccine. Another expert asserted that slow and unclear policy recommendations are "inevitable," but agreed that NITAGs can be strengthened. **Muhib (PATH) suggested that SAGE recommendation in addition to a request from the national government to evaluate the vaccine, is essential for NITAGs to consider recommending a vaccine's introduction**, and that they will otherwise not recommend on their own.

Hausdorff (PATH) lamented the "inability of SAGE to signal what vaccines in the future will be recommendable," and asserted that "not explicitly favoring combinations of [the vaccines'] standalone components" leads to uncertainty among manufacturers about which (combination) vaccines to develop.

Vaccine affordability issues

When asked about costs of existing vaccines, all experts agreed that Gavi had largely resolved the issue of affordability. One said that **Gavi had "taken price out of the equation"** and that it is almost never the case that "countries want the vaccines but can't afford them." On this front, however, they mentioned that pooled demand may be worth investigating. Hausdorff (PATH) similarly dismissed the importance of cost up to about $5/dose, and warned that **pressure from funders to reach the "lowest price possible regardless of cost-effectiveness may very well dissuade vaccine developers**, even based in LMICs, from pursuing some vaccines mainly for LMICs, because it's not clear how the revenue can support a business."

Shimp (JSI) mentioned that high prices are a big issue for non-Gavi countries, and she and Muhib (PATH) both highlighted the **relevance of affordability for countries that "graduate" from Gavi eligibility to ineligibility, after which prices can increase 2x-4x** (e.g., we came across a paper, Le et al. (2016), that discusses this issue in the Hib vaccine context). Given the observed tendency for countries to neglect to plan for this transition, Muhib said the answer is not "necessarily all vaccines being available for $1/dose, but rather **advocacy for governments to increase their health budgets and prioritize immunizations.**" Shimp alluded to the example of Tanzania, which ultimately and unsustainably reallocated operational funds to pay for increased vaccine copays and cost, due to the overall limitation of the vaccine line item in the health budget. The Learning Network for Countries in Transition may help these countries to learn from other countries' experiences, she said.

Time lapsed between HIC licensure and WHO prequalification

Gaps between HIC licensure and WHO prequalification did not seem to pose a major threat to delivery as they are shrinking, according to an expert. However, Muhib (PATH) said that **WHO prequalification is necessary for UNICEF to buy vaccines**, which can create the necessary source of demand for manufacturers in HICs to prioritize LMIC access. Similarly, Hausdorff (PATH) emphasized the **need for "tangible demand" from LMIC markets,** which could include advance market commitments or clear signs of Gavi or donor interest.

Supply constraints and low predictability of demand

Hausdorff (PATH) cautioned that **low predictability of demand may deter manufacturers' involvement**, which could be the case for Shigella vaccines' ability to attract support for Phase 3 clinical trials and licensure. Muhib (PATH) mentioned a **need for a "market for vaccines that has some sort of sustained demand over time** … that could justify investment in developing and dedicating vaccine manufacturing facilities to a new vaccine that has never been produced before" and where the "benefits of being first to market outweigh the risks."

One expert agreed that demand predictability is problematic for new vaccines (though not established ones). They alluded to a need for much better forecasting. Shimp (JSI) agreed that supply constraints may cause delays but that countries are willing to wait.

Potentially cost-effective opportunities

We also asked experts what they perceived to be the most cost-effective opportunities to speed up vaccine delivery timelines.

One expert's "wishlist" focused on ways to improve LMIC agency and learning in the vaccine delivery process. First on their list were **improvements to HR (e.g., salaries, reduction in turnover and migration) and professional training**. Second, they would like to see **improved accountability mechanisms, particularly cocreation of goals** with not only countries but also health workers and personnel throughout the supply chain. When asked which organizations to fund to improve in these areas, they mentioned evidence-based organizations like the Child Health Research Foundation in Bangladesh — which they said most countries have — as well as offices on the ground affiliated with PATH, CHAI, and universities. They said that Gavi has done well on helping countries to come up with their own solutions, which is key. Over the course of the interview, they also mentioned the **need for twinning programs,[48] increasing contextual understanding and experience for all players involved, and facilitating more cross-sectoral learning and support.[49]**

