I'm seeing some (entirely justified) concern about the possibility of the US no longer having a polio vaccination program given the threat posed by the incoming administration and I feel like this is a really good opportunity to explain some things about polio to clarify what the risks are 🧵

To start, we should talk about how polio is spread. People infected with polioviruses can shed them in their stool because the virus replicates in their gut, and also through upper respiratory secretions. This mode of transmission has some interesting consequences for the spread of polio.

A common refrain from the antivax lobby is that improvements in treatments, nutrition, and hygiene are responsible for our victories against vaccine-preventable diseases. While it is of course true that all of these things were positive developments for the human condition as a whole...

sanitation actually made polio significantly worse. Why? It goes back to the nature of polio spread. Before sanitation of the water supply, polio was ubiquitous in the environment. Exposure happened very early in life, even in infancy- at which point maternal antibodies were present.

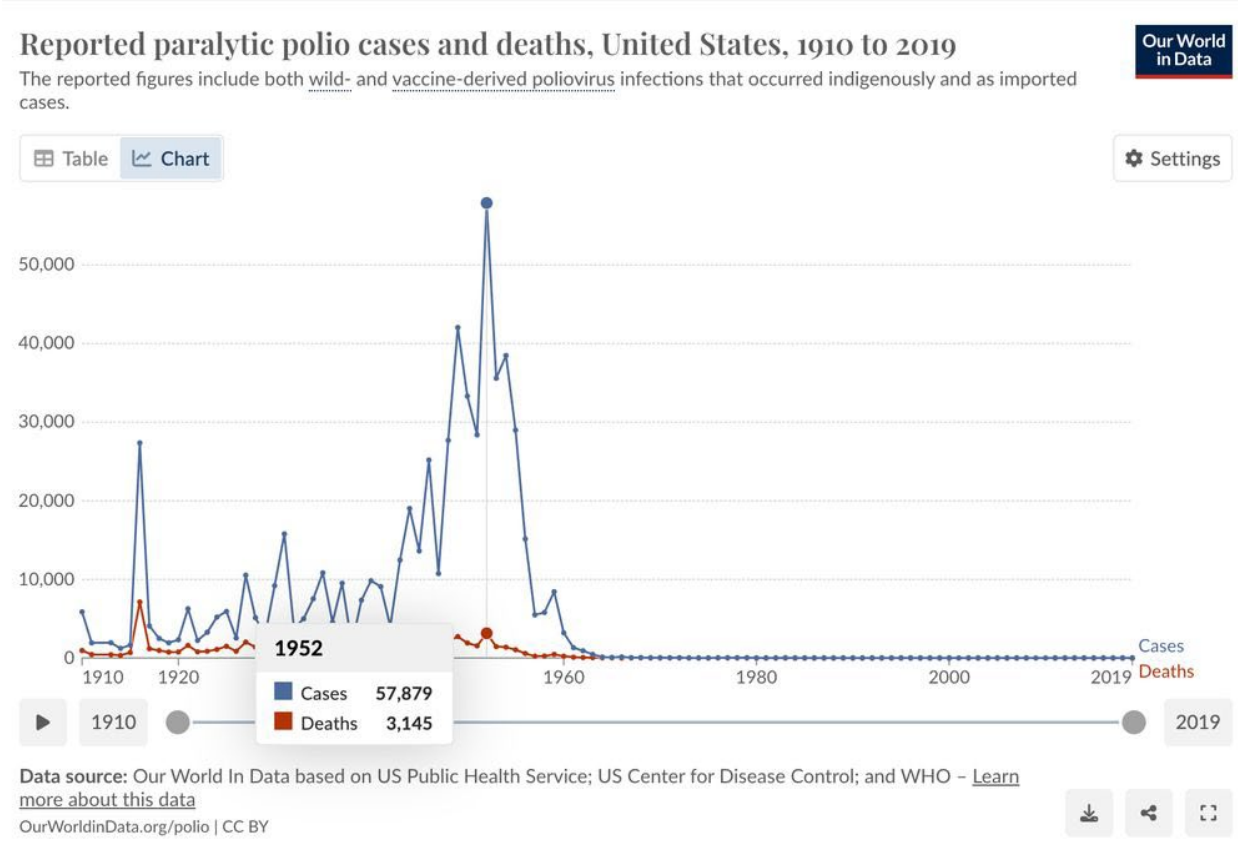
The maternal antibodies in turn prevented the virus from reaching the nervous system wherein it would cause paralysis and the devastating harms polio is classically known for- but that changed with improvements to sanitation because people stopped being exposed to polio early in life.

Now, people encountered polio after the protection of maternal antibodies disappeared- there were no brakes to stop it from reaching the nervous system. This led to a drastic rise in paralysis. 1952 was a particularly bad year.
ourworldindata.org/polio
Lien G, Heymann DL. The problems with polio: toward eradication. Infect Dis Ther. 2013 Dec;2(2):167-74. doi: 10.1007/s40121-013-0014-6. Epub 2013 Sep 17. PMID: 25134479; PMCID: PMC4108111. https://pmc.ncbi.nlm.nih.gov/articles/PMC4108111/pdf/40121_2013_Article_14.pdf


Polio

By: Saloni Dattani, Fiona Spooner, Sophie Ochmann and Max Roser

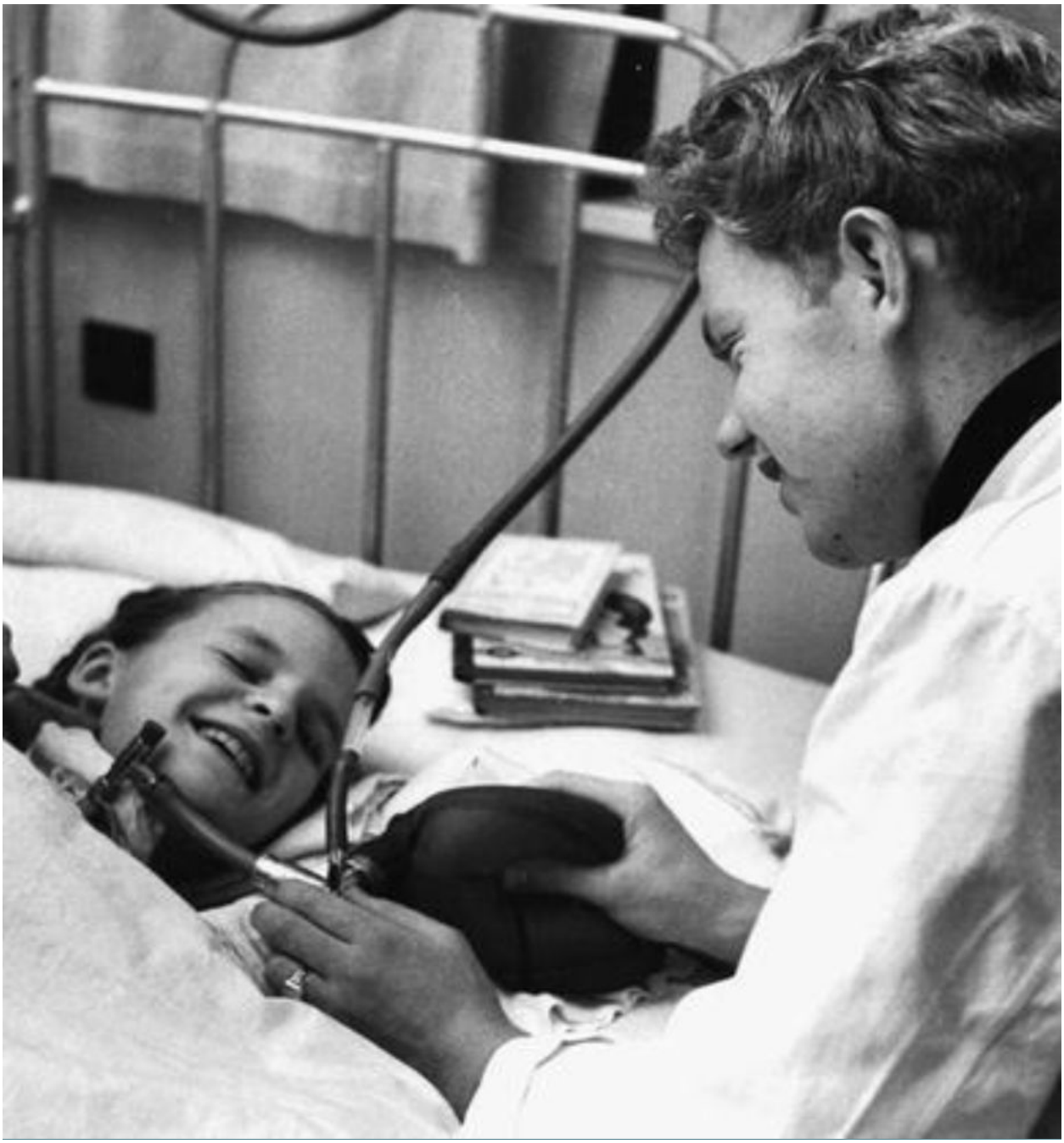
This article was first published in November 2017, and last updated in May 2024.



ALT

An underappreciated aspect of the history of polio is actually that the epidemics of polio led to the emergence of the field of intensive care medicine. In the face of a raging epidemic in Denmark, an anaesthetist tried to translate his skills from the OR to...

Reisner-Sénélar, L. The birth of intensive care medicine: Björn Ibsen's records. *Intensive Care Med* **37**, 1084–1086 (2011). https://doi.org/10.1007/s00134-011-2235-z



The birth of intensive care medicine: Björn Ibsen's records - Intensive Care Medicine The birth of intensive care medicine was a process that took place in Copenhagen, Denmark, during and after the poliomyelitis epidemic in 1952/1953. The events that led to the creation of the first in...link.springer.com

the care of a young girl experiencing respiratory failure because of paralytic polio. Eventually, Dr. Björn Ibsen helped the Municipal Hospital in Copenhagen establish the first intensive care unit to address the needs of these patients. Anyway- back to polio, the disease:

Because polio is a human-only disease, it is in principle a candidate for eradication. The Global Polio Eradication Initiative (GPEI) has been working towards this goal since 1988: https://polioeradication.org/about-polio/history-of-polio/
The major barriers to eradication are both political and scientific.

Political because you need to vaccinate tons of people to do it which means coordinating with governments who may have... other priorities. The scientific issue has to do with the challenges of polio vaccines. There are two basic types of polio vaccines. Jonas Salk invented the first.

Salk created inactivated polio vaccines. In these vaccines, the virus is cultured in cells that can make high numbers of it, and then treated to render it incapable of replicating and causing disease in people. The vaccine is extremely effective in preventing paralytic polio- but has more modest...

effects on the transmission of the virus. Transmission of the virus can be brought to heel with the use of oral polio vaccines which use polioviruses adapted to be unable to cause disease in humans but still capable of replicating within the gut. They therefore induce good mucosal immunity to...

interfere with the spread of polio. The problem with these is that the viruses you vaccinate people with, if they replicate enough times, can regain the mutations that enable them to cause paralytic disease. This is mainly a risk in the context of populations where there are low levels of...

immunity to polio. The circulation of the vaccine viruses actually helps in getting populations to herd immunity to polio. This can lead to circulating vaccine-derived polioviruses (cVDPV) in the environment, which themselves can go on to cause paralytic polio (known as VAPP). Unfortunately...

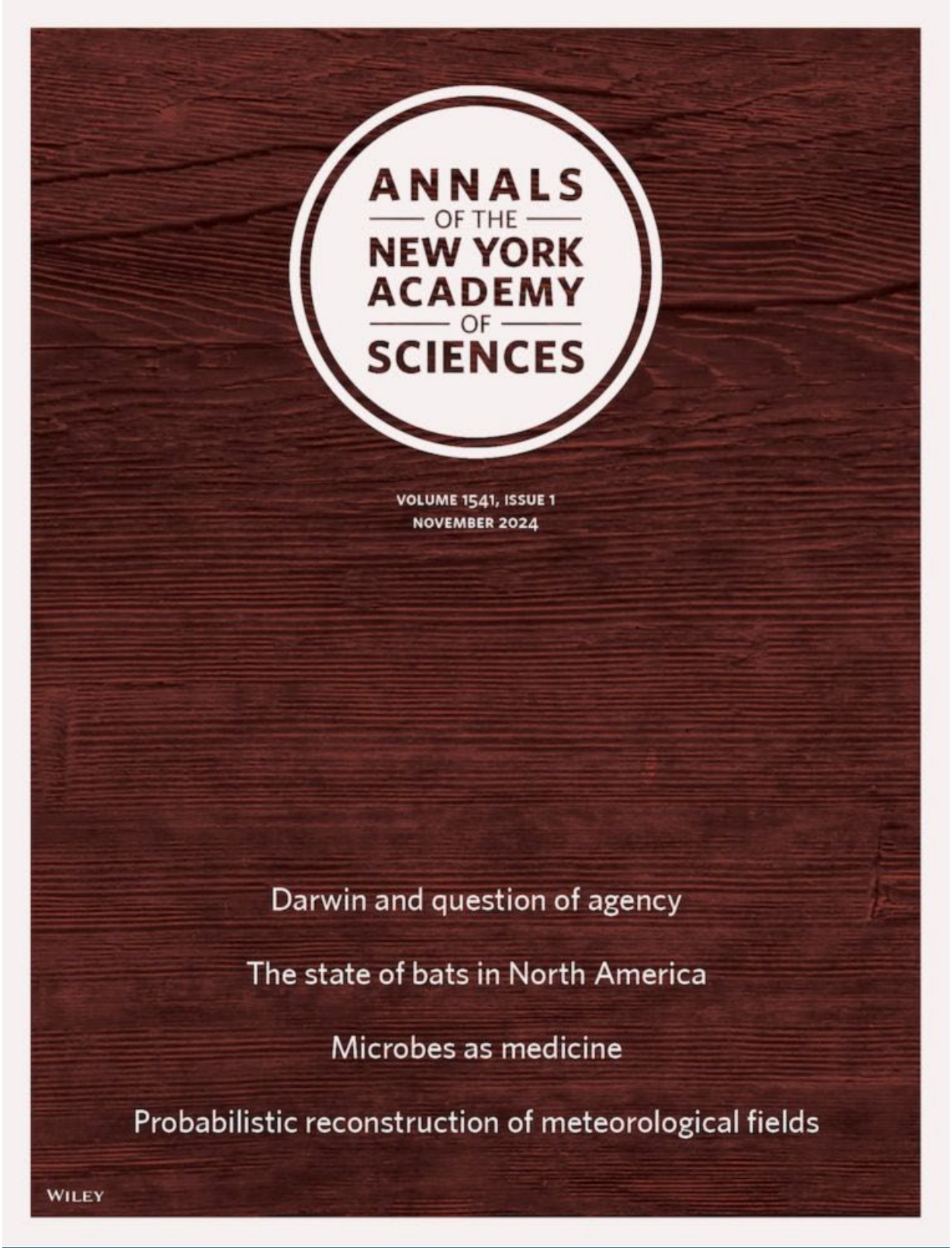
because these vaccines have made paralytic cases of polio so rare, most cases of paralytic polio today are actually cases of VAPP from cVDPV. To help address this, we've made vaccine strain viruses with additional mutations that can't readily revert back to polio that can cause paralysis...

and these have been rolled out in outbreaks, but, unfortunately, they do not completely eliminate the risk of VAPP. GPEI is reconsidering strategies for eradication in light of this. Fortunately, there is no possibility of VAPP from inactivated vaccine, so countries where there isn't...

epidemic polio can safely conduct vaccination using IPV-only schedules barring special circumstances. IPV is also safe to give to immunocompromised people. This leads us to the question of what would happen if we stopped polio vaccination altogether. The answer is not entirely clear-cut.

