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Chasing Polio Eradication: Vaccine Development

In mid-2018, Dr. Steve Cochi, former chair of the Advisory Committee on Polio Eradication, and Dr. Bruce Aylward and Dr. Roland Sutter of the World Health Organization (WHO) sat together reflecting on what the bivalent oral polio vaccine (bOPV) had done to change the trajectory of the single-largest internationally coordinated public health effort in history—the Global Polio Eradication Initiative. After a peak of around 600,000 polio cases per year in the mid-twentieth century before the introduction of vaccine, case numbers had decreased to 13 wild-type and 16 vaccine-derived cases in 2018. Cochi and Sutter had managed the bOPV development starting in 2007. It was integrated into supplementary immunization activities in 2009 and became used in all routine immunization activities in 2016. They had been hopeful bOPV would allow endemic countries to eliminate polio once and for all, but vaccination, and therefore elimination efforts, were impeded by ongoing insecurity in several regions. With the delay, the molecular epidemiology of the disease continued to evolve. Over a decade after Cochi and Sutter's initial push to integrate the new tool, it wasn't clear whether bOPV was the answer or just a piece of the puzzle. What could they learn from the experience to expedite the final mile of eradication? What could other disease elimination efforts learn from the experience?

Polio

Poliovirus is an enterovirus with three different serotypes: 1, 2 and 3. The virus is transmitted predominantly via the fecal-oral route, particularly in developing countries where sanitation and hygiene are a problem. People infected with polio, whether or not they have symptoms, excrete, or "shed," the virus in their stool for four to six weeks after contracting the virus. Once a person contracts polio, she develops lifelong immunity to the serotype of the virus that infected her but is still susceptible to the other serotypes.

In 1988, when 125 countries were polio endemic and the virus paralyzed more than 350,000 children (fewer than 1% of polio infections are associated with paralysis), the World Health Assembly passed a resolution committing to eradicate poliomyelitis.[1] The disease burden; the availability of an affordable, safe, and effective vaccine; and early evidence of the feasibility of polio eradication inspired the policy. Later that

Julie Rosenberg and Rebecca Weintraub prepared this case with assistance from Amy Madore for the purposes of classroom discussion rather than to illustrate either effective or ineffective health care delivery practice.

year, national governments worked with four partners—WHO, Rotary International, the US Centers for Disease Control and Prevention (CDC), and the United Nations Children's Fund (UNICEF)—to form a public-private partnership, the Global Polio Eradication Initiative (GPEI), to eradicate polio through vaccination and surveillance (see **Exhibit 1** for the roles of each partner**)**. Over time, USD 15 billion had been donated to the program; a fifth partner—the Bill & Melinda Gates Foundation—joined the partnership; and an estimated 17.5 million cases of paralysis in children had been prevented (see **Exhibit** 2 for yearly case estimates). It was estimated that eradicating polio would save USD 50 billion.

Vaccines

Two different types of vaccines were used to immunize against polio: an inactivated polio vaccine (IPV) and an orally administered polio vaccine (OPV).[1] IPV—developed by Jonas Salk and first licensed for use in 1955—was a chemical mixture of killed virus. It induced an antibody-mediated immune response that prevented the virus from spreading to the nervous system. It induced little gut immunity, however, and therefore did not prevent immunized persons from carrying and spreading poliovirus to others through the fecal-oral route. The vaccine required at least two doses and cost more than five times as much as OPV.[2]

OPV—developed by Albert Sabin and approved for use in the 1960s—contained attenuated or weakened live virus. The trivalent oral poliovirus vaccine (tOPV) consisted of live, attenuated wild poliovirus strains 1, 2, and 3. Monovalent OPVs (mOPVs) induced immunity to just one of the three serotypes, but at a higher rate of seroconversion than tOPV; thus, OPV induced a more robust immune response. OPV could be delivered by untrained volunteers but was very sensitive and lost potency when exposed to heat. Because live virus was shed in stool, by fecal-oral spread, it could confer some immunity on close contacts of immunized individuals. A person was considered fully immunized to polio after receiving at least three doses.[3] There was a slight risk (2–4 cases/million doses of tOPV administered) that the attenuated virus would revert to its more virulent wild-type strain and cause vaccine-associated paralysis in vaccine recipients or their close contacts.[4] In April 2016, through an unprecedented globally synchronized set of activities, 155 countries and territories phased out the use of tOPV in routine immunization schedules and for supplementary immunization activities, replacing it with bOPV.

Global Polio Eradication

The 1990s saw progress in polio eradication. WHO certified the Americas, Western Pacific, and Europe regions as "polio-free." Type 2 wild poliovirus was eradicated in 1999, with the last naturally acquired case occurring in Aligarh, India. By early in the new millennium, overall polio disease incidence had declined by 99%, primarily due to the use of tOPV. Soon, however, progress began to plateau. In 2007, polio types 1 and 3 were considered endemic in key areas of four countries: India, Nigeria, Pakistan, and Afghanistan (see **Exhibit 3** for map of cases). On several occasions, mOPV1 campaigns reduced type 1 cases, but saw a coinciding spike in type 3 cases. Additionally, there were an increasing number of outbreaks in previously polio-free countries, due to international spread.