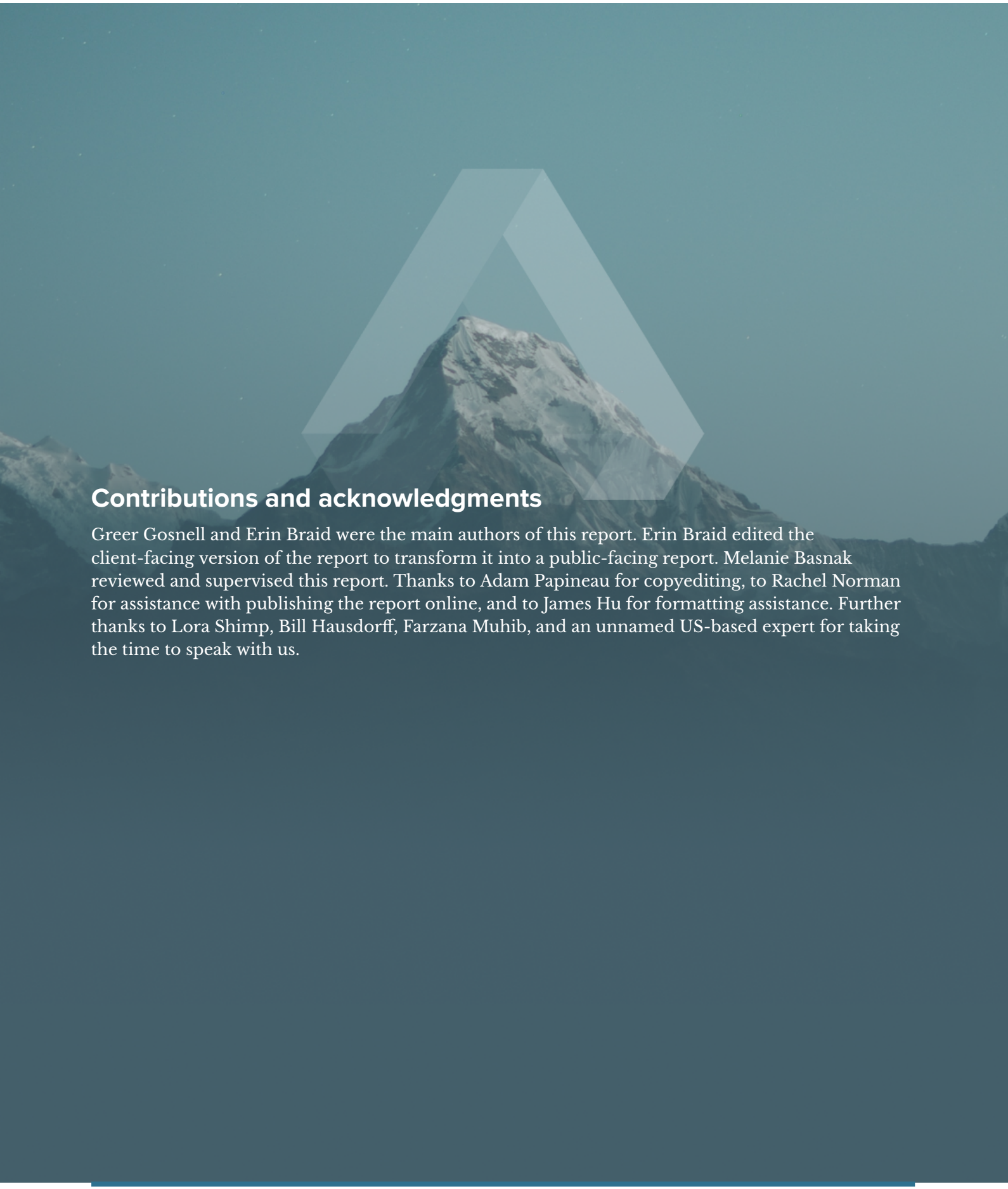
Hausdorff (PATH) emphasized the **need for a "mechanism to signal to vaccine developers what vaccines in the future will be priorities, and what combinations will be priorities** (and will be preferred over standalones)," perhaps from SAGE or Gavi. He mentioned that **AMCs could also provide such a signal.**

Shimp (JSI) and Muhib (PATH) both focused on ensuring that the vaccines themselves are fit for purpose. Shimp wants increased focus on delivery mechanisms in LMIC settings during product development, while ensuring that the product itself is not inferior. She is keen to see **new technologies that will increase compliance and service experience in the long-run (e.g., commercialization of microarray patches)**. Similarly, Muhib suggested the development of a vaccine with "minimal cold chain requirements, that would require fewer doses, and could be administered without requiring injections," which would reduce procurement costs and improve administration and storage. She mentioned that investments in tracking systems are underway, and that their development is also crucial.

[48] Twinning programs match countries that face similar issues related to vaccine delivery to share knowledge and resources (e.g., see this example from Sri Lanka and Timor-Leste).
[49] This expert mentioned an interesting recent case where Pakistan involved their military in deploying Covid-19 vaccines, since militaries "have excellent logistics" capabilities. They do not expect this particular cross-sectoral collaboration to continue, though emphasized the importance of facilitating such opportunities for learning (e.g., from the private sector).

Finally, Shimp also mentioned the **need to convene people to answer this very question of how to speed up vaccine delivery timelines, specifically particular EPI immunization managers from different (and preferably smaller and therefore more overlooked[50]) countries along with personnel from organizations that provide technical support** (such as JSI, PATH, CHAI, and VillageReach). The WHO and Gavi do such convening, but usually around a "specific need" or planning cycle, and often retrofit or added on to overall EPI program design and support. She emphasized the importance of the knowledge sharing and network building that can happen at such convenings, particularly with the rise of WhatsApp. She also mentioned the need for investments in "program maturity", i.e., the ability to tailor vaccine delivery to different populations (e.g., rural vs. urban).

[50] Shimp sympathized with "zero-dose" efforts — i.e., efforts to reach children without a first dose — but she said it "leaves behind a lot of countries where a little bit of support could go a long way." She said even a small amount of technical support could help countries like Malawi and Benin make rapid and significant progress. She recommends convening these smaller countries (also including Ghana, Liberia, Zambia, Côte d'Ivoire, Burkina Faso, and potentially others) so they can make connections and learn from one another.