Polio infection causes a wide spectrum of disease, with only paralytic polio being clearly recognizable as polio. But, paralytic polio only accounts for about 0.5-2 cases of all polio infections with the rest being asymptomatic, causing a nonspecific flu-like illness, or aseptic meningitis.

As far as protection goes, we have a reasonable idea of what it takes to prevent paralytic polio. The answer seems to be: any level of neutralizing antibody in blood that covers that strain of polio seems to be solidly protective against paralysis:
nyaspubs.onlinelibrary.wiley.com/doi/abs/10.1...



NYAS Publications Click on the article title to read more.nyaspubs.onlinelibrary.wiley.com

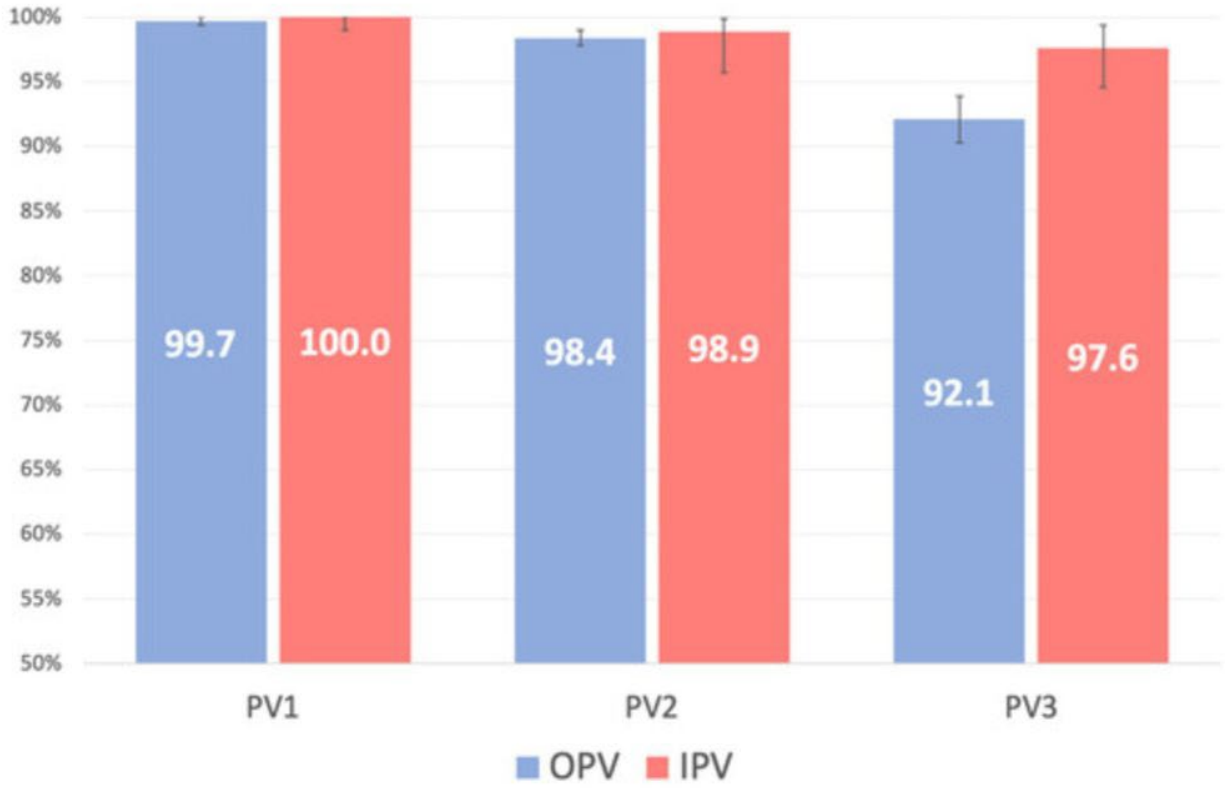
The follow-up question to that though is: how long do these antibodies last? Here we do have some data gaps. First though, it is thought that even if antibodies are undetectable among those who have previously been vaccinated against polio, they should still be protected against paralytic disease through immunological memory. Memory B cells can expand and differentiate into antibody secreting cells to block polio before it gets to the nerves. Whether or not this is possible for an infectious disease depends on how long it takes for the disease to start causing symptoms.

The different polio vaccines are different with regard to their immunity. Mucosal immunity from the oral vaccine seems to fade relatively quickly but can rapidly be recalled if poliovirus is encountered. Among those completing vaccine series, protective antibody responses have been seen in those...

as long as 18 years after the last dose in a large majority:

Vaccines **2022**, *10*(8), 1329; **https://doi.org/10.3390/vaccines10081329**

Interestingly though, serum antibodies don't seem to affect shedding of the virus in stool, which is a problem for eradication efforts:
The Journal of Infectious Diseases, Volume 191, Issue 6, 15 March 2005, Pages 990–999, https://doi.org/10.1086/427810



Long-Term Immunogenicity of Inactivated and Oral Polio Vaccines: An Italian Retrospective Cohort Study www.mdpi.com

One of the consequences of polio elimination is that people do not encounter the virus as much to get boosted by it, which means that maternal antibodies to the virus would be expected to be lower. Whether this would have a clinically meaningful effect as far as infant protection is not obvious...

but given that the bar for preventing paralytic disease seems to be so relatively low, it is probably okay. It may however result in shorter duration protection from paralytic disease. This suggests that the major group at risk here would be as it was in the past- young children too old for...

maternal antibodies and not yet vaccinated at all. The extent to which we have a buffer in the US with regard to herd immunity is also not entirely clear. In the US, IPV has been used exclusively since 2000, after the US experienced its last case of VAPP from the oral vaccine. Use of the...

inactivated vaccine before the oral vaccine will reliably prevent VAPP by inducing antibodies to the virus, and the oral vaccine will add mucosal immunity to interrupt spread, but this has not been done in the US in decades. IPV does have some effect on transmission, but not enough to eliminate the virus. Presumably, if there is enough coverage with IPV, however, people can experience clinically unimportant infections with wild polio (or cVDPV) and acquire mucosal immunity by that route, thereby contributing to herd immunity. Nonetheless, this is not a game we should be playing.

I do not know how realistic the elimination of polio vaccination in the US is or the extent to which guardrails exist to prevent abuse by malicious actors. I think it is likely that the effects of stopping the vaccination campaign would be delayed and in the short-term this would be regarded as...

a victory in that we removed an "unnecessary" vaccination, but once enough susceptibles accumulated in the population (in this case, that would mainly be children > 6 months old) we would be confronted with the reality of a generation afflicted by a pestilence that should be banished to the past.

Anyway, this is my plea to please ensure you and your loved ones are up to date on vaccination. The schedule has been thoughtfully considered for a number of scenarios, all of the vaccines on it are important, and we have extensive data on the safety and effectiveness of each of them.

Polio

By: Saloni Dattani, Fiona Spooner, Sophie Ochmann and Max Roser

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Polio is an infectious disease that can lead to the permanent paralysis of various body parts and can ultimately cause death by immobilizing the patient's breathing muscles. It primarily affects children.

No cure exists for the symptoms, but in the 1950s effective vaccines were developed and have been used around the world since then. This allowed some richer countries to eliminate the disease in the 1960s and '70s. But large outbreaks continued around the world. In the early 1980s, there were hundreds of thousands of cases globally each year[1] and the disease was still prevalent in over a hundred countries.

As a response the "Global Polio Eradication Initiative" (GPEI) was founded in 1988 to fight the virus's spread and disease burden through a global vaccination campaign.

Since then, the world has made rapid progress against the disease. Two of the three types of wild poliovirus have been eradicated worldwide, and one remains.

See all interactive charts on polio ↓

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- Estimation of the number of paralytic polio cases by region

Polio

Symptoms and transmission of polio

Polio, short for poliomyelitis, is an infectious disease that is caused and

transmitted by a virus called the poliovirus. Polio can cause paralysis and the disease is therefore also known as "infantile paralysis". The name poliomyelitis is derived from Greek and translates to gray (polios) marrow (myelon), which refers to the tissue in the center of the spinal cord, which when affected causes paralysis. Paralyzed limbs, such as arms or legs, waste away over time — this is why deformed legs are commonly associated with the disease.

The symptoms vary widely between patients. Most infections do not lead to any symptoms, but others suffer terribly and for some, it leads to death. Between 1 in 50 and 1 in 500 infections result in paralysis, among people who have not been vaccinated.[2]

The majority of infections (72%) do not lead to any symptoms. About a quarter of cases (24%) result in “abortive” poliomyelitis which leads to nonspecific symptoms for a few days, such as a fever or a cold, and 1–5% of cases lead to “non-paralytic aseptic meningitis”, in which the patient suffers from stiff limbs for up to 10 days.[3]

The poliovirus is found only among humans and is transmitted via the so-called fecal-oral route. In other words, polio is mostly transmitted by drinking water that has been contaminated by the feces of a person carrying the poliovirus.

The virus therefore spreads especially well in conditions of poor sanitation — for example, when people defecate in the open or do not filter their water before drinking it. The fact that the virus can only survive in humans (and no other animals) makes it possible to completely eradicate the disease from the world.

Polio is difficult to track in the population because it has a relatively long incubation period of up to 10 days and around three-quarters of infections do not cause symptoms, so the virus can spread for several months without being detected.

Monitoring has to focus on identifying patients that suffer from symptoms or rely on stool samples. Because any single cases that have been identified might suggest there are larger outbreaks, the WHO recommends that a single case of wild polio in a child should be treated as a public health emergency, in a country that was previously declared polio-free.[4]

Fighting polio's symptoms: The "Iron Lung'

Polio can lead to the death of infected patients if the paralysis immobilizes their breathing muscles, leading to suffocation.[5] To prevent death by suffocation, Harvard professors Philip Drinker and Louis Agassiz

Shaw invented the so called “iron lung”[6] (shown in the picture) in 1928.
Infected patients would be placed in an air-tight tube — with their heads outside — and the machine would reduce the pressure inside the box, to induce inhalation, before returning to the normal outside pressure conditions, to induce exhalation.

Most patients would spend one to two weeks in an iron lung before their paralytic symptoms faded and they could breathe independently once again. If people experienced permanent paralysis, on the other hand, they would be bound to live inside the iron lung for years.

A boy with polio in the Emerson Respirator, known as an “iron lung”, looking at the photographer through a mirror.[7]

As it is often the case with innovations, the iron lung became only widespread when the price declined substantially. John Emerson managed to construct an iron lung at half the cost in 1931. In the meantime, Philip

Drinker had tried to protect his invention with a patent and therefore filed a lawsuit against Emerson for using the original iron lung set-up. Emerson did not succumb, claiming that life-saving devices should be made available to the public at low cost rather than be used for private financial gains, and in the end, Drinker's lawsuit failed.[8]

The falling price of the Iron Lung enabled mass distribution and widespread use from the end of the 1930s onwards. The cost of one iron lung in the 1930s amounted to US-$1,500, which is the equivalent of approximately US-$26,000 in 2016 when accounting for inflation.[9] The design quickly spread to Western Europe and was widely used for polio patients there, too.

Empirical View

Historical Perspective

The history of polio can be divided into three major phases:[10]

- The *endemic phase* from antiquity to the nineteenth century in which the disease occurred relatively rarely and did not result in many paralytic cases.
- The *epidemic phase* until the mid-20th century, during which the world saw

large-scale outbreaks and increased geographic spread.

- The *vaccine phase* that followed the introduction of vaccines in 1955. In this phase, polio prevalence declined first in richer countries and over the last decades in poorer countries around the world.

The hope is that the world will see a fourth and final phase, in which polio is entirely eradicated from the world.

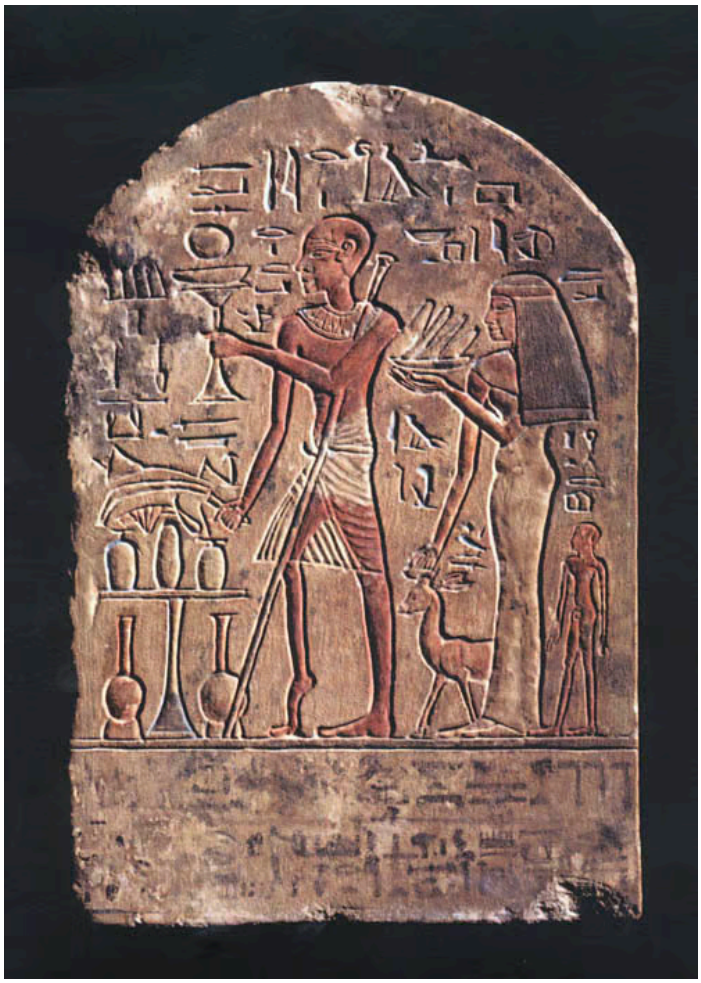
The origin of polio

Infectious diseases are generally believed to arise from the interplay of various developments such as human settlement in urban structures, crowding that causes poor hygiene, food shortages enhancing populations' morbidity, and the domestication of animals.