A New Tool

Co-circulation of poliovirus types 1 and 3 in the endemic countries (Nigeria, India, Pakistan, and Afghanistan) required frequent interchange of tOPV, mOPV1, and mOPV3 during supplementary immunization activities. Researchers had also found that those fully vaccinated with tOPV had a lower immune response than those vaccinated with mOPV.[5] "The failure to vaccinate was problematic but vaccine

failure was problematic too," commented Dr. Walter Orenstein, former Director of the United States Immunization Program and a WHO Strategic Advisory Group of Experts (SAGE) on Immunization member. Leaders decided the optimum way to address areas with co-circulation was through the development and large-scale administration of a new vaccine: bivalent OPV containing type 1 and 3 serotypes. Cochi explained, "It was really a question of maximizing the operational and epidemiological benefits of protecting children. We needed a tool to effectively and operationally tackle both serotypes at the same time."

Realizing that bOPV could be the missing link to eradication, leaders consulted the donor community. "Having the GPEI in place was critical because they provided funding as well as political support," Orenstein commented.

National regulatory authorities (NRAs)—the bodies responsible for ensuring that products (pharmaceutical and biological) were evaluated properly and met quality and safety standards—were hesitant about introducing bOPV without efficacy and safety data. It was not clear whether bOPV would be as immunogenic against type 1 poliovirus as mOPV: Could bOPV compromise efforts to eradicate type 1 poliovirus?

In November 2007, the Advisory Committee for Poliomyelitis Eradication—an independent technical oversight body of GPEI, composed of global public health, vaccinology, and epidemiology experts—recommended that bOPV be at least 80% as efficacious as mOPV1 and mOPV3 in terms of seroconversion to qualify for licensure. They advised conducting a clinical study. Given the urgency of the situation, they wanted to optimize time and resources to accelerate, or fast-track, the standard pharmaceutical research and development pathway (see **Exhibits 4a and 4b** for the standard biopharma research and development pipeline). As bOPV was created with the same formulation as tOPV, minus the mOPV2 component, it was not necessary to provide *de novo* evidence of vaccine safety. The clinical trial was therefore able to bypass clinical trial phases I and II and move directly to testing the new formulation (phase III trial).

Vaccine Research

Cochi and Sutter had to consider the cost of a clinical trial as they began to plan. The average cost of traditional phase III clinical trials, typically done in the private sector, ranged from USD 11.5 million to USD 52.9 million.[6] WHO's Research and Product Development team helped create a bOPV clinical trial protocol that would leverage funds from Gavi, the Vaccine Alliance. Ongoing co-circulation of both type 1 and type 3 poliovirus in India and the infrastructure and functioning regulatory authorities in place there made India an appealing site for the trial. The Drug Controller General of India, Indian National Regulatory Authority, would allow drug licensure only for data collected in India, which also made completing the study there efficient. Cochi and Sutter learned that an evaluation of mOPV and tOPV had already been planned in India, to which a further bOPV arm could easily be added.

WHO consulted with multiple pharmaceutical companies to generate interest in developing bOPV for the study; Panacea Biotech, based in India, was chosen. Panacea, which was already in compliance with national laws, was responsible for supplying the vaccines and monitoring the clinical trial to ensure it was conducted in accordance with Good Clinical Practice (GCP) guidelines. The Enterovirus Research Centre in Mumbai, which was part of the global polio laboratory network, was chosen for analysis of blood and stool samples.

WHO visited around 10 hospitals to select study sites with high birth rates, strong clinical and research expertise, previous clinical trial experience, established ethics committees, and enthusiasm for collaborating.

WHO and hospital ethics committees then had to approve the protocol. WHO informed India's National Ministry of Health and the local state health ministries of the trial, given its potential significance.

Trial

Infants identified at the antenatal stage or at admission of delivery with clear inclusion criteria (minimum birth weight, geographic proximity to the research study, etc.) born in August through October of 2008 were randomly allocated to one of the five study arms: bOPV, tOPV, mOPV1, mOPV2, and mOPV3 (see **Exhibit 5** for trial profile). Infants received one dose of vaccine at birth and again at 30 days, administered by local field volunteers specifically trained for the trial. Blood samples taken at birth, 30 days, and 60 days were shipped to the research center for seropositivity testing. The clinical trial, which enrolled 178 infants, was completed in five months by December 2008. The WHO Quality Safety and Standards of the Department for Immunization, Vaccines and Biologicals was responsible for testing the sampled lots of bOPV used in the trial for accuracy and quality.[7]

Results

Dr. Harish Verma, the clinical trial expert at the World Health Organization who coordinated and oversaw implementation in India, reported, "The clinical trial results demonstrated clearly that bOPV was significantly better at protecting children against type 1 and 3 polio than tOPV, and it offers similar protection against the type 1 and 3 serotypes, compared to the respective monovalent OPVs. It offered all the serological benefits of mOPV, without the operational drawbacks—the best of both worlds" (see **Exhibit 6** for trial results). The clinical trial for bOPV in total cost USD 300,000, including the cost of the three study sites, laboratory, trial insurance, independent monitoring, and the outsourced data management company.

Immediately after the clinical trial results became available in summer 2019, the Advisory Committee on Polio Eradication organized a conference call with the WHO polio team and reviewed the results. It concluded that bOPV should be rolled out in immunization campaigns on a large scale. Cochi explained, "bOPV was now an important new tool in the global eradication effort."

The Advisory Committee on Polio Eradication recommendation accelerated production and campaign planning. Areas reporting outbreaks of polio types 1 and 3 were prioritized. Soon a campaign calendar detailed where bOPV would be rolled out and on what scale, with two-year vaccine supply forecasts. This was shared with vaccine manufacturers, who were cautioned to maintain some flexibility.