Contributions and acknowledgments

Greer Gosnell and Erin Braid were the main authors of this report. Erin Braid edited the client-facing version of the report to transform it into a public-facing report. Melanie Basnak reviewed and supervised this report. Thanks to Adam Papineau for copyediting, to Rachel Norman for assistance with publishing the report online, and to James Hu for formatting assistance. Further thanks to Lora Shimp, Bill Hausdorff, Farzana Muhib, and an unnamed US-based expert for taking the time to speak with us.

References

Bandyopadhyay, A. S., Garon, J., Seib, K., & Orenstein, W. A. (2015). Polio vaccination: Past, present and future. *Future Microbiology*, *10*(5), 791–808. https://doi.org/10.2217/fmb.15.19

Berg, A. H., & Blume, S. S. (2020). Reasonable Grounds? The Delayed Introduction of MMR Vaccine in Denmark and the Netherlands, 1977–87. *Medical History*, *64*(3), 355–373. https://doi.org/10.1017/mdh.2020.19

Bernstein, D. I. (1995). Evaluation of Rhesus Rotavirus Monovalent and Tetravalent Reassortant Vaccines in US Children. *JAMA: The Journal of the American Medical Association*, *273*(15), 1191. https://doi.org/10.1001/jama.1995.03520390051032

Bharat Biotech. (2013). *Bharat Biotech Launches Typbar-TCV™, world's first clinically proven typhoid conjugate vaccine for infants 6 months & older and Adults*. https://perma.cc/M9SX-3ZQC

Bland, J., & Clements, J. (1998). Protecting the world's children: The story of WHO's immunization programme. *World Health Forum*, *19*(2), 162–173.

Blankenhorn, A.-L., Cernuschi, T., & Zaffran, M. J. (2017). Exceptional Financial Support for Introduction of Inactivated Polio Vaccine in Middle-Income Countries. *The Journal of Infectious Diseases*, *216*(suppl_1), S52–S56. https://doi.org/10.1093/infdis/jiw573

Bryan, J. T., Buckland, B., Hammond, J., & Jansen, K. U. (2016). Prevention of cervical cancer: Journey to develop the first human papillomavirus virus-like particle vaccine and the next generation vaccine. *Current Opinion in Chemical Biology*, *32*, 34–47. https://doi.org/10.1016/j.cbpa.2016.03.001

Bryant, K. A., Block, S. L., Baker, S. A., Gruber, W. C., Scott, D. A., & for the PCV13 Infant Study Group. (2010). Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine. *Pediatrics*, *125*(5), 866–875. https://doi.org/10.1542/peds.2009-1405

Burke, R. M., Tate, J. E., Kirkwood, C. D., Steele, A. D., & Parashar, U. D. (2019). Current and new rotavirus vaccines: *Current Opinion in Infectious Diseases*, *32*(5), 435–444. https://doi.org/10.1097/QCO.0000000000000572

Center for Global Development. (2005). *Making Markets for Vaccines – Ideas to action*. https://perma.cc/S3T9-SUD5

Centers for Disease Control and Prevention. (1991). *Haemophilus b Conjugate Vaccines for Prevention of Haemophilus influenzae Type b Disease Among Infants and Children Two Months of Age and Older Recommendations of the ACIP*. https://perma.cc/K23U-4BTT

Centers for Disease Control and Prevention. (2008a). Progress in Introduction of Pneumococcal Conjugate Vaccine—Worldwide, 2000—2008. *Morbidity and Mortality Weekly Report*, *57*(42), 1148–1151.

Centers for Disease Control and Prevention. (2008b). Progress Toward Introduction of Haemophilus influenzae type b Vaccine in Low-Income Countries—Worldwide, 2004—2007. *Morbidity and Mortality Weekly Report*, *57*(06), 148–151.

Centers for Disease Control and Prevention. (2021a). Chapter 8: Haemophilus influenzae. In *Epidemiology and Prevention of Vaccine-Preventable Diseases* (14th ed.). https://perma.cc/5UY9-WZYY

Centers for Disease Control and Prevention. (2021b). Chapter 13: Measles. In *Epidemiology and Prevention of Vaccine-Preventable Diseases* (14th ed.). https://perma.cc/FW6S-H348

Centers for Disease Control and Prevention. (2022). *About Pneumococcal Vaccines*. https://perma.cc/4Z5J-M4E6

Centers for Disease Control and Prevention. (2023). *Pneumococcal Vaccination: What Everyone Should Know*. https://perma.cc/P3U5-ZPVS

Chandran, A., Watt, J. P., & Santosham, M. (2008). Haemophilus influenzae vaccines. In *Vaccines* (pp. 157–176). Elsevier. https://doi.org/10.1016/B978-1-4160-3611-1.50015-5

ClinicalTrials.gov. (2023a). *Broad Spectrum HPV (Human Papillomavirus) Vaccine Study in 16-to 26-Year-Old Women (V503-001)*. https://perma.cc/54GD-QSS5

ClinicalTrials.gov. (2023b). *Cervical Intraepithelial Neoplasm (CIN) in Women (Gardasil) (V501-015) (FUTURE II)*. https://perma.cc/Z8XM-S96C

ClinicalTrials.gov. (2023c). *Haemophilus Influenzae Type b | Phase 3*. https://perma.cc/69PC-7EJA