The exact origins of the disease are unknown, but based on the characteristics of the disease, epidemiologists can hypothesize how the disease has evolved and spread.[11]

Because the disease requires a human host and does not survive outside the human body for longer than one to two weeks, the disease could only have developed when humans started to settle in larger groups.

Various skeletons have been found with deformations similar to polio[12] but the most widely-referenced indication of polio has been an Egyptian stele (pictured) depicting Doorkeeper Roma with one leg skinnier and deformed, both typical symptoms of paralytic polio.



An Egyptian Stele dating back to 1403–1365 BC of a man with polio.[13]

The prevalence of polio in the past

Since then, evidence of occurrences of polio has been scarce. But, at different time

points, records of polio-like diseases have appeared.

The poet Sir Walter Scott was infected with polio at the age of eighteen months in 1773 and the disease paralyzed his right leg for life. In his *Treatise on the Diseases of Children* in 1789 the London pediatrician Michael Underwood writes about a children's disease, possibly polio, that is a "debility of the lower extremities".[14]

Other outbreaks in the 19th century, which recorded a smaller number of cases, can be seen in the table taken from Smallman-Raynor & Cliff (2006).[15]

POLIO-LIKE OUTBREAKS IN THE 19TH CENTURY[16]

Year	Location	Cases (deaths)
1808	Göteborg, Sweden	4 (-)
1835	Worksop, UK	4 (-)
1841	Louisiana, USA	10 (-)
1868	Modums, Norway	14 (4)

Polio in the epidemic phase

Until the 19th century, populations experienced relatively small outbreaks. This changed around the beginning of the 20th

century. Major epidemics occurred in Norway and Sweden around 1905 and later also in the United States.[17]

Why did we see such large outbreaks of polio only in the 20th century? Or, in other words, why did the transition from the *endemic* to the *epidemic* phase take place?

The answer, again, lies with hygiene standards. As polio is transmitted via the fecal-oral route, the lack of flush toilets and the lack of safe drinking water meant that children in the past had usually been exposed to the poliovirus before their first birthday.

At such a young age, children still benefit from "passive immunity", which is passed on from their mothers in the form of antibodies. These are proteins that identify the poliovirus as something foreign and therefore signal to the body that they should be eliminated by the immune system. Thereby, virtually all children would contract the poliovirus at a very young age.

In addition, while protected from developing the disease thanks to the maternal antibodies, children would also produce memory cells in response to the virus, which ensured long-term immunity against polio. The latter is important as the mother's cells have a half-life of only around a month, starting from the last day of breastfeeding.[18]

Once the maternal antibodies decrease sufficiently, children lose their passive immunity.

As hygiene standards improved, the average age at which children were first exposed to the poliovirus increased, which meant that maternal antibodies were no longer present to protect children from polio.

For example, during five epidemics in the US between 1907 and 1912, most reported cases occurred in one- to five-year-olds, whereas during the 1950s, the average age of contraction was 6 years, with "a substantial proportion of cases occurring among teenagers and young adults".[19]

Being exposed to the poliovirus after losing the protection from maternal antibodies meant that they were more likely to get polio, which increased the number of cases and deaths around the start of the 20th century.

The history of polio in the US

The chart here shows the annual absolute number of reported deaths and cases in the United States over the last century; the corresponding perspective on the *rate* of deaths and cases is shown in this visualization.

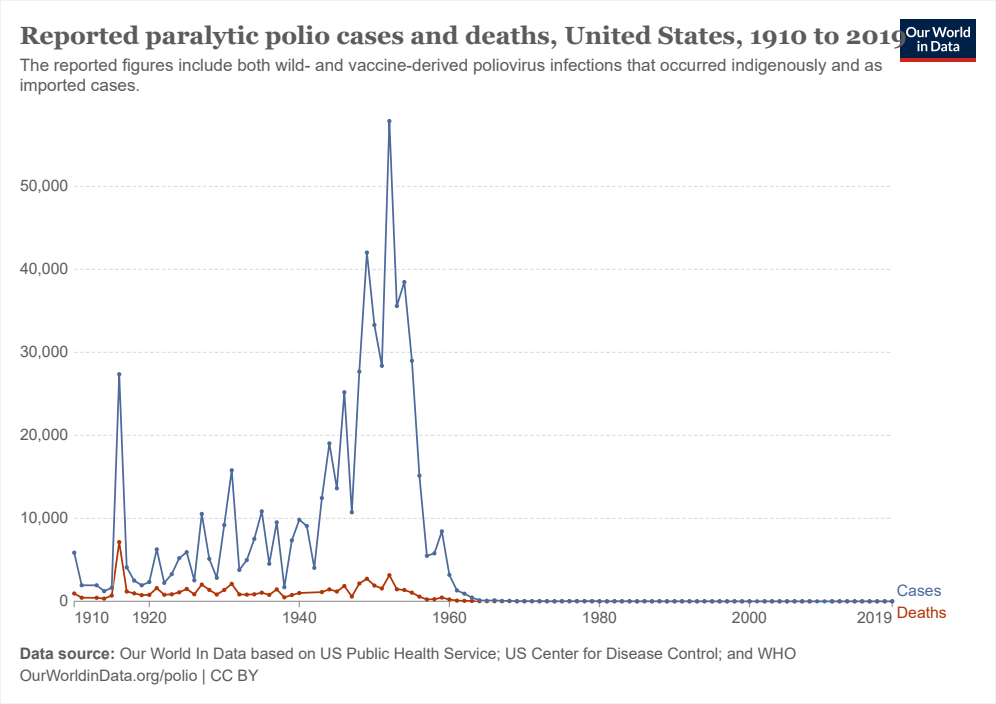
Big outbreaks happened frequently. In 1916 for example, the poliovirus infected more than 27,000 Americans and killed more than 7,000 people. At that time, the cause of the disease and how it spread were not yet known, so panicked New Yorkers shut down schools, public cinemas, and swimming pools. For a while, it was believed that cats or mosquitoes were spreading the virus, which led to the killing of more than 72,000 cats and the extensive spraying of the insecticide DDT, in a futile attempt to interrupt the transmission of the virus.[20]

Each of these large outbreaks came to an end because, like most viral diseases, the spread of the poliovirus in moderate climates like in the USA is seasonal and is mostly transmitted during the summer months.

By October 1916, enough New Yorkers had been infected and developed immunity in response so that in combination with the natural seasonal decline of the virus's spread the case numbers had already dramatically dropped and would not surge again.

This can be seen in the graph as the US recorded less than 5,000 cases in the following year. The second major outbreak in the USA in the 1950s, on the other hand, was largely contained by the successful

development of polio vaccines that would hinder the transmission of the virus.



The vaccine against polio

The development of the polio vaccine

What changed the history of polio forever was the development of a vaccine against the disease.

US President Franklin D. Roosevelt himself had been diagnosed with polio at the age of 39 and subsequently bound to a wheelchair for the rest of his life. While this might have been a misdiagnosis in Roosevelt's case,[21] his presidential influence was crucial in the set-up of the *National Foundation for Infantile Paralysis*. The non-profit organization soon became known as "The March of Dimes Foundation", referring to

polio victims' inability to walk, and successfully collected a substantial amount of donations for vaccine research and its "Iron Lung" distribution program.
Years of research went into the effort to develop an effective vaccine.

The medical doctor and virologist Jonas Salk put forward a promising vaccine — known as the inactivated polio vaccine or the Salk vaccine — and in the spring of 1953, the foundation rolled out a large-scale trial for which 1.83 million children in 44 US states received either a placebo or the vaccine shot.[22] Salk's supervisor Thomas Francis insisted on introducing a control group into the trial design, which was a step towards the development of randomized controlled trials in medicine.

The foundation was supported mainly by donations from the American people, who were collecting dimes, quarters, and dollars for decades in the hope of research finally uncovering a way to protect oneself against polio. Oshinsky (2005) even reports that the foundation received donations from two-thirds of the US population and a poll claims that more Americans knew about the field trials than about the president's full name (Dwight David Eisenhower).[23]

On April 12, 1955, the tenth anniversary of Roosevelt's death, Francis announced that Salk's vaccine was effective and potent in preventing polio. Within just two hours, the

US Public Health Service issued a production license and the foundation prepared for a national immunization program. The conference had been live-broadcasted to physicians all over the country who had gathered in movie theaters to watch the announcement, millions of Americans received the news over the radio, spontaneously putting down their work in celebration of the news.[24]

At 10:30 PM of the same day, Thomas Francis and Jonas Salk gave a televised live broadcast interview in which Salk, when asked who owned the patents to the vaccine, famously answered *"Well, the people I would say. There is no patent. Could you patent the sun?"*[25]

His answer was in the spirit of the foundation having funded the vaccine research with donations from the American public and his conviction that life-saving technology should be for the benefit of society as a whole rather than for private financial gains.

Shortly afterward, Dr. Albert Sabin introduced a live polio vaccine that could be administered orally (in contrast with Salk's vaccine, which was given by injection), the oral polio vaccine (OPV).[26]

While Salk's vaccine only protected the central nervous system, Sabin's vaccine also protected the digestive tract and thereby

prevented the spread of the wild poliovirus more effectively.
The easier administration also made vaccination efforts less expensive as it did not require trained health workers to provide injections. For these reasons, OPV has been used around the world and it is the vaccination that is responsible for the dramatic reduction in polio infections globally that we document below.

Polio prevalence in the developing world and the global spread of the polio vaccine

Dr. Sabin's *Oral Poliovirus Vaccine* (OPV) was tested on more than 100 million people in the Soviet Union before obtaining its license in 1961. Because its production costs were lower and the oral administration easier, OPV was and still is the predominant vaccination serum in many countries.

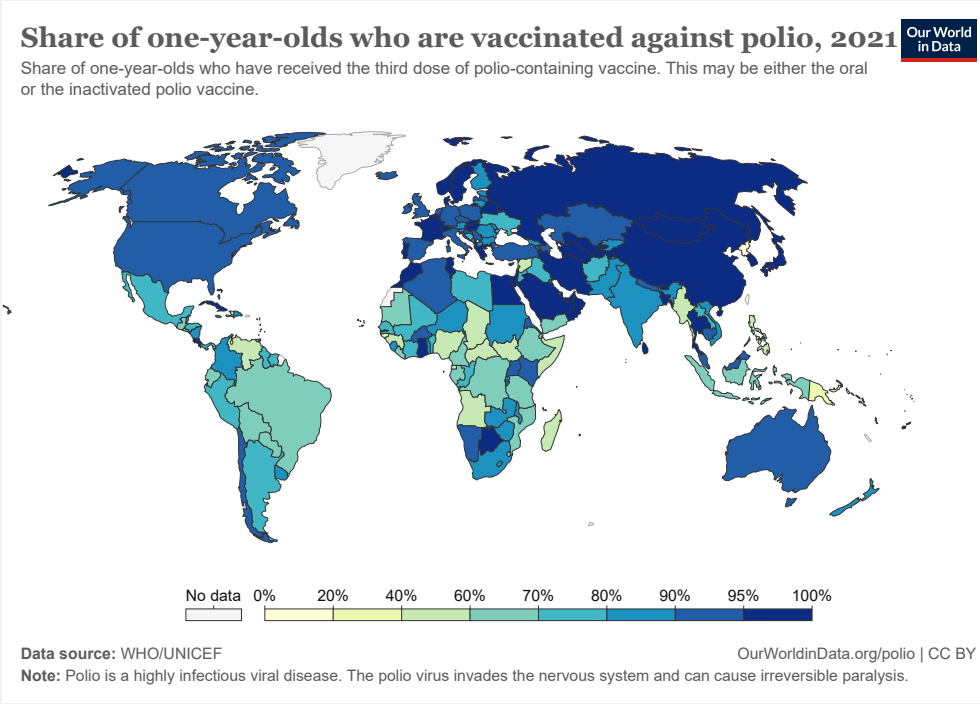
It only became apparent during the 1970s and 1980s, through several polio surveys in poorer countries that became known as "lameness surveys", that polio was as much a problem in developing countries as it was in Western Europe and the United States.

Bernier (1984)[27] cites 46 of these "lameness surveys" in 24 countries, with a prevalence of paralytic polio ranging from less than one to 19 cases per 1,000

children. Modlin (2010)[28] claims that these countries suffered from a higher prevalence of polio than the USA during its peak polio outbreaks.[29]
Mass campaigns in Brazil, Cuba, and Mexico proved the vaccine's effectiveness in different geographical areas but only with the foundation of the *Global Polio Eradication Initiative* at the *World Health Assembly* in 1988 did the polio vaccine find its place in many national routine immunization programs.

The visualization below shows how vaccine coverage against polio among one-year-olds has substantially risen around the world since 1980.

By switching to the chart view, you can see the change over time for each country and the world as a whole. Globally you can see that in 1980 only 22% of one-year-olds were vaccinated against polio. By the 2010s, over 80% were vaccinated.



Vaccine-induced polio

In rare cases, the altered live poliovirus that is used in the oral poliovirus vaccine (OPV) can mutate and regain its ability to attack the central nervous system ("neurovirulence"). This means that a small share of people who receive the OPV vaccine develop paralysis, which has the same symptoms as paralysis from the wild poliovirus.

There are two ways this can occur:

- *Vaccine-associated paralytic poliomyelitis (VAPP).* If the mutations to regain neurovirulence occur spontaneously — in a person who was recently vaccinated — it is called vaccine-associated paralytic poliomyelitis (VAPP). This is very rare: for every million doses of oral poliovirus

vaccines, there have been between 0.09 and 25 cases of vaccine-associated paralytic poliomyelitis.[30]

- *Vaccine-derived poliovirus (VDPV).* If the mutations to regain neurovirulence occur over a longer period, it is known as vaccine derived poliovirus (VDPV). This can be identified by its genetic similarity to the genome of the virus used in the vaccine.

Vaccine-derived polioviruses

Let's look into VDPVs in more detail. There are several types of VDPVs. They are defined by the GPEI as follows.[31]

- *Immune deficiency associated vaccine derived poliovirus (iVDPVs)* — these are VDPVs that come from people who have primary immunodeficiencies.
- *Circulating vaccine derived poliovirus (cVDPVs)* — these are VDPVs for which there is evidence that they have been transmitted between people in the community (i.e. they are found in multiple individuals who are not direct contacts; from an individual and an environmental sample; or from two environmental samples from different sites or at different times). These can spread in the community and cause new outbreaks.