Getting to Market

The WHO vaccine prequalification team was responsible for approving the acceptability of drugs for various UN agencies. The team developed a regulatory paper on bOPV, which justified why an extensive clinical trial was not required for this vaccine and why the non-inferiority trial in India was sufficient for licensure. The WHO Essential Medicines and Health Products department was responsible for working closely with countries and their National Regulatory Authorities (NRAs) to promote affordable, quality, safe, and effective access to medications, diagnostics, and products. WHO, in collaboration with Panacea, had also developed a clinical trial report that was released to vaccine manufacturers in July 2009. The WHO Essential Medicines and Health Products team had ample information to support bOPV approvals.

To engage manufacturers to produce vaccine for the public market and connect them to the GPEI, the WHO Polio Eradication team and UNICEF held a manufacturers' consultation meeting for OPV and IPV manufacturers, national regulatory authorities, and GPEI partners. The UNICEF Supply Division—

responsible for procuring vaccine for the GPEI campaign and outbreak requirements and routine immunization for 80 countries at a preferential price—presented a global update, programmatic timelines, a vaccine forecast, and production requirements. WHO's dedicated polio prequalification expert addressed queries from manufacturers, and the GPEI team spoke about the importance of ongoing close collaboration among all involved in the effort.

Shortly after the meeting, five manufacturers sought national licensure for bOPV production: Panacea (India), Haffkine (India), Bharat Serums and Vaccines (India), Sanofi-Pasteur (France), and GlaxoSmithKline (GSK; Belgium). Based on the supply capacity from these manufacturers, the annual requirement of at least one billion doses per year was secured. (The costs of OPV formulations from different manufacturers are provided in **Exhibit 7**.) While typically each manufacturer would have to repeat phase III clinical trials to show clinical efficacy and safety of its product before applying for licensure to the relevant NRAs, WHO engaged in discussions with the NRAs and shared the clinical trial reports with the manufacturers for discussions with NRAs to see whether these could be used to license their product.

Dr. Jacqueline Fournier-Caruana, a scientist at WHO who worked on vaccine licensing and prequalification, commented, "The very rapid process from field test to actual field application of this vaccine was the result of an extraordinary collaboration between governments, WHO, UNICEF, vaccine manufacturers, and national regulatory authorities."

WHO's prequalification team had to formally certify the quality, safety, and efficacy of bOPV after national licensure to enable the UN to purchase the vaccine. They reviewed the bOPV dossier in parallel with the NRAs to shorten process times for prequalification. Countries in which NRAs had limited capacity relied on WHO prequalification process.

GSK and Panacea were granted bOPV licensure in Belgium and India in October and November of 2009, respectively, with prequalification following shortly. Afghanistan accepted WHO prequalification as sufficient to allow bOPV delivery to the country. While Pakistan required a review by the national regulatory authority for full national licensure before accepting the product, it did not require further clinical trials, and the NRA of Pakistan granted licensure in February 2010 for GSK bOPV.

Initial Roll-out/Production-Distribution

The first Supplementary Immunization Activity (SIA) using bOPV took place in Afghanistan on December 15–17, 2009, administering approximately 3.5 million doses to children aged 0–5 years. The roll-out of bOPV in Afghanistan, combined with an increasing number of vaccine manufacturers with licensed and prequalified vaccines, spurred rapid scale-up in supply during the first half of 2010. Further SIAs using bOPV were conducted in Afghanistan, and national and subnational immunization days using bOPV were held across Somalia, Nigeria, India, Bangladesh, Pakistan, Sudan, Niger, Benin, and Nepal. The first half of 2010 saw the roll-out of 485 million doses of bOPV; 266 million of these were in India (see **Exhibit 8** for the supply of bOPV from 2008 to 2012). Demand grew quickly. "The vaccine was rolled out—from idea to field implementation—in record time," stated Dr. Arshad Quddus, polio team leader, WHO Afghanistan.

Communication Strategies

When bOPV was introduced the public polio vaccination messaging from the WHO and UNICEF remained almost entirely unchanged. During supplementary immunization activities, caregivers were still informed that the vaccine was an oral poliovirus vaccine, and immunization activities were conducted as normal. "We did not want any possible rebranding of the vaccine to result in communities believing it to be entirely different and less likely to trust its safety than before, making high coverage

harder to achieve," explained Jalaa' Abdelwahab, Deputy Director to Polio Eradication at UNICEF Headquarters. "Our ultimate goal was still reaching and vaccinating every child under 5 years of age with a sharp focus on the most disadvantaged and marginalized."

GPEI did conduct a comprehensive communication campaign targeting policymakers and healthcare providers about the new formulation and why it was superior to tOPV, with emphasis placed on the fact it was just like the normal tOPV in all ways (administration, action, content) except for the removal of the polio type 2 component and a better immunity response for the other two polio serotypes (1 and 3). With GPEI support, ministries of health then informed district-level staff and vaccinators of the new vaccine and its efficacy and offered the opportunity to engage in an open dialogue.

Looking to the Future

The roll-out of bOPV brought new hope. "Bivalent OPV was really a game-changer," said Dr. Jay Wenger, polio director at the Bill & Melinda Gates Foundation. "When we were using mOPV1 and mOPV3 in different areas in India, we ended up getting outbreaks of type 3 where we had been vaccinating for type 1, and vice versa. With bOPV, we now had all the necessary tools to stop polio in India. And if we could do it there, we could do it anywhere."