ClinicalTrials.gov. (2023d). *Human Papilloma Virus (HPV) Vaccine Efficacy Trial Against Cervical Pre-cancer in Young Adults With GlaxoSmithKline (GSK) Biologicals HPV-16/18*. https://perma.cc/K9LW-ADLP

ClinicalTrials.gov. (2023e). *PCV10 | Phase 3*. https://perma.cc/ACD3-6QT9

ClinicalTrials.gov. (2023f). *Safety & Immunogenicity Study of 10-Valent Pneumococcal Conjugate Vaccine When Administered as a 2-Dose Schedule*. https://perma.cc/SPZ4-CXEX

Conis, E. (2019a). Measles and the Modern History of Vaccination. *Public Health Reports*, *134*(2), 118–125. https://doi.org/10.1177/0033354919826558

Conis, E. (2019b). Measles and the Modern History of Vaccination. *Public Health Reports*, *134*(2), 118–125. https://doi.org/10.1177/0033354919826558

Developing Countries Vaccine Manufacturers Network. (2023). *List of vaccines from DCVMN corporate members*. https://perma.cc/5W3L-KLJC

Eskola, J., Peltola, H., Takala, A. K., Käyhty, H., Hakulinen, M., Karanko, V., Kela, E., Rekola, P., Rönnberg, P.-R., Samuelson, J. S., Gordon, L. K., & Mäkelä, P. H. (1987). Efficacy of *Haemophilus Iinfluenzae* Type b Polysaccharide–Diphtheria Toxoid Conjugate Vaccine in Infancy. *New England Journal of Medicine*, *317*(12), 717–722. https://doi.org/10.1056/NEJM198709173171201

European Medicines Agency. (2011). *Prevenar*. https://perma.cc/5GUU-H39E

European Medicines Agency. (2023). *Rotarix*. https://perma.cc/2RR9-LUJR

Fahlgren, K. (1988). Two Doses of MMR Vaccine—Sufficient to Eradicate Measles, Mumps and Rubella? *Scandinavian Journal of Social Medicine*, *16*(3), 129–135. https://doi.org/10.1177/140349488801600301

Francis, T. (1955). EVALUATION OF THE 1954 POLIOMYELITIS VACCINE FIELD TRIAL: FURTHER STUDIES OF RESULTS DETERMINING THE EFFECTIVENESS OF POLIOMYELITIS VACCINE (SALK) IN PREVENTING PARALYTIC POLIOMYELITIS.

Journal of the American Medical Association, *158*(14), 1266. https://doi.org/10.1001/jama.1955.02960140028004

Gavi, the Vaccine Alliance. (2007). *GAVI Alliance announces dramatic funding boost for Hib vaccine*. https://perma.cc/HJ6N-TMLS

Gavi, the Vaccine Alliance. (2009). *The Gambia introduces vaccine against pneumococcal disease*. https://perma.cc/69AY-GR7V

Gavi, the Vaccine Alliance. (2011). *Hib Initiative: A GAVI success story*. https://perma.cc/SMK9-6RCH

Gavi, the Vaccine Alliance. (2013a). *GAVI Alliance to support introduction of inactivated polio vaccine in world's 73 poorest countries*. https://perma.cc/2MFP-G6N8

Gavi, the Vaccine Alliance. (2013b). *Millions of girls in developing countries to be protected against cervical cancer thanks to new HPV vaccine deals*. https://perma.cc/EV7A-SD8D

Gavi, the Vaccine Alliance. (2018a). *Human papillomavirus vaccine support*. https://perma.cc/D8D2-RQ9L

Gavi, the Vaccine Alliance. (2018b). *Inactivated polio vaccine (IPV) support*. https://perma.cc/BZV4-K9CA

Gavi, the Vaccine Alliance. (2018c). *Measles and measles-rubella vaccine support*. https://perma.cc/9MUQ-MPEV

Gavi, the Vaccine Alliance. (2018d). *Pentavalent vaccine support*. https://perma.cc/2Z5T-U83U

Gavi, the Vaccine Alliance. (2018e). *Rotavirus vaccine support*. https://perma.cc/CW59-JELK

Gavi, the Vaccine Alliance. (2019). *ADIPs and Hib Initiative evaluation*. https://perma.cc/7SQL-49BS

Gavi, the Vaccine Alliance. (2020a). *More typhoid conjugate vaccines, more impact*. https://perma.cc/8N97-YWHN

Gavi, the Vaccine Alliance. (2020b). *Pneumococcal AMC Timeline*. https://perma.cc/K9J6-RJME

Gavi, the Vaccine Alliance. (2022). *Five charts on 15 years of the HPV vaccine*. https://perma.cc/4C2G-P5S6

Gavi, the Vaccine Alliance. (2023a). *Eligibility*. https://perma.cc/Y7Y8-8VEZ

Gavi, the Vaccine Alliance. (2023b). *Facts and figures*. https://perma.cc/6GT3-NK79

Gavi, the Vaccine Alliance. (2023c). *Pneumococcal vaccine support*. https://perma.cc/L36M-HWDU

Gavi, the Vaccine Alliance. (2023d). *Typhoid conjugate vaccine (TCV) support*. https://perma.cc/FG7D-BMMG

Guerrant, R. L., & Kosek, M. (2001). Polysaccharide Conjugate Typhoid Vaccine. *New England Journal of Medicine*, *344*(17), 1322–1323. https://doi.org/10.1056/NEJM200104263441709

Hanson, C., Eckert, L., Bloem, P., & Cernuschi, T. (2015). Gavi HPV Programs: Application to Implementation. *Vaccines*, *3*(2), 408–419. https://doi.org/10.3390/vaccines3020408

Heath, P. (1998). Haemophilus influenzae type b conjugate vaccines: A review of efficacy data. *The Pediatric Infectious Disease Journal*, *17*(9), S117–S122.