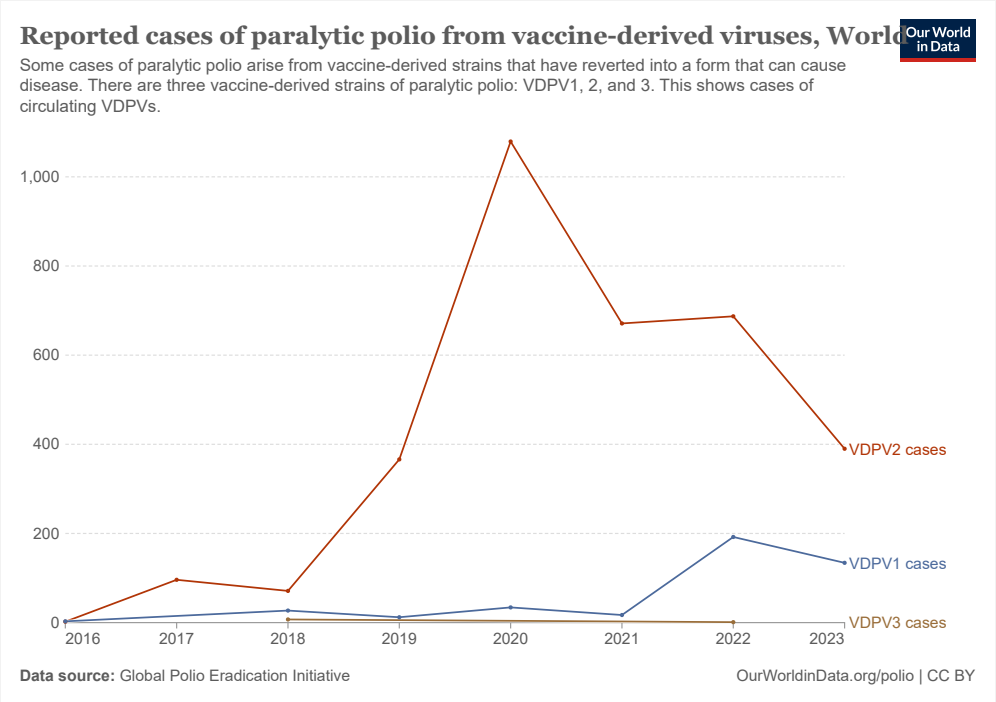
- *Ambiguous vaccine derived poliovirus (aVDPVs)* — these are VDPVs for which there isn't evidence that they come from people with primary immunodeficiencies or have been transmitted between people in the community.

The risk of vaccine-derived polioviruses circulating in the population is generally very low, and the world now has new effective vaccines to contain them, called novel Oral Poliovirus Vaccines (nOPV).[32]

The vast majority of cases of cVDPVs come from the oral poliovirus vaccine against poliovirus serotype 2, rather than vaccines against other serotypes. You can see this in the chart.

In the vaccines against serotypes 1 and 3, many genetic mutations distinguish them from the wild poliovirus strains, which means it is extremely unlikely that they can revert into a form that can cause disease.

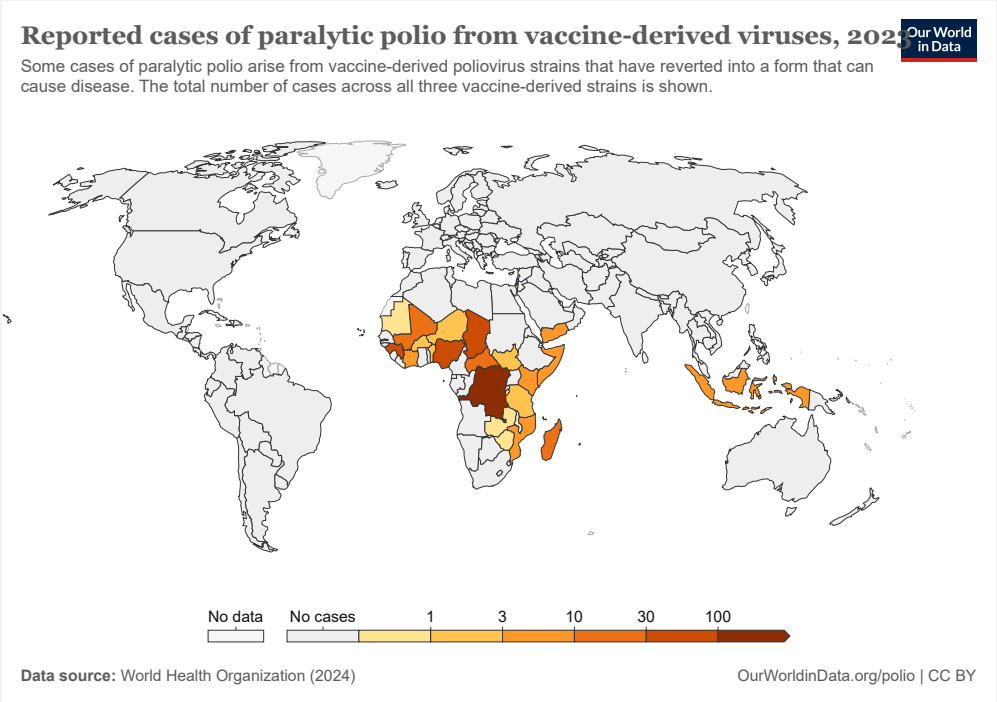
However, in the vaccine against serotype 2, fewer genetic mutations distinguish it from the wild poliovirus strain, meaning that in some rare cases, it can revert into a form that can cause disease.[33]



Although it may seem counterintuitive, cVDPV2 outbreaks are more likely in communities with *lower* coverage of vaccines for poliovirus serotype 2, such as OPV2 vaccines. This is because these communities have lower immune protection against poliovirus serotype 2, which some vaccine-derived viruses have reverted into.[34]

Although the wild poliovirus serotype 2 was eradicated — it was last reported worldwide in 1999 — cVDPV2 cases have occasionally occurred in under-vaccinated communities in the years that followed.

In the map, you can see the number of cases of all cVDPVs in each country.



How can vaccine-derived polioviruses be contained?

There are multiple ways to contain cases of cVDPVs.

In 2016, the Global Polio Eradication Initiative recommended in 2016 that countries switch the vaccines they used — from using an OPV that contains vaccines for all three serotypes (called a trivalent vaccine) to another OPV which contains vaccines for only serotype 1 and 3 (called a bivalent vaccine).[35]

Along with this, they also recommended countries use inactivated poliovirus vaccines (IPV) towards serotype 2 instead of the OPV, because it does not have the risk of mutating to regain neurovirulence.[36] However, this comes with a trade-off: the

OPV vaccines are much cheaper and easier to administer than the IPV vaccines, which typically require injections.[37]

Since 2019, all 126 countries that previously used OPV now use at least one dose of IPV.[38]

Since 2020, countries have had a new vaccine to use against serotype 2: the novel oral poliovirus vaccine (nOPV2). These new vaccines are much more genetically stable than the previous OPV2 vaccines, which makes it much less likely that they will revert and gain neurovirulence.[32]

Like the previous OPV vaccines, the nOPV vaccines are easy to administer as they are given orally, and they are being rolled out to countries with cases of VDPV2 to contain those outbreaks.[39]

Global decline of polio

The campaign to eradicate polio globally: the Global Polio Eradication Initiative (GPEI)

In 1988, the *World Health Assembly* — the governing body of the *World Health Organization (WHO)* — launched the *Global Polio Eradication Initiative (GPEI)* which was tasked with eradicating the disease globally by the year 2000.[40] The eradication of the disease in just 12 years was an ambitious

plan, since polio was endemic in 125 countries of the world in 1988.
The GPEI was set up as a public-private-partnership and today brings together several organizations, among which are the WHO, UNICEF, the US Center for Disease Control and Prevention (CDC), Rotary International and the Bill and Melinda Gates Foundation.[41]

They had achieved that by way of routine immunization programs which entails the basic schedule of each infant receiving three Oral Polio Vaccines (OPV) before they reached the age of one.

Since its inauguration in 1988, the GPEI has offered support for these routine immunization programs to governments. But in addition to these the GPEI also ran:

- *National Immunization Days* (NIDs), on which children receive two doses of OPV 4-8 weeks apart regardless of their immunization history,
- *outbreak response immunization programs*, for which all children below the age of five years in the vicinity of a detected case of paralytic polio receive one OPV dose, and
- *mopping-up immunization programs*, during which under-five-year-olds living in outbreak-prone areas are visited in their homes and receive two OPV doses one month apart.

Even though the GPEI has not yet reached the goal of eradicating polio, it has been successful in reducing the prevalence of polio around the world: reported polio cases have been reduced greatly and two of three wild poliovirus serotypes have already been eradicated.

The number of estimated polio cases by world region

The interactive visualization highlights the global decline in the number of paralytic polio cases from 1980 onwards. In the early 1980s, an estimated 300,000 to 400,000 people suffered from paralytic polio cases every year. In 2020 there were 1873 paralytic polio cases. In the 1980s the world saw many more paralytic polio cases every week than today in an entire year.

The cases are shown for each of the six WHO world regions and you can change the view from absolute to relative numbers of polio cases by clicking on “Relative” in the chart. In the 1980s between 50% and 75% of all estimated cases occurred in the South-East Asia region, this region has not recorded a single case after 2011 and was certified to be polio-free in 2014.

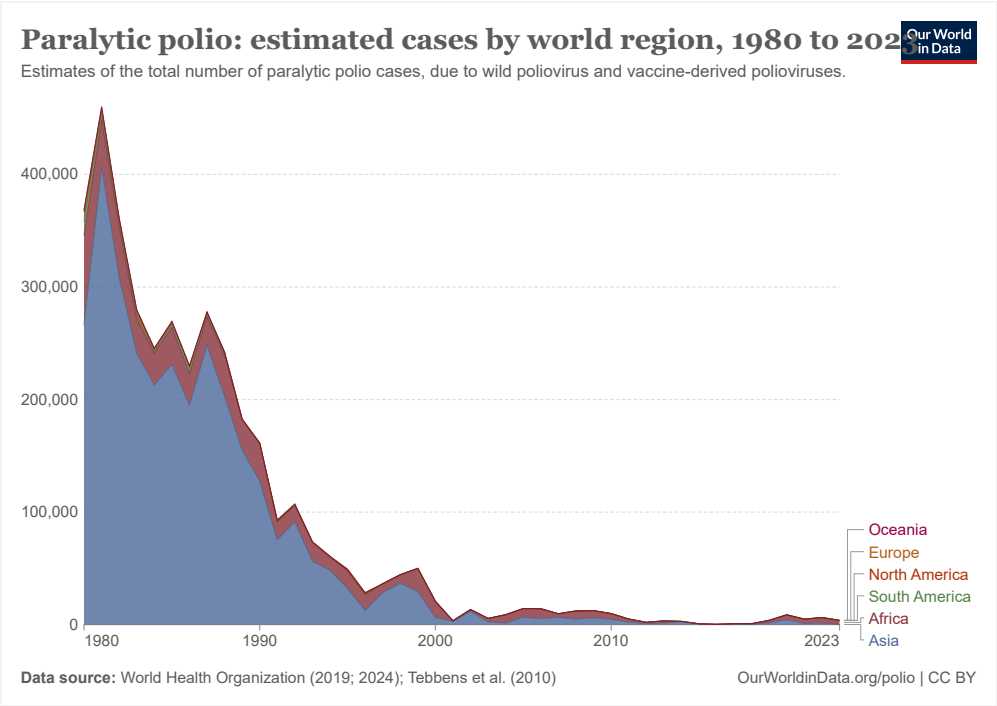
This data shows the *estimated* total number of paralytic polio cases, which is adjusted from the number of *reported* paralytic polio cases.

Our estimations of the total number follow the methodology by Tebbens et al. (2010)[42] who estimate the degree of underreporting — especially in earlier periods — of polio is and then adjust the number of paralytic polio cases to arrive at the total number of estimated cases.

Read more on how we adapted their method to apply correction factors here:

Estimation of the number of paralytic polio cases by region

In this post we explain how we estimate the number of cases of paralytic polio by country and region.



The total number of reported polio cases

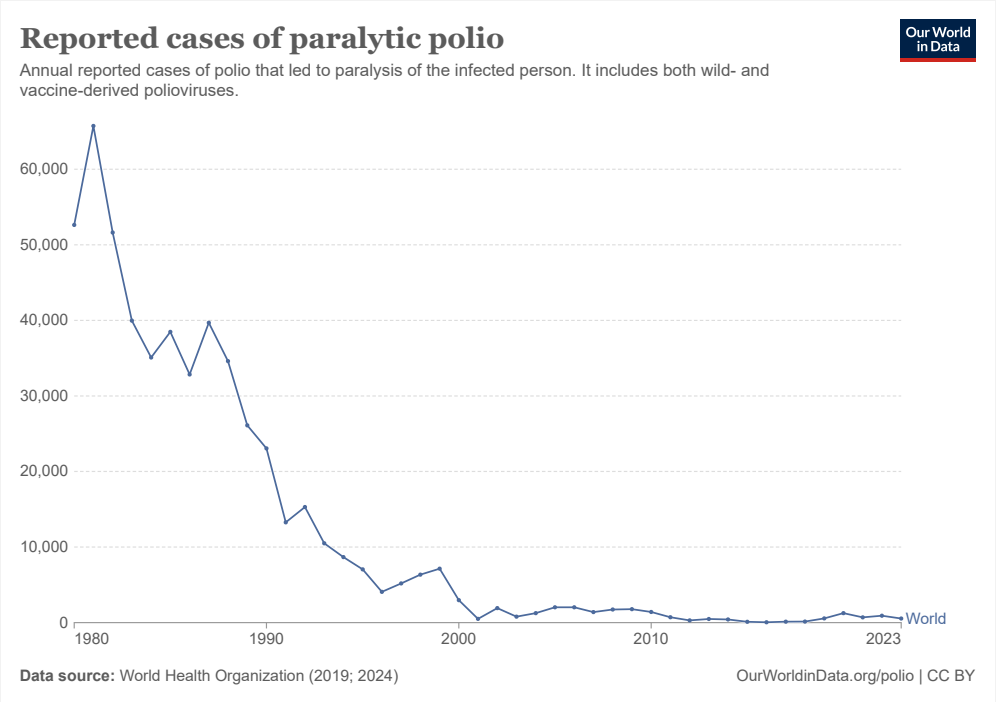
The visualization documents the number of reported polio cases by country from 1980 onwards. The number of reported cases is an underestimate of actual polio cases, because some cases go undetected or unreported.

Reported polio cases include endemic, imported, and vaccine-derived cases.

For instance, the United States, which eliminated polio in 1978, still recorded some polio cases in the 1980s because imported cases were included.