Sutter explained:

> Success, in particular in India, clearly demonstrated to the world that polio eradication is indeed feasible [see **Exhibit 9** for cases in India]. If it can be done here, it can be done everywhere. This meant that the remaining challenges were no longer technical in nature, but political and societal. Essentially, if we now do not eradicate polio, we can only blame ourselves for not coming up with the necessary political will to fully implement or fund the eradication strategies. But failure will not have been because we did not have the tools.

Few, if any, other diseases had the same potential for eradication. Cochi added:

> Everybody shifted up a gear. WHO declared ending polio a programmatic emergency for global public health. Countries declared any polio transmission "national public health emergencies." There was gain in political desire and momentum, and institutions such as the G7 committed to call for the resources to be in place for polio eradication.

The World Health Assembly called on the WHO Director-General to develop and finalize a comprehensive polio endgame strategy.

While bOPV would be a critical tool for polio eradication due to the association of vaccine-derived poliovirus with OPV, particularly type-2, countries would eventually need to stop use of all OPVs and move to an IPV-only routine immunization schedule. "We had learned that we needed to measure vaccine impact not by coverage but by disease surveillance," Orenstein explained. The first step in the phased cessation of OPV was the globally synchronized switch from tOPV to bOPV for routine polio immunization and supplementary immunization activities (which account for 75% of demand) in April 2016 among 155 countries and territories having an all OPV schedule.

Type 2 poliovirus had been declared globally eradicated in 2015, and type 3 poliovirus had not been detected anywhere since 2012. In mid-2018, large-scale administration of bOPV was continuing, with fewer cases of disease reported from fewer areas of fewer countries than ever before in history. The world stood on the cusp of a historic public health success, unparalleled since the eradication of smallpox.

"The big issue is insecurity. I don't think it's any coincidence that Afghanistan and Pakistan are the two biggest problems. That's not a technological issue. If your vaccinators are killed, the issue is building trust and capacity. That's what we have to do to eradicate polio." Orenstein concluded.

What could other eradication and elimination efforts learn from the polio experience? And how could the last decade of polio eradication inform future efforts? How much should the global community continue investing in disease surveillance? In the next generation of vaccines, or in building the human capital to deliver to the last mile?

Exhibit 1 *Roles of Partners in Global Polio Eradication Initiative*

- WHO, as the lead organization, provides overall strategic planning, technical direction and support, and is responsible for the surveillance and certification process. WHO also coordinates operations, resource mobilization, donor contributions, and advocacy activities.

- Rotary International's primary responsibilities include fundraising, advocacy, and volunteer recruitment. It was the first to inspire the vision of a polio-free world. Over the years more than a million Rotarian volunteers have taken part in national immunization days, joining in social mobilization activities and administering oral polio vaccine to children.

- The CDC deploys epidemiologists, public health experts, and other scientists to WHO and UNICEF for the eradication initiative. It also provides funding for the oral polio vaccine and for a wide range of technical expertise and laboratory support.

- UNICEF's role is to secure, procure, and deliver vaccines and support countries in developing and implementing communication and social mobilization strategies. Together with partners, it supports countries in running national immunization days, sub-national immunization days, and mop-up campaigns, as well as resource mobilization and advocacy efforts. It also works with the vaccine industry on long-term planning to maintain sufficient supplies through a healthy supplier base of oral and injectable polio vaccines required by the GPEI to achieve and maintain a polio-free world.

Although not anticipated at the outset, the GPEI gradually evolved into a broad-based global public-private initiative. In recent years, the Bill & Melinda Gates Foundation joined the four spearheading partners as a leading partner and major funder. The World Bank and donor governments are also major GPEI funders. Other partners include the United Nations Foundation and other private foundations, development banks, the European Commission, humanitarian and non-governmental organizations, corporate partners, and volunteers.

Source: UNICEF's Engagement in the Global Polio Eradication Initiative.

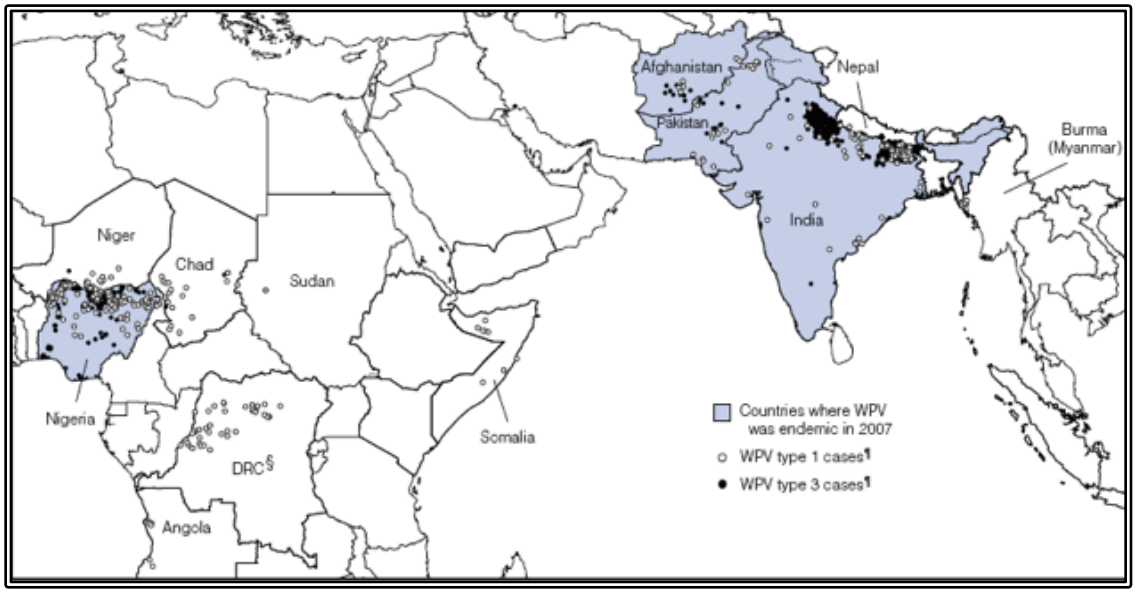
Exhibit 2 *Estimated Number of Polio Cases Adverted with GPEI*