Hendriks, J., & Blume, S. (2013). Measles Vaccination Before the Measles-Mumps-Rubella Vaccine. *American Journal of Public Health*, *103*(8), 1393–1401. https://doi.org/10.2105/AJPH.2012.301075

Immunize.org. (2021). *Vaccine Timeline*. https://perma.cc/RU5E-M54W

International Finance Facility for Immunisation. (2007). *Worldwide drive against measles receives financial "Shot in the Arm."* https://perma.cc/CYJ5-V2RD

International Vaccine Access Center. (2013). *VIMS Report: Global Vaccine Introduction*. https://web.archive.org/web/20160303233204/http://www.jhsph.edu/research/centers-and-institutes/ivac/vims/IVAC-VIMS-Report-2013-03.pdf

Jadhav, S., Datla, M., Kreeftenberg, H., & Hendriks, J. (2008). The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries. *Vaccine*, *26*(13), 1611–1615. https://doi.org/10.1016/j.vaccine.2008.01.034

Jaupart, P., Dipple, L., & Dercon, S. (2019). Has Gavi lived up to its promise? Quasi-experimental evidence on country immunisation rates and child mortality. *BMJ Global Health*, *4*(6), e001789. https://doi.org/10.1136/bmjgh-2019-001789

Jin, C., Gibani, M. M., Moore, M., Juel, H. B., Jones, E., Meiring, J., Harris, V., Gardner, J., Nebykova, A., Kerridge, S. A., Hill, J., Thomaides-Brears, H., Blohmke, C. J., Yu, L.-M., Angus, B., & Pollard, A. J. (2017). Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: A randomised controlled, phase 2b trial. *The Lancet*, *390*(10111), 2472–2480. https://doi.org/10.1016/S0140-6736(17)32149-9

Joura, E. A., Giuliano, A. R., Iversen, O.-E., Bouchard, C., Mao, C., Mehlsen, J., Moreira, E. D., Ngan, Y., Petersen, L. K., Lazcano-Ponce, E., Pitisuttithum, P., Restrepo, J. A., Stuart, G., Woelber, L., Yang, Y. C., Cuzick, J., Garland, S. M., Huh, W., Kjaer, S. K., … Luxembourg, A. (2015). A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. *New England Journal of Medicine*, *372*(8), 711–723. https://doi.org/10.1056/NEJMoa1405044

Jumaan, A. O., Ghanem, S., Taher, J., Braikat, M., Awaidy, S. A., & Dbaibo, G. S. (2013). Prospects and Challenges in the Introduction of Human Papillomavirus Vaccines in the Extended Middle East and North Africa Region. *Vaccine*, *31*, G58–G64. https://doi.org/10.1016/j.vaccine.2012.06.097

Kapikian, A. Z. (2011). History of Rotavirus Vaccines Part I: RotaShield. In S. A. Plotkin (Ed.), *History of Vaccine Development* (pp. 285–314). Springer New York. https://doi.org/10.1007/978-1-4419-1339-5_28

Le, P., Nghiem, V. T., & Swint, J. M. (2016). Post-GAVI sustainability of the *Haemophilus influenzae* type b vaccine program: The potential role of economic evaluation. *Human Vaccines & Immunotherapeutics*, *12*(9), 2403–2405. https://doi.org/10.1080/21645515.2016.1175695

Leach, A., Hilton, S., Greenwood, B. M., Manneh, E., Dibba, B., Wilkins, A., & Mulholland, E. K. (1999). An evaluation of the informed consent procedure used during a trial of a Haemophilus influenzae type B conjugate vaccine undertaken in The Gambia, West Africa. *Social Science & Medicine*, *48*(2), 139–148. https://doi.org/10.1016/S0277-9536(98)00317-7

Lewis, I., Ottosen, A., Rubin, J., Blanc, D. C., Zipursky, S., & Wootton, E. (2017). A Supply and Demand Management Perspective on the Accelerated Global Introductions of Inactivated Poliovirus Vaccine in a Constrained Supply Market. *The Journal of Infectious Diseases*, *216*(suppl_1), S33–S39. https://doi.org/10.1093/infdis/jiw550

Lin, F. Y. C., Ho, V. A., Khiem, H. B., Trach, D. D., Bay, P. V., Thanh, T. C., Kossaczka, Z., Bryla, D. A., Shiloach, J., Robbins, J. B., Schneerson, R., Szu, S. C., Lanh, M. N., Hunt, S., Trinh, L., & Kaufman, J. B. (2001). The Efficacy of a *Salmonella typhi* Vi Conjugate Vaccine in Two-to-Five-Year-Old Children. *New England Journal of Medicine*, *344*(17), 1263–1269. https://doi.org/10.1056/NEJM200104263441701