This is also the case for countries that only recently achieved their polio-free status, such as India and Nigeria. Although Nigeria has been certified polio-free, this status refers to the wild poliovirus specifically. As you can see, several countries continue to report polio cases in 2021, which is due to vaccine-derived polioviruses.

Cases of polio have fallen dramatically over time. In 1980, there were over 50,000 reported cases of polio worldwide. But in 2021, this number was down to 649.

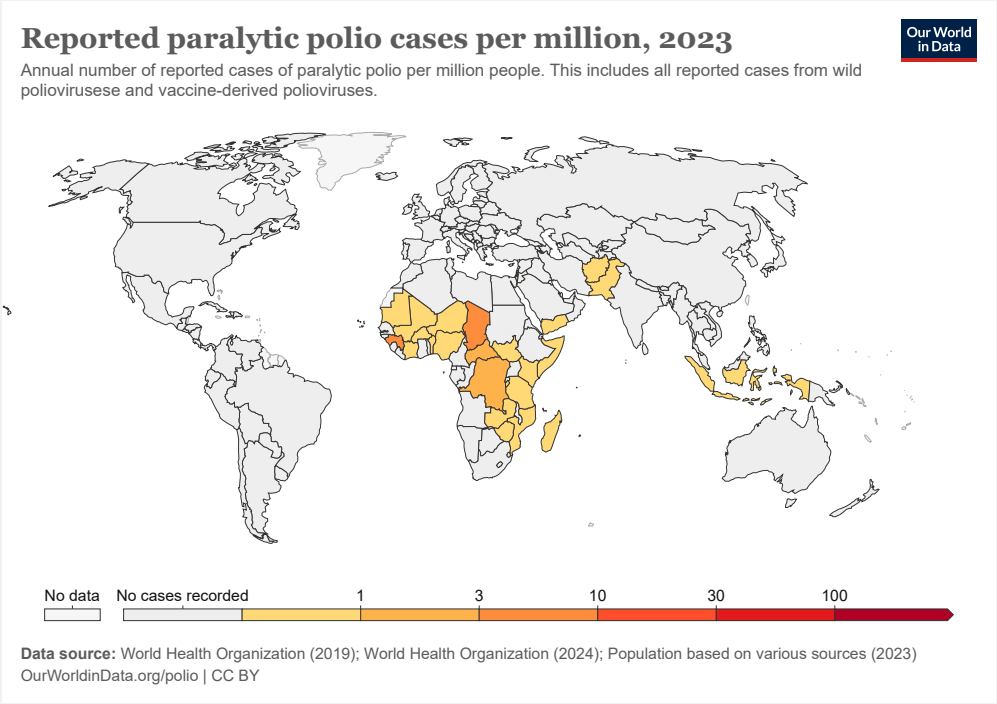


Country by country: The prevalence of polio

The interactive map presents the number of polio cases per 1 million inhabitants of each country, to account for differences in the population size and make comparisons between countries more meaningful.

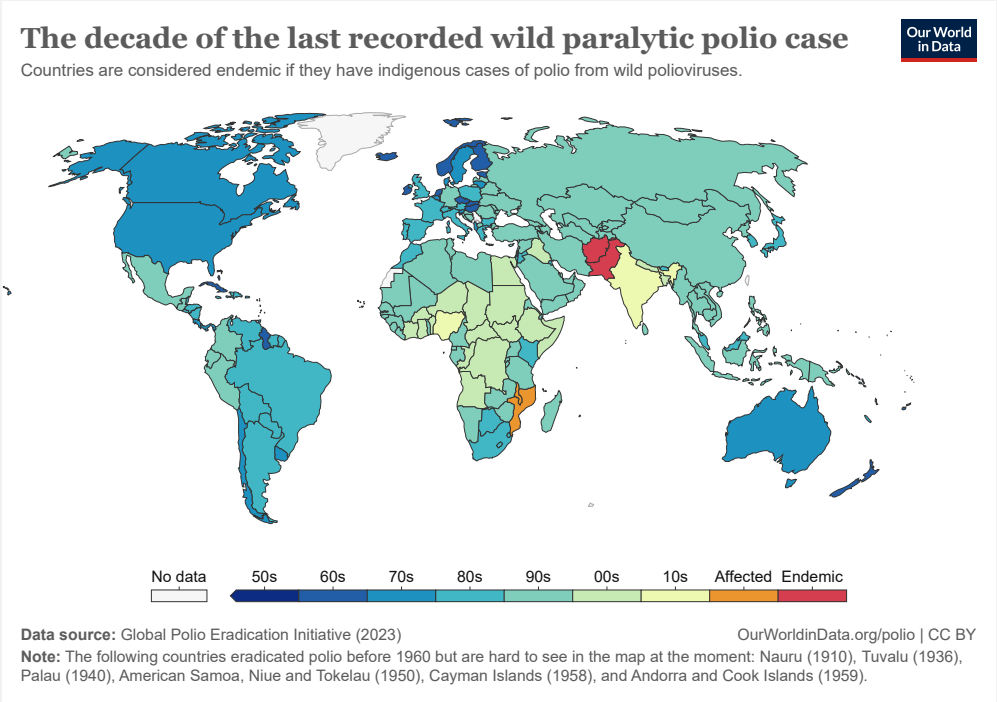
You can press play in the bottom left corner to show the change over time. It can be clearly seen how the WHO regions achieved their polio-free status, the Americas for example were certified in 1994.

By clicking on any country you can see the change over time of the polio rate in that country.



In 2017 the wild poliovirus is only endemic in a few countries, shown in red on the map.

The map displays the year of the last recorded case of polio for each country and each decade is color-coded. You can see that the Americas were the first world region to be certified polio-free in 1994.



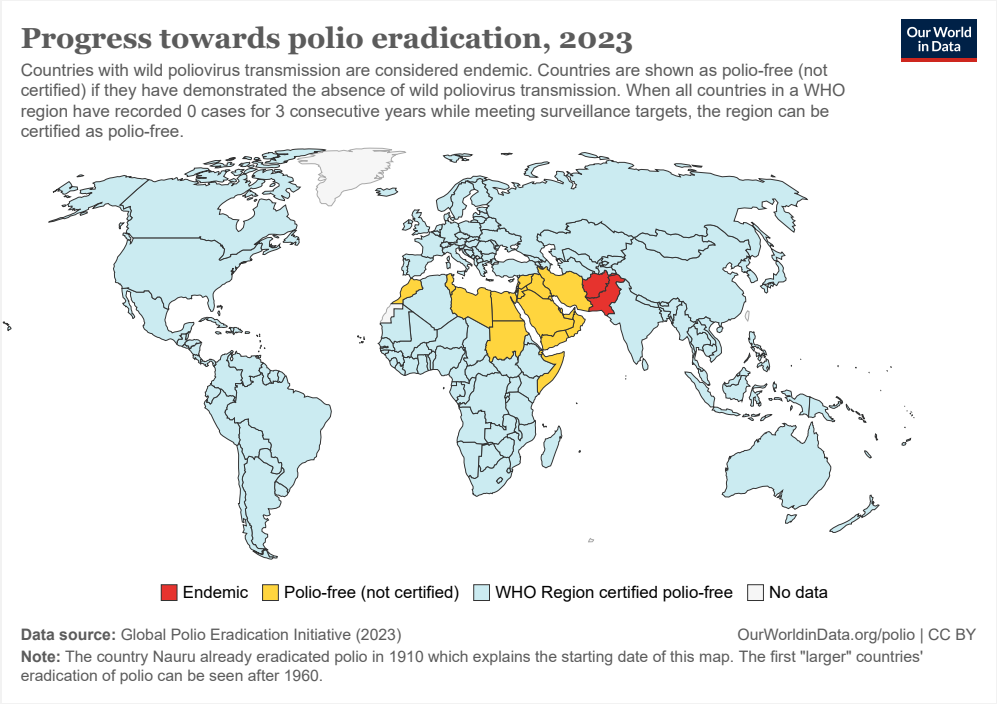
WHO-certified polio-free world regions and countries

The WHO certifies world regions as polio-free, rather than individual countries. The considered world regions are the six WHO world regions: Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, and Western Pacific.

To be certified polio-free, a WHO region needs to (i) record no wild indigenous polio case for at least three years, (ii) have a reliable surveillance system in place, and (iii) prove its capacity to detect and respond to imported polio cases.[43]

The interactive map shows for each country when the last case of endemic paralytic polio was recorded. The map also shows when the four polio-free WHO regions

achieved this status, three years after the last country in that WHO region recorded the last endemic polio case.



The number of reported polio cases from wild polioviruses

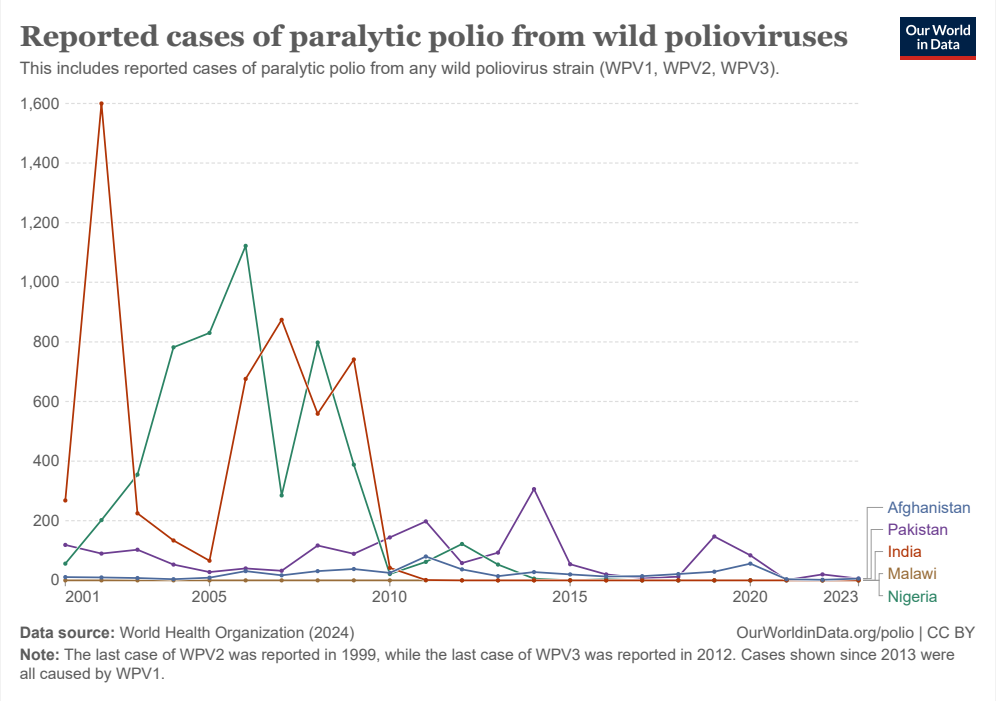
The visualization documents the number of reported polio cases from wild poliovirus (WPVs) by country. The number of reported cases is an underestimate of actual polio cases, because some cases go undetected or unreported.

Wild polioviruses refer to the polioviruses that have been historically endemic in many countries, and excludes vaccine-derived polioviruses. You can explore this data for other countries by clicking the “Edit countries and regions” button.

In 2001, 14 countries reported cases of wild polioviruses. By 2021 there were only three countries where wild poliovirus cases were recorded: Afghanistan, Pakistan, and Malawi.

Until recently, there were three strains of wild polioviruses. Poliovirus serotypes 2 and 3 have both been eradicated globally. The last case of wild poliovirus serotype 2 was seen in 1999 in India, while the last case of wild poliovirus serotype 3 was seen in 2012 in Nigeria. That means they were declared globally eradicated by the WHO in 2015 and 2019 respectively.

All reported cases since 2013 from wild polioviruses have been caused by wild poliovirus serotype 1.



The costs and benefits of eradicating polio

Health benefits

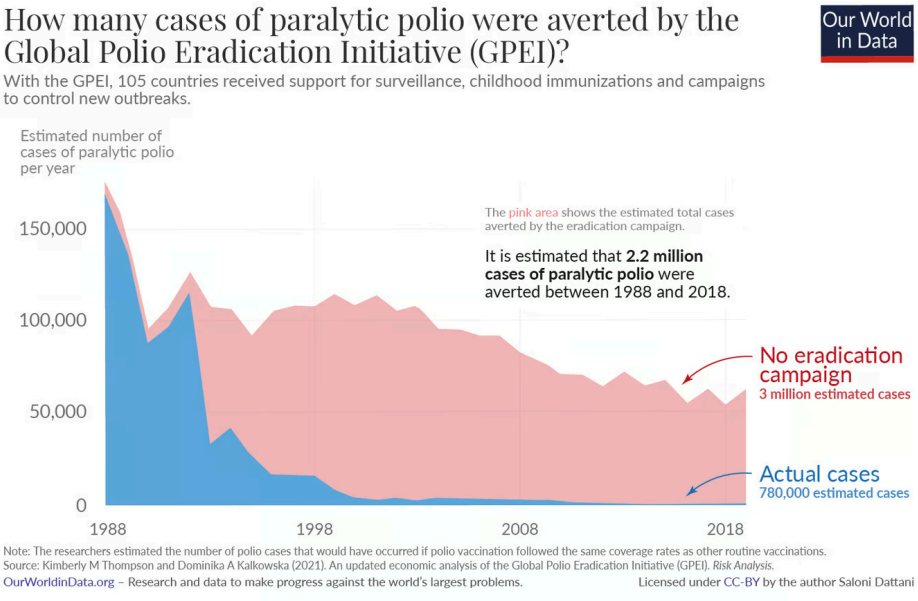
It is estimated that the Global Polio Eradication Initiative led to the prevention of 2.17 million cases of paralytic polio between 1988 (when the GPEI began) and 2018.[44]

The chart visualizes the benefit of the eradication campaign by comparing the actual cases with an alternative history in which the GPEI did not exist.

The red part of the chart is based on a model that estimates the number of paralytic polio cases without the eradication campaign, for the 105 countries that received support from the GPEI. Without the eradication campaign, this study assumed that the coverage rates of polio vaccines would match the rates of other routine vaccines in countries during the same time period.