Year	Potential polio cases	Polio cases	Polio cases averted
1988	632,676	350,000	282,676
1989	643,954	261,000	382,954
1990	592,830	233,000	359,830
1991	605,651	134,000	471,651
1992	615,193	137,000	478,193
1993	624,735	76,000	548,735
1994	634,277	73,000	561,277
1995	586,475	60,000	526,475
1996	599,725	33,000	566,725
1997	607,813	18,000	589,813
1998	615,901	10,000	605,901
1999	623,989	10,000	613,989
2000	595,557	719	594,838
2001	611,090	483	610,607
2002	618,830	1,918	616,912
2003	626,570	784	625,786
2004	634,310	1,255	633,055
2005	614,794	1,979	612,815
2006	630,567	1,997	628,570
2007	638,399	1,315	637,084
2008	646,231	1,651	644,580
2009	654,063	1,604	652,459
2010	632,550	1,352	631,198
2011	646,322	650	645,672
2012	654,044	223	653,821
2013	661,766	416	661,350
2014	669,488	359	669,129
2015	635,321	72	635,249
2016	649,679	37	649,642
2017	657,884	22	657,862
Total	18,860,683	1,411,836	17,448,847

Note: The number of polio cases adverted was calculated as the difference between the number of potential polio cases in the absence of any vaccination and the reported polio cases per year. Potential polio cases were based on annual births, under-5 infant mortality, and a poliovirus case-to-infection ratio of 1:200.

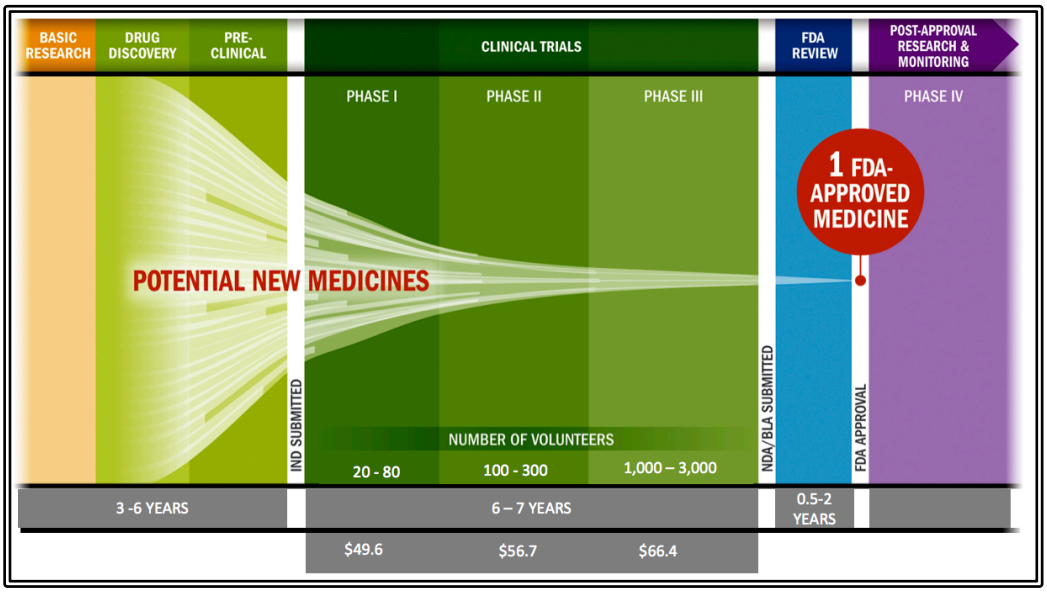
Source: GPEI analysis.

Exhibit 3 *Map of Wild Polio Cases in 2007*



Source: Centers for Disease Contol Prevention. Progress toward interruption of wild poliovirus transmission worldwide, January 2007–April 2008. MMWR Morb Mortal Wkly Rep. 2008;57(18):489-494.

Exhibit 4a *Standard Biopharma Research and Development Timeline and Cost (US Millions) for a Pharmaceutical Medicine (Drug or Vaccine)*



Source: Adapted from PhRMA, US Food and Drug Administration drug infographic and Di Masi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ. 2016.

Exhibit 4b *Vaccine Clinical Development in the US Under the US Food and Drug Administration (FDA), the National Regulatory Authority*

Vaccine clinical development follows the same general pathway as for drugs and other biologics. A sponsor who wishes to begin clinical trials with a vaccine must submit an Investigational New Drug application (IND) to FDA. The IND describes the vaccine, its method of manufacture, and quality control tests for release. Also included are information about the vaccine's safety and ability to elicit a protective immune response (immunogenicity) in animal testing, as well as the proposed clinical protocol for studies in humans.