Luthra, K., Zimmermann Jin, A., Vasudevan, P., Kirk, K., Marzetta, C., & Privor-Dumm, L. (2021). Assessing vaccine introduction and uptake timelines in Gavi-supported countries: Are introduction timelines accelerating across vaccine delivery platforms? *BMJ Global Health*, *6*(5), e005032. https://doi.org/10.1136/bmjgh-2021-005032

Malaria Vaccine Initiative. (2023). *RTS,S/AS01*. https://perma.cc/4PWB-4AMN

Malhame, M., Baker, E., Gandhi, G., Jones, A., Kalpaxis, P., Iqbal, R., Momeni, Y., & Nguyen, A. (2019). Shaping markets to benefit global health – A 15-year history and lessons learned from the pentavalent vaccine market. *Vaccine: X*, *2*, 100033. https://doi.org/10.1016/j.jvacx.2019.100033

Markowitz, L. E., Tsu, V., Deeks, S. L., Cubie, H., Wang, S. A., Vicari, A. S., & Brotherton, J. M. L. (2012). Human Papillomavirus Vaccine Introduction – The First Five Years. *Vaccine*, *30*, F139–F148. https://doi.org/10.1016/j.vaccine.2012.05.039

Measles & Rubella Partnership. (2023). *About Us*. https://perma.cc/4CVU-EXAB

Mele, A., Jefferson, T., Franco, E., & Salmaso, S. (2002). Change from oral poliovirus vaccine to inactivated poliovirus vaccine. *The Lancet*, *360*, 1178.

Mitchell, V., Philipose, N., & Sanford, J. (1993). 4, Vaccine Demand and Supply. In *The Children's Vaccine Initiative: Achieving the Vision*. https://perma.cc/VES7-JS92

Mitra, M., Shah, N., Ghosh, A., Chatterjee, S., Kaur, I., Bhattacharya, N., & Basu, S. (2016). Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study. *Human Vaccines & Immunotherapeutics*, *12*(4), 939–945. https://doi.org/10.1080/21645515.2015.1117715

Mohan, V. K., Varanasi, V., Singh, A., Pasetti, M. F., Levine, M. M., Venkatesan, R., & Ella, K. M. (2015). Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clinical Infectious Diseases*, *61*(3), 393–402. https://doi.org/10.1093/cid/civ295

Morris, S. K., Moss, W. J., & Halsey, N. (2008). Haemophilus influenzae type b conjugate vaccine use and effectiveness. *The Lancet Infectious Diseases*, *8*(7), 435–443. https://doi.org/10.1016/S1473-3099(08)70152-X

Mulholland, K., Smith, P. G., Broome, C. V., Gaye, A., Whittle, H., & Greenwood, B. M. (1999). A randomised trial of a Haemophilus influenzae type b conjugate vaccine in a developing country for the prevention of pneumonia—Ethical considerations. *The International Journal of Tuberculosis and Lung Disease: The Official Journal of the International Union Against Tuberculosis and Lung Disease*, *3*(9), 749–755.

Paavonen, J., Jenkins, D., Bosch, F. X., Naud, P., Salmerón, J., Wheeler, C. M., Chow, S.-N., Apter, D. L., Kitchener, H. C., Castellsague, X., De Carvalho, N. S., Skinner, S. R., Harper, D. M., Hedrick, J. A., Jaisamrarn, U., Limson, G. A., Dionne, M., Quint, W., Spiessens, B., … Dubin, G. (2007). Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: An interim analysis of a phase III double-blind, randomised controlled trial. *The Lancet*, *369*(9580), 2161–2170. https://doi.org/10.1016/S0140-6736(07)60946-5

Paavonen, J., Naud, P., Salmerón, J., Wheeler, C., Chow, S.-N., Apter, D., Kitchener, H., Castellsague, X., Teixeira, J., Skinner, S., Hedrick, J., Jaisamrarn, U., Limson, G., Garland, S., Szarewski, A., Romanowski, B., Aoki, F., Schwarz, T., Poppe, W., … Dubin, G. (2009). Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double-blind, randomised study in young women. *The Lancet*, *374*(9686), 301–314. https://doi.org/10.1016/S0140-6736(09)61248-4

Pérez-Schael, I., Guntiñas, M. J., Pérez, M., Pagone, V., Rojas, A. M., González, R., Cunto, W., Hoshino, Y., & Kapikian, A. Z. (1997). Efficacy of the Rhesus Rotavirus–Based Quadrivalent Vaccine in Infants and Young Children in Venezuela. *New England Journal of Medicine*, *337*(17), 1181–1187. https://doi.org/10.1056/NEJM199710233371701

Reddy, R., Reddy, B., Sarangi, V., Reddy, S., Ella, R., & Vadrevu, K. M. (2022). A multi-centre, post-marketing surveillance study of Vi polysaccharide–tetanus toxoid conjugate vaccine (Typbar TCV®) in India. *Human Vaccines & Immunotherapeutics*, *18*(1), 1947761. https://doi.org/10.1080/21645515.2021.1947761