The benefits of this global health campaign are not limited to polio itself. In addition to preventing paralytic polio, many children around the world have received other health benefits that were made available to them as part of the polio immunization campaigns. These are called supplementary immunization activities (SIAs), where other

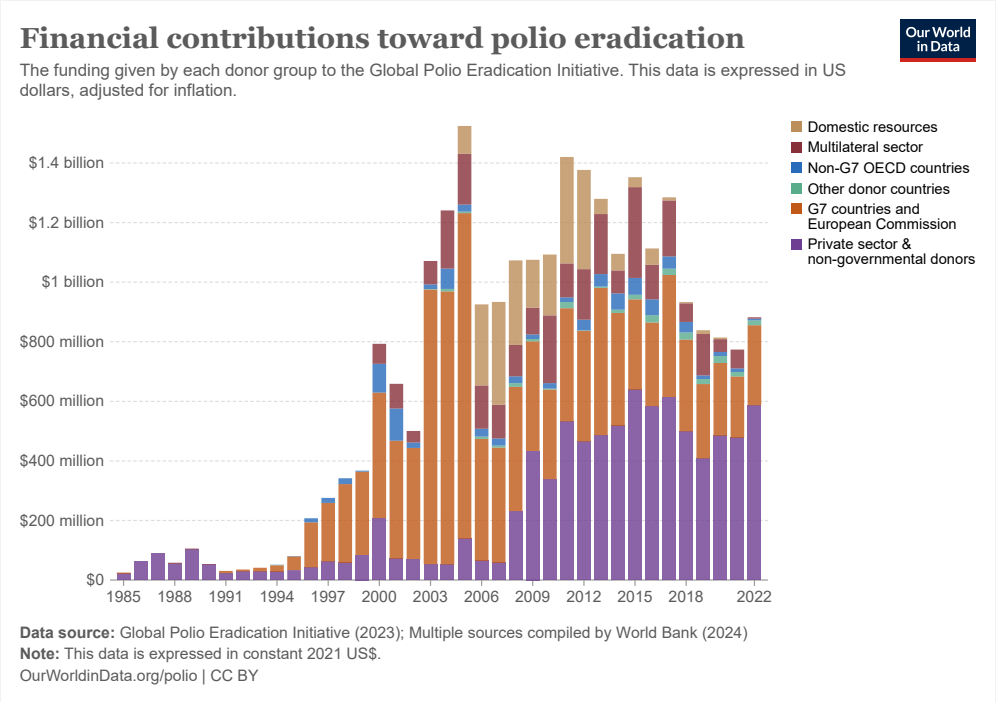
vaccinations and nutritional supplements have been distributed.[45]



Economic costs of the Global Polio Eradication Initiative

The GPEI has received funding towards polio eradication from different sectors, including domestic resources, G7 countries and the European Commission, the private sector and non-governmental donors, as the chart below shows.

The large majority was only received from 2000 onwards. This funding contributed to additional polio eradication efforts in the form of National Immunization Days (NIDs), outbreak response immunization and mopping-up immunization.



Current expenditure on polio eradication and the *Endgame Strategic Plan*

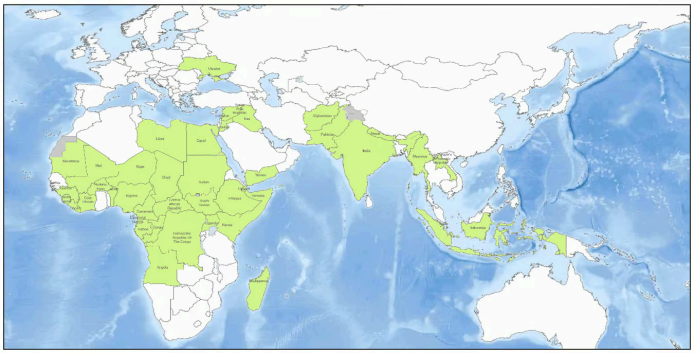
In 2013, the GPEI launched an ambitious five-year plan to fully eradicate polio called Polio Eradication & Endgame Strategic Plan 2013-2018 which would cost US-$5.5 billion (in 2015 it was increased by a year and extended to US-$7 billion), also see the section on the benefits of eradication rather than reduction for more information.

Even though polio was endemic in only Nigeria, Pakistan, and Afghanistan in 2013, it proved especially difficult to monitor the virus and to reach every child for immunization in these contexts which makes the endgame strategy so expensive in comparison to the GPEI's previous budget.

That's why, in 2016, US-$536 million of the total GPEI budget of US-$925 million were spent in these three countries.[46]

The map indicates which countries received support from the GPEI in 2016. Only six of these fund their immunization efforts partially themselves.

FIGURE 3 | COUNTRIES WHERE SIA ACTIVITIES WILL BE CONDUCTED, 2016



Countries receiving support for polio immunization from the GPEI in 2016[47]

The cost of the GPEI in a comparative perspective

To put these numbers into perspective, global malaria financing amounted to US-$2.9 billion in 2015 which was more than twice as large as the GPEI's budget of US-$1.39 billion one year later in 2016.

Or, to give a second comparison, in 2016, the US government spent US-$1,116 billion on major health care projects, a budget that is more than 800 times larger than the GPEI's global spending on polio in the same year.

Benefits of eradication rather than reduction

In 2013, the GPEI implemented “The Polio Eradication and Endgame Strategic Plan 2013-2018”, costing an additional $5.5 billion in addition to the already $9 billion spent by the organization since its implementation in 1988.

The initiative hopes to especially finance the last stretch of vaccination campaigns in the countries where polio is still endemic, keep the remaining countries polio-free, and closely monitor the occurrence for at least three years after the last reported case.

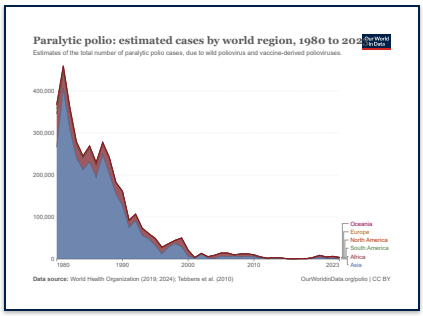
Even though the additional financial needs seem very high, the GPEI argues that eradication is the most cost-effective strategy, by illustrating that the long-term costs of controlling rather than eradicating will be substantially higher.

The benefits of eradicating polio extend beyond the health domain of having fewer people suffering from paralytic polio. In the economic domain, fewer polio patients translate into lower healthcare costs. Furthermore, once the virus has been eradicated, the world can stop producing and administering the polio vaccine as well as surveilling paralytic diseases suspected to be polio.

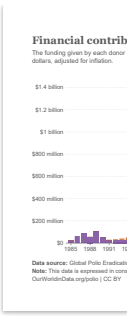
The GPEI argues that the discontinuation of these costly activities will therefore result in extensive economic gains from eradication as well. It is very difficult to accurately estimate these economic gains as it requires assumptions on for example the marginal economic value of a healthy person over a paralyzed polio patient or until what year you calculate these gains for. Tebbens et al. (2010)[42] have attempted such a modeling exercise and arrived at a net benefit of US-$40-50 billion — when comparing the GPEI against just national routine immunization — in the time horizon between 1988 to 2035.

Such a cost-benefit analysis is made even more difficult by having to extrapolate the actual case counts from reported incidence figures, which is explained in more detail in our article here.

Interactive charts on polio



Paralytic polio: estimated cases by world region



Financial c
eradication

Chart 1 of 21

ENDNOTES

1. Badizadegan, K., Kalkowska, D. A., & Thompson, K. M. (2022). Polio by the Numbers–A Global Perspective. *The Journal of Infectious Diseases*.

2. Nathanson, N., & Martin, J. R. (1979). The epidemiology of poliomyelitis: enigmas surrounding its appearance, epidemicity, and disappearance. *American Journal of Epidemiology*, *110*(6), 672-692.

3. See "The Pinkbook" on poliomyelitis by the US *Center for Disease Control and Prevention* (CDC) here.

4. As a response, several million children under five years old are recommended to receive the vaccination.

   See: Grassly, N. (2013). The final stages of the global eradication of poliomyelitis. *Philosophical Transactions Of The Royal Society B: Biological Sciences*, 368(1623), 20120140-20120140. Freely available online here.

5. As explained in the WHO's Factsheet on Polio.

6. For an introduction to the iron lung, the National Museum of American History has a good summary here.

7. Photo by Joe Clark. Repository: National Museum of Health and Medicine. Available online.

8. Here, you can read a condensed version from an article in *The Nation*, 1 March 1933, by Stewart Grimson, detailing the developments of the patent fight between Drinker and Emerson.

9. The amount of $1,500 stems from the National Museum of American History's summary. That sum of 1939 US-$ was then multiplied by the annualized inflation rate in the US from 1939 to 2016 and taken to the power of 77 (the number of years from 1939 to 2016) to arrive at 2016 US-$25,919.17 as the equivalent cost of an iron lung today).

10. Page 61 of Smallman-Raynor, M., & Cliff, A. (2006). *Poliomyelitis* (1st ed.). Oxford: Oxford University Press. Parts are available on Google Books.

11. The interested reader should refer to for example Eichner, M., Hadeler, K., & Dietz, K. (1996). Stochastic models for the Eradication of Poliomyelitis: Minimum Population Size for Polio Virus Persistence. In V. Isham & G. Medley, *Models for Infectious Diseases: Their Structure and Relation to Data* (pp. 315-330). Cambridge: Cambridge University Press. Partly available online on Google Books.

    Their mid-point estimate of the size of a human community necessary for poliovirus to survive is 250,000 which would make the earliest surviving infections possible in Egypt (3,000 BC) or Sumeria, today's southern Iraq (2,700 BC).

12. Some of these paleopathologists have found skeletons with typical polio marks stemming from:

    4000-2400BC Sussex, England (Wells, C. (1965). *Bones, Bodies and Disease. Evidence of disease and abnormality in early man.* London: Frederick A. Praeger.)

    2000-500BC Norfolk, England (Roberts, C., & Manchester, K. (1995). *The Archeology of Disease* (2nd ed.). Stroud: Alan Sutton.)

    3700BC Deshane, Egypt (Mitchell, J.K. (1900). *Study of a Mummy Affected With Anterior Poliomyelitis*. Transactions, 1. US: Transactions of the Association of American Physicians.)

    1225BC Egypt (Pharaoh Siptah) (Nunn, J. (1996). *Ancient Egyptian Medicine*. London: University of Oklahoma Press.)

13. The picture is available on Wikimedia Commons.

14. Lockhart, J. (1837). *Memoirs of the life of Sir Walter Scott.* Edinburgh: Robert Cadell. Available online: https://archive.org/details/memoirslifesirw85lockgoog. and Underwood, M. (1789). *Treatise on the Diseases of Children. Two Volumes*. London: J. Matthews. Available online: https://archive.org/details/2575056R.nlm.nih.gov.

15. Their book is called *Poliomyelitis* (1st ed.). Oxford: Oxford University Press. Parts are available on Google Books.

16. The table is taken from Smallman-Raynor, M., & Cliff, A. (2006). *Poliomyelitis* (1st ed.). Oxford: Oxford University Press. Parts are available on Google Books.

    It is based on

    Holt, L. E., & Bartlett, F. H. (1908). The Epidemiology Of Acute Poliomyeitis. *The American Journal of the Medical Sciences*, 135(5), 647-661.

    Batten, F. E. (1911). The epidemiology of poliomyelitis. Available online here.

    Low, R. B. (1917). Forty-fifth annual report of the Local Government Board, 1915–16. Supplement containing the Report of the Medical Officer for 1915–16.

    Lavinder, C., Freeman, A., & Frost, W. (1918). *Epidemiologic Studies of poliomyelitis in New York City and the northeastern United States during the year 1916.* Washington: Issue 91 of Public Health Bulletin (U.S. Government Printing Office).

17. A first large one happened in 1916 and a particularly large outbreak with 57,000 reported cases happened in the United States in 1952.

18. On page 3 of Robertson, S. (2017). *The Immunological Basis for Immunization Series, Module 6: Poliomyelitis.* Geneva: World Health Organization. Available online http://www.who.int/ihr/polio1993en.pdf.

19. Hall, W., Nathanson, N., & Langmuir, A. (1957). The Age Distribution of Poliomyelitis in the United States in 1955. *American Journal Of Hygiene*, 66(2), 214-34.

    This trend was also observed across Scandinavia and Northern Europe, see for example Burnet, F. (1940). The epidemiology of poliomyelitis with special reference to the Victorian epidemic of 1937-1938. *Medical Journal Of Australia*, 1, 325-336.

20. Read a more detailed description of the 1916 outbreak in New York City in this article, written by Merelli, A. (2017). 100 years ago, New York City declared war against polio and killed 72,000 cats (and 8,000 dogs). *Quartz.* Retrieved from https://qz.com/787385/the-history-of-polio-in-new-york-includes-unnecessarily-killing-72000-cats-and-8000-dogs/.

21. Researchers recently re-evaluated the president's symptoms from his historical medical records and questioned whether he actually contracted polio or rather suffered from an auto-immune disease called Guillain-Barré syndrome (GBS). Goldman, A. S., Schmalstieg, E. J., Freeman Jr, D. H., Goldman, D. A., & Schmalstieg Jr, F. C. (2003). What was the cause of Franklin Delano Roosevelt's paralytic illness?. *Journal of Medical Biography*, 11(4), 232-240. It can be freely accessed online here.

22. Page 435 of Smallman-Raynor, M., & Cliff, A. (2006). *Poliomyelitis* (1st ed.). Oxford: Oxford University Press. Parts are available on Google Books.

23. Page 188 in Oshinsky, D. (2005). Polio: An American Story (1st ed.). New York: Oxford University Press. Parts are available on Google Books.

24. Illustrated in this article: King, G. (2013). Salk, Sabin and the Race Against Polio. Smithsonian. Retrieved from https://www.smithsonianmag.com/history/salk-sabin-and-the-race-against-polio-169813703/.

25. Oshinsky, D. (2005). Polio: An American Story (1st ed.). New York: Oxford University Press. Parts are available on Google Books.

26. For more information see the University of Virginia's overview of the development of the iron lung and polio vaccine which is available here.

27. Bernier, R. (1984). Some Observations on Poliomyelitis Lameness Surveys. *Clinical Infectious Diseases*, *6* (Supplement_2), S371-S375.

28. Modlin, J. (2010). The Bumpy Road to Polio Eradication. New England Journal Of Medicine, 362(25), 2346-2349. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMp1005405.

29. It is unfortunately not comparable to our graph of the United States' rate of paralytic polio cases, as it depicts the number of cases per population and not per children.

30. Some countries such as Romania, Belarus and Hungary have seen higher than average rates of VAPP in the population. High rates of VAPP in those countries have been linked to the use of intramuscular injections of antibiotics to treat other conditions, which led to a syndrome called "provocation polio." In other countries, the rates of VAPP have been far lower — with Brazil at the lowest end, having only 0.09 cases per million doses.

    Platt, L. R., Estívariz, C. F., & Sutter, R. W. (2014). Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. *The Journal of infectious diseases*, *210*(suppl_1), S380-S389.