Pre-marketing (pre-licensure) trials are typically done in three phases. Initial human studies, referred to as Phase 1, are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies are dose-ranging studies and may enroll hundreds of subjects. Finally, Phase 3 trials typically enroll thousands of individuals and provide the critical documentation of effectiveness and important additional safety data required for licensing. At any stage of the clinical or animal studies, if data raise significant concerns about either safety or effectiveness, FDA may request additional information or studies, or may halt ongoing clinical studies.

If successful, the completion of all three phases of clinical development can be followed by the submission of a Biologics License Application (BLA). To be considered, the license application must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the efficacy and safety information necessary to make a risk/benefit assessment and to recommend or oppose the approval of a vaccine. Also during this stage, the proposed manufacturing facility undergoes a pre-approval inspection during which production of the vaccine as it is in progress is examined in detail.

Following FDA's review of a license application for a new indication, the sponsor and the FDA may present their findings to FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). This non-FDA expert committee (scientists, physicians, biostatisticians, and a consumer representative) provides advice to the Agency regarding the safety and efficacy of the vaccine for the proposed indication.

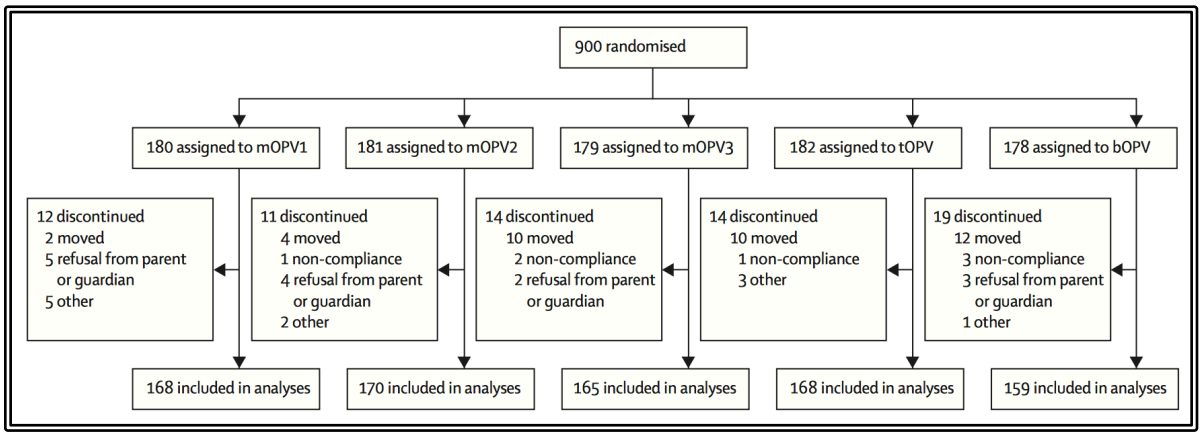
Vaccine approval also requires the provision of adequate product labeling to allow health care providers to understand the vaccine's proper use, including its potential benefits and risks, to communicate with patients and parents, and to safely deliver the vaccine to the public.

Until a vaccine is given to the general population, all potential adverse events cannot be anticipated. Thus, many vaccines undergo Phase 4 studies-formal studies on a vaccine once it is on the market.

The FDA continues to oversee the production of vaccines after the vaccine and the manufacturing processes are approved, in order to ensure continuing safety.

Source: US Food and Drug Administration. Available at: https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/ucm133096.html

Exhibit 5 *Trial Profile of Bivalent Oral Poliovirus Vaccine Clinical Trial in India, 2008*



Source: Sutter RW, John TJ, Jain H, Agarkhedkar S, Ramanan PV, Verma H, et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet. 2010;376(9753):1682-1688.

Exhibit 6 *Results of Bivalent Oral Poliovirus Vaccine Clinical Trial, India 2008*

	mOPV1 (n=168)	mOPV2 (n=170)	mOPV3 (n=165)	tOPV1 (n=168)	bOPV1 (n=159)	p value
At 30 days						
To poliovirus type 1	33/168 (20%, 14–26%)	9/170 (5%, 3–10%)	7/165 (4%, 2–8%)	25/168 (15%, 10–21%)	32/159 (20%, 14–27%)	NS
To poliovirus type 2	7/168 (4%, 2–8%)	35/170 (21%, 15–27%)	4/165 (2%, 1–6%)	42/168 (25%, 19–32%)	6/159 (4%, 2–8%)	NS
To poliovirus type 3	5/168 (3%, 1–7%)	0 (0%, 0–2%)	20/165 (12%, 8–18%)	7/168 (4%, 2–8%)	11/159 (7%, 4–12%)	0.01 for mOPV3 vs tOPV
At 60 days						
To poliovirus type 1	117/135 (87%, 80–92%)	19/161 (12%, 8–18%)	13/158 (8%, 5–13%)	77/143 (54%, 46–62%)	102/127 (80%, 73–87%)	<0.0001 for mOPV1 and bOPV vs tOPV
To poliovirus type 2	14/161 (9%, 5–14%)	114/135 (84%, 78–90%)	17/161 (11%, 6–16%)	107/126 (85%, 78–90%)	12/153 (8%, 4–13%)	NS
To poliovirus type 3	8/163 (5%, 2–9%)	8/170 (5%, 2–9%)	117/145 (81%, 74–89%)	79/161 (49%, 41–57%)	105/148 (71%, 63–78%)	<0.0001 for mOPV3 and bOPV;* 0.0002 for bOPV vs tOPV
Cumulative						
To poliovirus type 1	151/168 (90%, 85–94%)	29/170 (17%, 12–23%)	21/165 (13%, 8–19%)	106/168 (63%, 56–70%)	136/159 (86%, 79–90%)	<0.0001 for mOPV1 and bOPV vs tOPV
To poliovirus type 2	22/168 (13%, 9–19%)	153/170 (90%, 85–94%)	21/165 (13%, 8–19%)	153/168 (91%, 86–95%)	18/159 (11%, 7–17%)	NS
To poliovirus type 3	13/168 (8%, 4–13%)	8/170 (5%, 2–9%)	138/165 (84%, 77–89%)	87/168 (52%, 44–59%)	117/159 (74%, 66–80%)	<0.0001 for mOPV3 and bOPV vs tOPV