Ruiz-Palacios, G. M., Pérez-Schael, I., Velázquez, F. R., Abate, H., Breuer, T., Clemens, S. C., Cheuvart, B., Espinoza, F., Gillard, P., Innis, B. L., Cervantes, Y., Linhares, A. C., López, P., Macías-Parra, M., Ortega-Barría, E., Richardson, V., Rivera-Medina, D. M., Rivera, L., Salinas, B., … O'Ryan, M. (2006). Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis. *New England Journal of Medicine*, *354*(1), 11–22. https://doi.org/10.1056/NEJMoa052434

Sahastrabuddhe, S., & Saluja, T. (2019). Overview of the Typhoid Conjugate Vaccine Pipeline: Current Status and Future Plans. *Clinical Infectious Diseases*, *68*(Supplement_1), S22–S26. https://doi.org/10.1093/cid/ciy884

Schiller, J. T., Castellsagué, X., & Garland, S. M. (2012). A Review of Clinical Trials of Human Papillomavirus Prophylactic Vaccines. *Vaccine*, *30*, F123–F138. https://doi.org/10.1016/j.vaccine.2012.04.108

Smithsonian. (2023). *Measles, Mumps, and Rubella Vaccines*. https://perma.cc/ZH5G-KYE7

Stokes, J., Weibel, R., & Villarejos, V. (1971). Trivalent Combined Measles-Mumps-Rubella Vaccine: Findings in Clinical-Laboratory Studies. *JAMA*, *218*(1), 57. https://doi.org/10.1001/jama.1971.03190140033006

Sutter, R. W., Platt, L., Mach, O., Jafari, H., & Aylward, R. B. (2014). The New Polio Eradication End Game: Rationale and Supporting Evidence. *Journal of Infectious Diseases*, *210*(suppl 1), S434–S438. https://doi.org/10.1093/infdis/jiu222

Thiem, V. D., Lin, F.-Y. C., Canh, D. G., Son, N. H., Anh, D. D., Mao, N. D., Chu, C., Hunt, S. W., Robbins, J. B., Schneerson, R., & Szu, S. C. (2011). The Vi Conjugate Typhoid Vaccine Is Safe, Elicits Protective Levels of IgG Anti-Vi, and Is Compatible with Routine Infant Vaccines. *Clinical and Vaccine Immunology*, *18*(5), 730–735. https://doi.org/10.1128/CVI.00532-10

UNICEF. (2013a). *Measles-Containing Vaccines: Supply Update*. https://perma.cc/9CEL-SJS2

UNICEF. (2013b). *Pneumococcal Conjugate Vaccine: Current Supply & Demand Outlook*. https://perma.cc/R58M-NVNE

UNICEF. (2014). *Rotavirus Vaccine: Supply & Demand Update*. https://perma.cc/B6PU-484Q

UNICEF. (2017). *Pentavalent vaccine (DTwP-HepB-Hib): Market & Supply Update*. https://perma.cc/M3ZY-7YEE

UNICEF. (2019a). *Inactivated Polio Vaccine: Supply Update*. https://perma.cc/W4FB-LJAS

UNICEF. (2019b). *MARKET UPDATE – Inactivated Polio Vaccines*. https://perma.cc/9RKU-46GK

UNICEF. (2020a). *Human Papillomavirus Vaccine: Supply and Demand Update*. https://perma.cc/PMP4-B55U

UNICEF. (2020b). *Pneumococcal Conjugate Vaccine: Supply and Demand Update*. https://perma.cc/G9HK-ZTN7

UNICEF. (2022a). *DTP-HepB-Hib (Pentavalent) vaccine price data*. https://perma.cc/USL7-AWUF

UNICEF. (2022b). *Market & Supply Update – Typhoid Conjugate Vaccine (TCV)*. https://perma.cc/5252-3J7B

UNICEF. (2022c). *Measles and Measles-Rubella Combination Vaccines: Supply and Demand Update*. https://perma.cc/4R83-GLU8

UNICEF. (2022d). *Typhoid Conjugate Vaccine: Supply and Demand Update*. https://perma.cc/M8NW-KNZ3

United Nations Foundation. (2002). *The Measles Initiative Launched*. https://perma.cc/74QV-KG9A

United States Food and Drug Administration. (2006). *FDA Approves New Vaccine to Prevent Rotavirus Gastroenteritis in Infants*. http://wayback.archive-it.org/7993/20170112213635/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108588.htm

United States Food and Drug Administration. (2011). *Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) Prevnar®*. https://perma.cc/5QGC-TA3C

Van Den Biggelaar, A. H. J., & Pomat, W. S. (2013). Immunization of newborns with bacterial conjugate vaccines. *Vaccine*, *31*(21), 2525–2530. https://doi.org/10.1016/j.vaccine.2012.06.019

Vesikari, T., Matson, D. O., Dennehy, P., Van Damme, P., Santosham, M., Rodriguez, Z., Dallas, M. J., Heyse, J. F., Goveia, M. G., Black, S. B., Shinefield, H. R., Christie, C. D. C., Ylitalo, S., Itzler, R. F., Coia, M. L., Onorato, M. T., Adeyi, B. A., Marshall, G. S., Gothefors, L., … Heaton, P. M. (2006). Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine. *New England Journal of Medicine*, *354*(1), 23–33. https://doi.org/10.1056/NEJMoa052664

VIEW-hub. (2023a). *Hib – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/R6H9-YW57