31. *Classification and reporting of vaccine-derived polioviruses (VDPV)*. (2016). Global Polio Eradication Initiative. https://polioeradication.org/wp-content/uploads/2016/09/Reporting-and-Classification-of-VDPVs_Aug2016_EN.pdf

32. Sáez-Llorens, X., Bandyopadhyay, A. S., Gast, C., Leon, T., DeAntonio, R., Jimeno, J., Caballero, M. I., Aguirre, G., Oberste, M. S., Weldon, W. C., Konopka-Anstadt, J. L., Modlin, J., Bachtiar, N. S., Fix, A., Konz, J., Clemens, R., Costa Clemens, S. A., & Rüttimann, R. (2021). Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials. *Lancet (London, England)*, *397*(10268), 27–38. https://doi.org/10.1016/S0140-6736(20)32540-X

33. Savolainen-Kopra, C., & Blomqvist, S. (2010). Mechanisms of genetic variation in polioviruses: Mechanisms of genetic variation in polioviruses. *Reviews in Medical Virology*, *20*(6), 358–371. https://doi.org/10.1002/rmv.663

    Jorgensen, D., Pons-Salort, M., Shaw, A. G., & Grassly, N. C. (2020). The role of genetic sequencing and analysis in the polio eradication programme. *Virus Evolution*, *6*(2), veaa040. https://doi.org/10.1093/ve/veaa040

    Yeh, M. T., Bujaki, E., Dolan, P. T., Smith, M., Wahid, R., Konz, J., Weiner, A. J., Bandyopadhyay, A. S., Van Damme, P., De Coster, I., Revets, H., Macadam, A., & Andino, R. (2020). Engineering the Live-Attenuated Polio Vaccine to Prevent Reversion to Virulence. *Cell host & microbe*, *27*(5), 736–751.e8. https://doi.org/10.1016/j.chom.2020.04.003

34. Macklin, G. R., O'Reilly, K. M., Grassly, N. C., Edmunds, W. J., Mach, O., Santhana Gopala Krishnan, R., ... & Sutter, R. W. (2020). Evolving epidemiology of poliovirus serotype 2 following withdrawal of the serotype 2 oral poliovirus vaccine. *Science*, *368*(6489), 401-405.

35. Global Polio Eradication Initiative. (2016, August 4). Global synchronisation and the switch. *News Stories*. https://polioeradication.org/news-post/global-synchronisation-and-the-switch/

36. Ramirez Gonzalez, A., Farrell, M., Menning, L., Garon, J., Everts, H., Hampton, L. M., ... & Patel, M. (2017). Implementing the synchronized global switch from trivalent to bivalent oral polio vaccines—lessons learned from the global perspective. *The journal of infectious diseases*, *216*(suppl_1), S183-S192.

37. Thompson, K. M., & Kalkowska, D. A. (2021). Potential Future Use, Costs, and Value of Poliovirus Vaccines. *Risk Analysis*, *41*(2), 349–363. https://doi.org/10.1111/risa.13557

38. Global Polio Eradication Initiative. (2019, September 5). Inactivated Polio Vaccine now introduced worldwide. *News Stories*. https://polioeradication.org/news-post/inactivated-polio-vaccine-now-introduced-worldwide/

39. Global Polio Eradication Initiative. (2021, October 10). Independent experts advise move to next use phase for novel oral polio vaccine type 2. *News Stories*. https://polioeradication.org/news-post/independent-experts-advise-transition-to-next-use-phase-for-novel-oral-polio-vaccine-type-2-nopv2/

40. This can be found in: World Health Assembly. Global eradication of poliomyelitis by the year 2000 (resolution 41.28). Geneva: World Health Organization; 1988.

41. Other partners include the United Nations Foundation and other private foundations, the World Bank, national governments, the European Commission, NGOs such as the International Red Cross and Red Crescent societies for example, private companies and 20 million volunteers. For more information on the GPEI's partners and donors, this is their website.

42. Tebbens, R., Pallansch, M., Cochi, S., Wassilak, S., Linkins, J., & Sutter, R. et al. (2010). Economic analysis of the global polio eradication initiative. *Vaccine*, 29(2), 334-343. Available online here.

43. As outlined in the WHO guidelines, for example here.

44. Thompson, K. M., & Kalkowska, D. A. (2021). An Updated Economic Analysis of the Global Polio Eradication Initiative. *Risk Analysis*, *41*(2), 393–406. https://doi.org/10.1111/risa.13665

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REVIEW

The Problems with Polio: Toward Eradication

Gemma Lien · David L. Heymann

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ABSTRACT

The global health effort to eradicate poliomyelitis (polio) has encountered a number of unforeseen and unpredictable challenges. This article provides a timely review of progress made toward eradication, including the polio vaccines in use, and explores the reasons for delays in eradication target dates. It provides an overview of some of the remaining barriers to eradication and looks toward overcoming these through the Polio Eradication and Endgame Strategic Plan.

Keywords: Polio; Polio eradication; Polio endgame; Polio vaccine; Poliomyelitis; Poliovirus

G. Lien (✉) · D. L. Heymann
Public Health England, Wellington House, 133-155 Waterloo Road, London SE1 8UG, UK
e-mail: gemma.lien@phe.gov.uk

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INTRODUCTION

The global health effort to eradicate poliomyelitis (polio) has encountered a number of unforeseen and unpredictable challenges which have been well documented [1]. This article provides a timely review of these challenges and looks toward overcoming the remaining barriers to eradication.

METHODS

The authors undertook a comprehensive literature review using the Internet and the databases JSTOR, PubMed, ScienceDirect and SwetsWise. The following search terms were used: "polio", "poliomyelitis", "polio eradication", "polio endgame", "polio vaccine" and "poliovirus".

DISCUSSION

Polio is a highly infectious viral disease, which can cause paralysis and, in some cases, death. Wild polioviruses are those that occur naturally. There are three serotypes of wild poliovirus: type-1, type-2, and type-3. The poliovirus enters

the body through the mouth, multiplies in the oropharynx and the small intestine and exits in the feces from which it can spread rapidly through a community, especially in areas with poor hygiene and sanitation. The virus invades the local lymphoid tissues in the gastrointestinal tract, and may then enter the bloodstream and spread to the central nervous system. The virus may also spread to the central nervous system along the peripheral nerves. Over 90% of people infected with poliovirus have either no or very mild symptoms, which can easily go unrecognized [2]. This makes it very difficult to identify an outbreak immediately as asymptomatic infections can spread the infection 'silently' to others before the first case of polio paralysis is detected. Therefore, herd immunity must be attained to prevent transmission and outbreaks of polio occurring.

Before the twentieth century, poor hygiene and sanitation meant that almost all children were exposed to poliovirus during infancy, which enabled natural immunity to build up in populations. The industrial revolution brought great sanitary improvements, including the separation of sewage from drinking water. While this proved vital in increasing public health standards in general, it initially had disastrous effects in relation to polio cases. It reduced childhood exposure to the virus and lowered immunity levels in communities, creating the perfect setting for epidemics to ignite [3].

By the late 1980s, polio had been eliminated from most industrialized countries by routine immunization programs. However, it was estimated that polio still paralyzed more than 1,000 children every day globally, and that the poliovirus was circulating in more than 125 lesser developed countries [4]. Building on the global health success of the eradication of smallpox, and encouraged by the progress made toward interrupting wild poliovirus transmission in the Americas in the early 1980s, in 1988 the World Health Assembly declared the commitment of the World Health Organization (WHO) to the global eradication of poliomyelitis by the year 2000 [5]. The Global Polio Eradication Initiative (GPEI) was formed to achieve this target, led by WHO, the United Nations Children's Fund, Rotary International, and the United States Centers for Disease Control and Prevention [6].

The GPEI understood that increasing population immunity by routine vaccination supplemented by national mass immunization campaigns, and enhancing the epidemiological surveillance of the disease so that outbreaks could be rapidly detected and contained, would be the key to interrupting the transmission of wild poliovirus and achieving eradication [6].

The vaccine most used globally is the trivalent oral polio vaccine (tOPV or 'Sabin vaccine'), which is effective against all three types of wild poliovirus. Use of tOPV can result in the 'passive' immunization of people living in areas of poor hygiene and sanitation who have not been directly vaccinated, as the virus continues to be excreted through the feces into the environment for several weeks after vaccination. A further advantage to its use is its cost, estimated to be between 11 and 14 US cents per dose [7].

There are also two more oral polio vaccines in use today: the monovalent vaccine (mOPV) and the bivalent vaccine (bOPV). In children being immunized for the first time, the monovalent vaccine (mOPV), consisting of just one type of the live attenuated strains of poliovirus, provides a greater immunity to the specific type of poliovirus being targeted and also provides increased immunity for the same number of doses compared with tOPV. This

may be because there is no competition from the other two virus types in the vaccine [8]. The bivalent vaccine (bOPV) consists of live attenuated strains of both type-1 and type-3 poliovirus and improves the efficiency and impact of vaccination campaigns in areas where both types of poliovirus co-circulate. It is more effective than tOPV and almost as effective as mOPV in achieving protection [9].

Unfortunately, in very rare cases, (approximately 1 in every 2.7 million first doses of the vaccine), the oral polio vaccines can cause a condition known as vaccine-associated paralytic polio [7]. Even more concerning is the potential for the live attenuated strains of the vaccine viruses to revert and re-acquire neurovirulence, resulting in circulating vaccine-derived polioviruses (cVDPVs) [10]. cVDPVs could pose a threat in a post-eradication world, with the ability to cause devastating outbreaks of polio at a time when immunity levels are reduced.

In most high-income countries, where the risk of polio infection is low, the inactivated polio vaccine (IPV or 'Salk vaccine') is used. IPV consists of "killed" strains of all three polioviruses, which is delivered via an injection. As it is not a "live" vaccine, IPV poses no risk to the recipient of vaccine-associated paralytic polio, nor is there any possibility of cVDPVs emerging [11]. However, it does need to be administered by a trained health worker, induces very low levels of immunity in the intestine and is over five times more expensive than the oral polio vaccine [11].

Following its launch in 1988, the GPEI had a promising start and the Americas was the first WHO Region to be certified polio-free of all three types of wild poliovirus in 1994. By the year 2000, the global incidence of polio had been reduced by over 99% [12] and every endemic country had implemented some form of polio-eradication strategy. Much effort had been made to attain herd immunity by supplementing the preceeding level of polio vaccination coverage in routine immunization programs with compaings [13].

However, delays in the global implementation of eradication strategies, in part due to lack of political commitment, funding and competing development and health priorities meant that the initial target for eradication by the year 2000 was missed. Nevertheless, progress continued with the certification of two more WHO Regions as polio-free: the Western Pacific Region in 2000 [14] and the European Region in 2002 [15].

In 2003, only six polio-endemic countries remained: Afghanistan, Egypt, India, Niger, Nigeria and Pakistan. Although Egypt and Niger were later declared polio-free by 2005, the remaining four countries faced various challenges to the eradication effort over the next 10 years. Following the elimination of type-2 wild poliovirus from human populations in 1999 when the last infection was identified in India [16], and because tOPV provides less optimum protection against poliovirus serotypes 1 and 3 in some tropical settings, the monovalent and bivalent formulations of the vaccine were introduced to more closely target and rapidly interrupt the remaining virus types in circulation, particularly in densely populated areas of high intensity of transmission [17].

India's greatest challenge to eradication was the sub-optimal effectiveness of tOPV in areas of high birth rates, poor sanitation as well as dense and migratory communities. This was particularly apparent in northern India and was only overcome by a substantial effort to push coverage rates to over 95% in particularly vulnerable populations and areas, and the

careful and tactical use of mOPV and bOPV [1]. India was finally removed from the WHO list of polio-endemic countries in early 2012; an enormous achievement, considering that in 2009, India had the highest number of polio cases in the world [18]. It is expected that India will be officially certified as polio-free in 2014 [19].

The nature of poliovirus has posed its own challenge to eradication. Every child needs to be vaccinated multiple times to ensure full immunity, depending on the vaccine used [20]. This provides a significant logistical challenge to vaccinators, especially with migratory, displaced or hard to access populations. It can be very difficult to ascertain when and how many doses of vaccine each child has received and how many children were missed on vaccination days [1]. This can pose a high risk to immunity levels as the virus may be transmitted over large distances with little warning.

Natural disasters such as floods, earthquakes, hurricanes and tsunamis can also contribute to delays in eradication efforts. These can all have a detrimental impact on communications and road and health infrastructures, in some cases making it impossible to reach people except by air. Hospitals, medical centers and cold chain storage facilities can be damaged or destroyed and local health workers displaced.

The re-importation of wild poliovirus to countries that were previously polio-free has also complicated efforts. Angola, Chad and the Democratic Republic of Congo have all experienced re-established transmission, resulting in reservoirs from where neighboring countries have been repeatedly infected. In addition, the transmission of cVDPVs has also caused problems in a number of countries. Poor management and oversight of polio and routine immunization campaigns continue to be a major risk factor for outbreaks following re-importation of the poliovirus into previously polio-free countries [1]. Gaps in the quality of acute flaccid paralysis surveillance have also compromised the speed of outbreak response activities.

Only three polio-endemic countries remain in 2013: Afghanistan, Nigeria and Pakistan. It can be argued that geopolitical events in all three countries, such as war and insecurity, in addition to the loss of community confidence in the immunization program in some areas of these countries, have continued to hamper eradication progress. Civil disturbance displaces children and can result in the blocking of access routes during vaccination campaigns. Deep distrust of perceived Western-led initiatives has also impacted on polio immunization efforts. False rumors, such as those that circulated in Nigeria in 2003 that the polio vaccine was being used to sterilize Muslim girls [21] and those that circulated in Pakistan in 2011 that the USA and its allies were running spying networks through vaccination campaigns [22] have contributed to a loss of community confidence in the immunization program. A series of fatal attacks in December 2012 and February 2013 targeting polio vaccination workers in Pakistan and Nigeria, respectively, has led to fear and confusion around vaccination campaigns and appears to have compromised the vaccine coverage in some areas. This continues to affect immunization uptake and intensive efforts have been made to engage local community and religious leaders to champion the cause.

The combination of missed targets for eradication and the high costs of implementing the GPEI's activities worldwide has prompted some public health officials to question the concept of eradication in favor of a strategy of "effective control". They argue that

maintaining less than 500 polio cases per year would be cheaper than completing eradication [23]. This suggestion has so far been rejected by the international public health and donor communities, and continued polio surveillance still requires extensive financial and operational efforts. Epidemiological modeling has suggested that in low-income countries alone, a switch to 'control' would result in an estimated 4 million polio-paralyzed children over the next 20 years [24]. Furthermore, a 2010 study based on GPEI activities from 1988 through 2035 estimated that the elimination of wild poliovirus by 2015 would produce net profits of around US $50 billion from reduced treatment costs and gains in economic productivity by preventing polio-related disability, with low-income countries accounting for approximately 85% of the net benefits [25].