Data are n/N (%, 95% CI). Only p values ≤0.01 are presented for poliovirus type-specific comparisons. NS = not significant.

Source: Sutter RW, John TJ, Jain H, Agarkhedkar S, Ramanan PV, Verma H, et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet. 2010;376(9753):1682-1688.

Exhibit 7 *Cost of Oral Polio Virus Vaccines, 2001–2021*

Presentation	Supplier Name	OPV									
		2001	2013	2014	2015	2016	2017	2018	2019	2020	2021
Trivalent OPV vaccine in a 10-dose vial presentation	GlaxoSmithKline Biologicals S.A.	$0.1020	$0.1800	$0.1800	$0.1800						
	Sanofi Pasteur	$0.0856	$0.2050	$0.2050	$0.2050						
	Novartis Vaccines and Diagnostics	*									
Bivalent OPV vaccine in a 10-dose vial presentation	Bharat Biotech							$0.1790	$0.1790		
	P.T. Bio Farma (Persero)							$0.1400	$0.1400	$0.1450	
	GlaxoSmithKline Biologicals S.A.					$0.1800	$0.1800	$0.1800	$0.1800		
	Serum Institute of India Ltd.*					$0.1900	$0.1900				
Trivalent OPV vaccine in a 20-dose vial presentation	Bharat Biotech				$0.1345	$0.1345					
	GlaxoSmithKline Biologicals S.A.	$0.0960	$0.1350	$0.1350	$0.1350	$0.1350					
	Haffkine Bio-Pharmaceutical Corp		0.1425-$0.1325	$0.1325	$0.1325						
	P.T. Bio Farma (Persero)		$0.1235	$0.1235	$0.1235	$0.1235					
	Panacea Biotec Ltd.										
	Sanofi Pasteur	$0.0791	$0.1400**	$0.1400**	$0.1400**	$0.1400					
	Serum Institute of India Ltd.		$0.1400	$0.1400	$0.1400	$0.1400					
	Statens Serum Institut	$0.0710									
	Novartis Vaccines and Diagnostics	*	*								
Monovalent type 1 OPV vaccine in a 20-vial presentation	GlaxoSmithKline Biologicals S.A.										
	Haffkine Bio-Pharmaceutical Corp										
	P.T. BioFarma (Persero)										
	Panacea Biotec Ltd.										
	Sanofi Pasteur										
	Statens Serum Institut										

	Novartis Vaccines and Diagnostics			*							
Monovalent type 3 OPV vaccine in a 20-vial presentation	GlaxoSmithKline Biologicals S.A.										
	Panacea Biotec Ltd.										
	Novartis Vaccines and Diagnosis										
Bivalent types 1 and 3 OPV vaccine in a 20-vial presentation	Beijing Bio-Institute Biological							$0.0952	$0.1200		
	Bharat Biotech				$0.1259	$0.1259	$0.1259	$0.1150	$0.1245		
	GlaxoSmithKline Biologicals S.A.		$0.1350	$0.1350	$0.1350	$0.1350	$0.1350	$0.1350	$0.1350		
	Haffkine Bio-Pharmaceutical Corp		$0.1300	$0.1300	$0.1300	$0.1300	$0.1300	$0.1100			
	P.T. Bio Farma (Persero)		$0.1200	$0.1200	$0.1200	$0.1200	$0.1200	$0.1200	$0.1200	$0.1200	
	Panacea Biotec Ltd.										
	Sanofi Pasteur		$0.1400**	$0.1400**	$0.1400**	$0.1450	$0.1450	$0.1750**	$0.1950	$0.1950	$0.1650**
	Serum Institute of India Ltd.										
	Novartis Vaccines and Diagnostics										