VIEW-hub. (2023b). *HPV – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/2EXY-7SHU

VIEW-hub. (2023c). *IPV – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/CRS6-Q53S

VIEW-hub. (2023d). *MCV-2 – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/Y2UM-F323

VIEW-hub. (2023e). *PCV – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/LJ5V-LHQQ

VIEW-hub. (2023f). *RV – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/GH47-6EX3

VIEW-hub. (2023g). *Typhoid – Vaccine Introduction – Current Vaccine Intro Status*. https://perma.cc/Q2HX-NH2H

Vogel, L. (2011). WHO mulls phase out of vaccine linked to polio outbreaks. *Canadian Medical Association Journal*, *183*(18), E1303–E1304. https://doi.org/10.1503/cmaj.109-4027

Ward, J., Brenneman, G., Letson, G. W., & Heyward, W. L. (1990). Limited Efficacy of a *Haemophilus influenzae* Type b Conjugate Vaccine in Alaska Native Infants. *New England Journal of Medicine*, *323*(20), 1393–1401. https://doi.org/10.1056/NEJM199011153232006

Wikipedia contributors. (2023). *Pentavalent vaccine*. Wikipedia, The Free Encyclopedia. https://perma.cc/2V3Q-XVWC

World Bank. (2023). *World Bank Country and Lending Groups*. https://perma.cc/MP9W-YKCG

World Health Organization. (2007a). Pneumococcal conjugate vaccine for childhood immunization—WHO position paper. *Weekly Epidemiological Record*, *82*(12), 93–104.

World Health Organization. (2007b). Rotavirus vaccines. *Weekly Epidemiological Record*, *82*(82), 285–295.

World Health Organization. (2009a). Meeting of the immunization Strategic Advisory Group of Experts, November 2008 – conclusions and recommendations. *Weekly Epidemiological Record*, *84*(1–2), 1–16.

World Health Organization. (2009b). Rotavirus vaccines: An update. *Weekly Epidemiological Record*, *84*(51–52), 533–537.

World Health Organization. (2013). *Polio Eradication & Endgame Strategic Plan 2013-2018*. https://perma.cc/NXT4-L6LQ

World Health Organization. (2017). *Human challenge trials for vaccine development: Regulatory considerations*. https://perma.cc/P22Q-SG3F

World Health Organization. (2018a). *Timor-Leste—Sri Lanka twinning arrangement for institutional strengthening in immunization programme management in Timor-Leste*. https://perma.cc/4STP-YC72

World Health Organization. (2018b). Typhoid vaccines: WHO position paper – March 2018. *Weekly Epidemiological Record*, *93*(13), 153–172.

World Health Organization. (2019). Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. *Weekly Epidemiological Record*, *94*(8), 85–104.

World Health Organization. (2021). *Comparison table of WHO prequalified typhoid conjugate vaccines (TCVs)*. https://perma.cc/ZAT6-8XU8

World Health Organization. (2022a). *MI4A Vaccine purchase data*. https://perma.cc/ZY94-QGPL

World Health Organization. (2022b). *WHO says just one dose of HPV vaccine protects against cervical cancer*. https://perma.cc/X4B9-SXSV

World Health Organization. (2023a). *History of measles vaccination*. https://perma.cc/ZXY8-SVWT

World Health Organization. (2023b). *History of polio vaccination*. https://perma.cc/5LAN-TSF5

World Health Organization. (2023c). *Measles vaccination coverage*. https://perma.cc/3R7T-4MW2

World Health Organization. (2023d). *National Immunization Technical Advisory Groups (NITAGs)*. https://perma.cc/E8RR-QCKN

World Health Organization. (2023e). *Pneumococcal Disease*. https://perma.cc/SAZ2-26YN

World Health Organization. (2023f). *Prequalified vaccines – Haemophilus influenzae type b*. https://perma.cc/63MQ-55QE

World Health Organization. (2023g). *Prequalified vaccines – Human Papillomavirus (Bivalent, Ninevalent, Quadrivalent)*. https://perma.cc/VW8A-B98Z

World Health Organization. (2023h). *Prequalified vaccines – Measles*. https://perma.cc/NR6P-PKMS

World Health Organization. (2023i). *Prequalified vaccines – Measles and Rubella*. https://perma.cc/P9XF-5XQ9

World Health Organization. (2023j). *Prequalified vaccines – Pneumococcal (conjugate)*. https://perma.cc/KVV3-CL4W

World Health Organization. (2023k). *Prequalified vaccines – Polio Vaccine—Inactivated (IPV)*. https://perma.cc/XC8C-2TRJ

Yeh, S. H., Gurtman, A., Hurley, D. C., Block, S. L., Schwartz, R. H., Patterson, S., Jansen, K. U., Love, J., Gruber, W. C., Emini, E. A., Scott, D. A., & on behalf of the 004 Study Group. (2010). Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine in Infants and Toddlers. *Pediatrics*, *126*(3), e493–e505. https://doi.org/10.1542/peds.2009-3027

Zarei, A. E., Almehdar, H. A., & Redwan, E. M. (2016). Hib Vaccines: Past, Present, and Future Perspectives. *Journal of Immunology Research*, *2016*, 1–18. https://doi.org/10.1155/2016/7203587