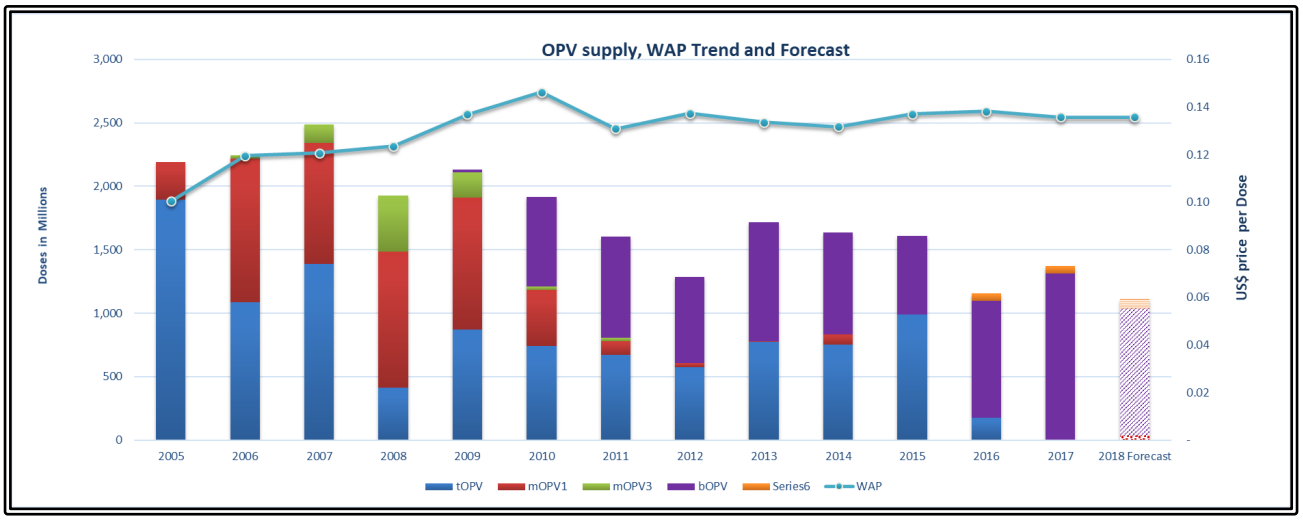
By 2018, there were nine pharmaceutical companies manufacturing 10- or 20-vial presentations of bOPV under five different NRAs.

* Supplier has not agreed to the publication of prices.

**Special terms apply.

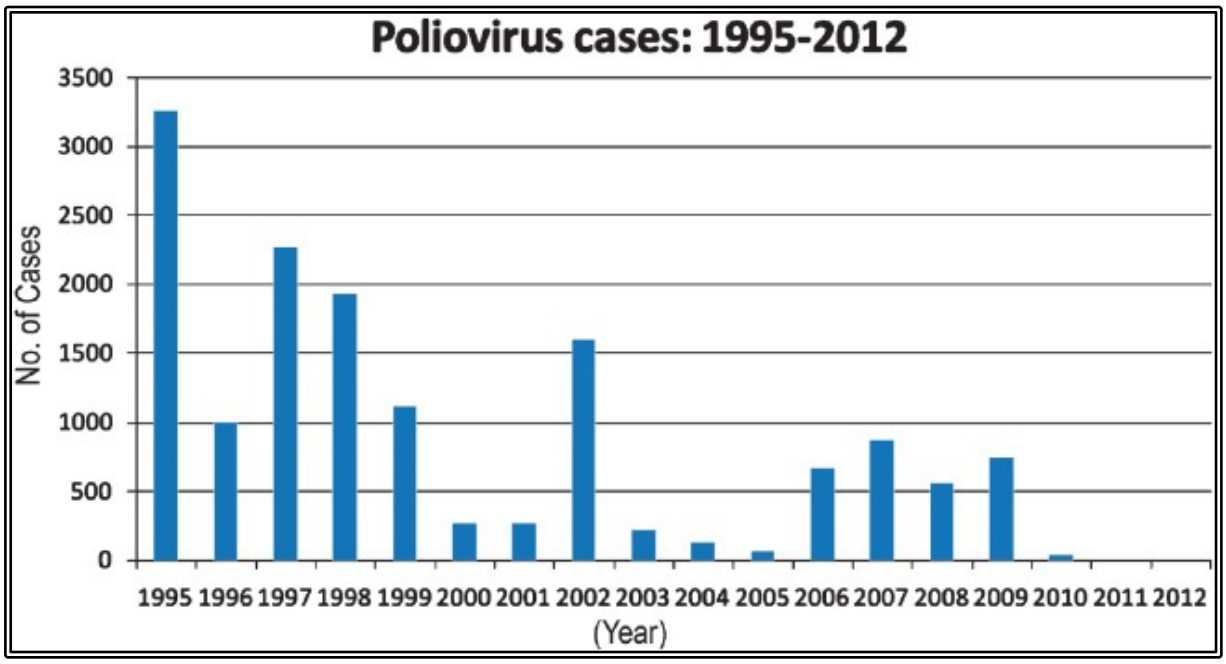
Source: UNICEF Supply Division.

Exhibit 8 *Supply History and Breakdown of OPV Vaccines*



Source: UNICEF Supply Division.

Exhibit 9 *Number of Wild Poliovirus Cases in India*



Source: Jacob John, T and Vashishtha, VM. Eradicating poliomyelitis: India's journey from hyperendemic to polio-free status. Indian Journal of Medical Research. 2013; 137(5):881-894.

References

1. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. Annu Rev Microbiol. 2005;59:587-635.
2. SabinVaccine Institute. Polio Vaccines 2007 [Available from: http://sabin.org/vaccine_science/polio.html.]
3. Centers for Disease Control and Prevention. Polio Disease: Questions and Answers 2007 [Available from: http://www.cdc.gov/vaccines/vpd-vac/polio/dis-faqs.htm.]
4. Global Polio Eradication Initiative. Polio Vaccines 2008 [Available from: http://www.polioeradication.org/vaccines.asp.]
5. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. Rev Infect Dis. 1991;13(5):926-39.
6. Sertkaya A, Wong H, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. Clinical Trials. 2016; 13(2): 117-126. doi.org/10.1177/1740774515625964
7. Sutter RW, John TJ, Jain H, Agarkhedkar S, Ramanan PV, Verma H, et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet (London, England). 2010;376(9753):1682-8.