The gains from the global implementation of polio eradication initiatives are not only monetary. The GPEI has trained an enormous cadre of staff who understand basic health care needs and can provide services to people in the poorest areas in the world. Activities undertaken under the auspices of the GPEI have also contributed to the improvement of public health at large and increased the effectiveness of other preventive programs. Polio program staff have supported the surveillance of and response to measles, tetanus, meningitis, yellow fever and cholera. Furthermore, in many countries, the GPEI successfully expanded its delivery model to include the distribution of Vitamin A supplements alongside polio immunizations, estimated to have averted at least 1.1 million Vitamin A deficiency-related deaths from 1988 to 2010 [25].

In 2012, the World Health Assembly requested a comprehensive polio endgame strategy [26], which culminated in the development of the Polio Eradication and Endgame Strategic Plan 2013–2018 [27]. The Plan is based on broad consultations with national health authorities, global health initiatives, scientific experts, donor partners and other stakeholders. The Plan has four main objectives: to stop all wild poliovirus transmission by the end of 2014 and new cVDPV outbreaks within 120 days of confirmation of the first case; to strengthen immunization systems, introduce IPV into the routine immunization schedule globally and withdraw the use of oral polio vaccines; certify all regions of the world polio-free by 2018 and ensure the safe containment of all poliovirus stocks; and to ensure that the world remains permanently polio-free with careful legacy planning as well as planning for the transition of assets and the infrastructure of the polio program to benefit other development goals and global health interventions.

The Plan aims to withdraw the use of the type-2 component of OPV in all routine immunization programs by mid-2016. The importance of withdrawing the type-2 component as quickly as possible was reinforced by the 2012 polio outbreaks caused by circulating type-2 vaccine-derived polioviruses, which left 65 children paralyzed in 7 countries: Afghanistan, Chad, the Democratic Republic of Congo, Kenya, Nigeria, Pakistan and Somalia [28]. As of August 13, 2013, 17 cases of polio due to circulating type-2 vaccine-derived polioviruses were reported in 6 countries: Afghanistan, Cameroon, Chad, Nigeria, Pakistan and Somalia [29].

The withdrawal of the type-2 component of OPV will require the strengthening of immunization systems, the introduction of at least one dose of affordable IPV into the routine immunization schedule globally and then the

replacement of tOPV with bOPV. This would pave the way for the eventual withdrawal of bOPV use in 2019–2020.

The GPEI is currently undertaking research to find ways of enabling low-income countries to access low-cost IPV options, instead of relying on costly imports. A multi-pronged research agenda is being pursued to investigate: a dose-reduction strategy using intradermal administration of fractional IPV doses; a schedule requiring fewer doses; adjuvant use to reduce the quantity of antigen required in the vaccine; and IPV production processes to facilitate manufacture in low-cost sites. The GPEI is also investigating the mucosal immune responses stimulated by IPV compared with those stimulated by OPV. In addition, work is being carried out to develop an IPV based on 'Sabin' attenuated virus seed-strains [30]. While traditional manufacturing of IPV involves large amounts of infectious 'Salk' seed strains, IPV containing the attenuated Sabin seed strains would reduce the severity of potential consequences in the event of a biocontainment failure at an IPV manufacturing facility.

Financing of the eradication effort remains a huge challenge. In the first quarter of 2012, GPEI activities were scaled down in 24 high-risk countries because of an acute funding shortage [31]. The budget for the Plan is US $5.5 billion, with a peak spending in 2013, then estimated to decline annually [32]. As of June 1, 2013, the GPEI was tracking over US$ 217 million in firm prospects, which if fully operationalized could close the 2013 funding gap, provided enough unspecified funds are secured to cover all cost categories [32]. However, pledges are very different to signed agreements and cash disbursements, and there is still a US $1.5 billion funding gap to fully resource the Plan. This shortfall has the potential to hamper the goal of eradication.

Today, eradication efforts continue. In 2012, 223 wild poliovirus cases were reported globally, more than a 60% decline compared with 2011 and only 5 countries reported cases in 2012 compared with 16 in 2011 [33]. As of August 13, 2013, 181 wild poliovirus cases had already been reported [33].

CONCLUSION

The global health effort to eradicate polio has faced numerous challenges since the launch of the GPEI. It is hoped that the last remaining obstacles have been identified and will be overcome within the established timeframe of the Polio Eradication and Endgame Strategic Plan. Crucially, success in the polio endgame would provide a strong evidence base and encourage political commitment to other such eradication initiatives. However, building on the lessons learned from the polio experience, any eventual strategy for measles eradication should strengthen routine immunization and not merely become a substitute [34].

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SPECIAL ARTICLE

Louise Reisner-Sénélar

The birth of intensive care medicine: Björn Ibsen's records

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L. Reisner-Sénélar (✉)
Berufsgenossenschaftliche Unfallklinik Frankfurt am Main, Anästhesie, Intensivmedizin und Schmerztherapie, Friedberger Landstraße 430, 60389 Frankfurt am Main, Germany
e-mail: LouiseReisner@hotmail.com
Tel.: +49-694752772
Fax: +49-6172-983348

Abstract The birth of intensive care medicine was a process that took place in Copenhagen, Denmark, during and after the poliomyelitis epidemic in 1952/1953. The events that led to the creation of the first intensive care unit in the world in December 1953 are well described. It is generally agreed upon that the start of the process was the fact that an anaesthesiologist (Björn Ibsen) was brought out of the operating theatre and asked to use his skills on a 12-year-old girl suffering from polio. The medical record of the girl contains a minute-by-minute description of the historical event. A translation of this part of the record is published as an Online Resource to the article. The role played by the epidemiologist Mogens Björneboe is further analysed. He was the catalyst of the process, being the one with the idea that the skills of an anaesthesiologist could be used for other purposes than surgery. When first Ibsen realised what could be done with his skills, he proved to be one of the most progressive and inventive doctors seen in modern medicine. An interview with Prof. Ibsen in 2006 is published as an Online Resource to the article.

Keywords Intensive care · Björn Ibsen · Mogen Björneboe · HCA lassen · Blegdam · Copenhagen · Poliomyelitis · Polio epidemic 1952 · Respiratory failure · Positive pressure ventilation · History of medicine

The birth of intensive care medicine, as it is generally acknowledged today, was the result of a succession of unconventional methods and solutions hastily improvised by a Danish hospital in order to cope with the overwhelming medical and organisational challenges of the poliomyelitis epidemic of 1952.

If 1952 can therefore be considered as the annus mirabilis of intensive care, the event was far more gradual in detail: A last desperate attempt to save the life of a 12-year-old turned out surprisingly well. This led to the organisation of a single-disciplinary unit to treat polio patients with respiratory failure. This unit developed into a multidisciplinary recovery room and finally ended up as a multidisciplinary intensive care unit. The entire process took just 17 months, and—more surprisingly—the honours for this remarkable achievement are widely conferred on only one man, who is recognised for having designed and performed each of these revolutionary steps: Dr. Björn Ibsen, also commonly known as the "father of intensive care medicine".

The events around the poliomyelitis epidemic in Copenhagen in 1952 have been widely published [1, 2–8] and shall therefore only be summarised in the first part of this article. However, there remains a question surrounding Ibsen; a man who performed such exceptional

achievements but long remained astonishingly silent about his intensive care contribution, Ibsen took more pride in his discoveries on the treatment of shock than his pioneering work on intensive care [9]. There have been speculations [10] over why Ibsen chose to publish his work concerning this new branch of anaesthesiology as late as 1958, in a small journal and in a language unknown to most of the world (Danish) [11]. Ibsen was nevertheless an ambitious physician: He decided to become an anaesthesiologist because it would take too long to reach a senior position as a surgeon, and travelled to the USA to learn state-of-the-art anaesthesia from Dr. Beecher (Massachusetts General Hospital) [12].

Ibsen humbly pointed out "what we did was just to use the principles and techniques, which served us well in the operating theatre, also on patients with medical diseases" [10]. After having carefully collected historical facts, some so far unpublished, and after interviewing Ibsen, I came to the conclusion that he placed his performance in perspective to the mentoring and inspirational role played in the development of intensive care by another colleague: Mogens Björneboe.

The poliomyelitis epidemic in Denmark in 1952 was dramatic by all standards. The number of patients with respiratory failure was higher than in any other European country [2]. The Blegdam Hospital, responsible for the treatment of poliomyelitis, counted only one tank respirator and six cuirass respirators for a daily admission of 6–12 patients with respiratory failure [13]. Additionally, all conventional treatments proved to be almost completely inefficient (27 of the first 31 patients with respiratory failure had died [2]). Blegdam Hospital's Chief Physician, Dr. Lassen, was desperately seeking good advice. Upon the suggestion of his colleague Dr. Björneboe, he contacted the anaesthesiologist Björn Ibsen. On 27 August 1952, Ibsen demonstrated his anaesthetic skills on a 12-year-old girl named Vivi E., who was in a state of severe respiratory failure. Ibsen ventilated the tracheotomised girl with a to-and-fro system, sucking the mucus from her lungs and narcotising her in order to release her bronchospasm. As it became clear that the available cuirass respirator could not provide sufficient ventilation, Ibsen continued to ventilate the girl manually and eventually saved her life. Within 8 days, the method of manual ventilation via tracheostomy was conducted on every patient with respiratory failure from poliomyelitis within Blegdam Hospital [1].

The author found the original and unpublished patient record of Vivi E., including a minute-by-minute transcription of the dramatic hours where Ibsen fought for Vivi's life. (For a translation of the medical record see Online Resource 1.)

Shortly after having successfully completed the first two steps on the way to intensive care medicine, Ibsen moved to the county hospital of Copenhagen (Kommunehospitalet) (Fig. 1). On 1 July, he opened a recovery room, which had become a multidisciplinary intensive care unit by December [6]. Bertelsen and Cronqvist determined that the first "real" intensive care patient was a 43-year-old male treated on 21 December 1953 [10].

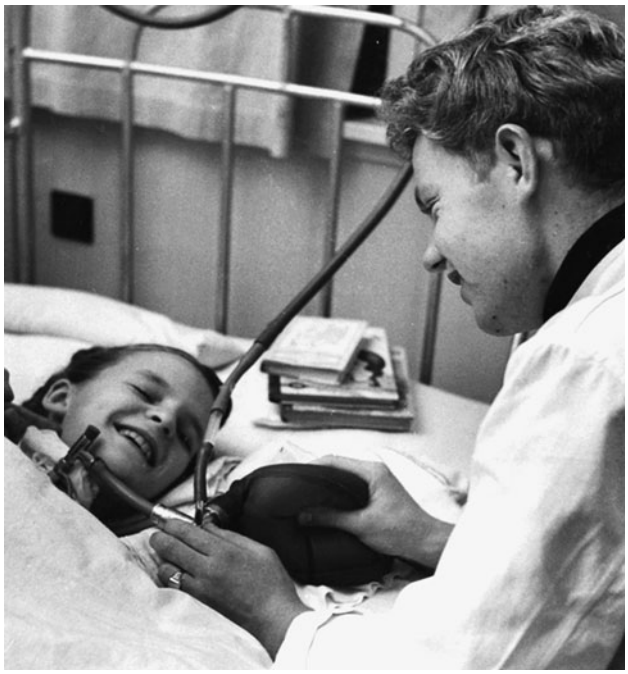

Fig. 1 A young patient with poliomyelitis being manually ventilated by a medical student during the poliomyelitis epidemic in Copenhagen, 1953 [Source: Medical History Museum in Copenhagen]

The influence of Mogens Björneboe

In 1952, Ibsen was a young and talented anaesthesiologist, but his organisational talents may have remained long undiscovered if he were not to have met a physician who quickly recognised his potential and who mentored and inspired him: Mogens Björneboe.

Björneboe was a Danish doctor, a singular physician who was not scared to develop new, audacious ways to treat his patients. As a young doctor, he witnessed patients being treated with electroshocks. The treatment implied that 40% of the patients seriously damaged their backs from muscular cramps. He realised that it was possible to reduce the cramps with curare and thus avoid the side-effects [14].

In 1950, Björneboe met Ibsen's wife on a transatlantic trip from America. Mrs. Ibsen, a trained nurse, described her husband's experience as an anaesthesiologist at the Massachusetts General Hospital. Björneboe's interest was aroused, and he took notice of Ibsen [15].

When, in January 1952, Björneboe was faced with a case of congenital tetanus, he intuitively thought that these cramps could also be treated with curare [14], but realised that he needed the skills of a well-trained anaesthesiologist. He contacted Ibsen.

Ibsen, who was a product of Beecher's schooling, had little curare experience [5]. He still agreed to assist Björnboe in tracheotomising the newborn to apply artificial ventilation on a rocking bed and eventually treating the convulsion with curare. As the effect of the curare wore off, the convulsions re-emerged, and the two doctors turned back to use conventional treatment for tetanus [6, 12, 16].[1] The baby eventually died, but Björneboe started to understand the potential of this treatment, and Ibsen's skills made a lasting impression.

After the "polio experience" (May 1953), a 10-year-old boy with tetanus was admitted to Bledgam. Björneboe contacted Ibsen, who worked at the Kommunehospital and as a consultant at Blegdam Hospital. Ibsen had meanwhile gained confidence to "turn the tetanus-case into a polio-case" and treat the patient with narcosis and curare over several days [6]. Over 17 days the boy was manually ventilated before he finally recovered [16].

Ibsen was not a pioneer concerning positive pressure ventilation outside the operating theatre; Bower and Bennet had used the method on polio patients in 1950, albeit only in the short term and as a supplement to a tank respirator, so the idea of using positive pressure ventilation on polio patients was not new [17]. Also, Clemmesen had developed a similar concept for treatment of barbituric intoxication.[2]

Ibsen's great achievement was to understand that, in terms of treatment, it was rather irrelevant which disease caused the respiratory failure; the treatment should remain fundamentally the same: secure proper ventilation. Today this seems evident, but at that time the idea was quite revolutionary. Starting from this conclusion he understood that patients could only be dealt with adequately if the hospital was reorganised to treat respiratory failures in a multidisciplinary centralised unit.

Ibsen did not only have this insight; he was also gifted with the organisational talent to improvise solutions and with the management skills to structure and maintain a long-term organisation within the hospital.

Online Resources 1 and 2 have previously been published in German in Reisner-Sénélar L (2009) *Der dänische Anästhesist Björn Ibsen—ein Pionier der Langzeitbeatmung über die oberen Luftwege*. Johann Wolfgang Goethe-Universität, Frankfurt am Main.

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[1] In the interview from 2006, Ibsen notes that the child was given narcosis and curare, and was tracheotomised and ventilated. In his recording of the event from 1975 [6], he notes that the child was treated with d-tubo-curare and ventilated on a rocking bed, but there is no mention of sedatives.

[2] In the 1940s, a physician named Clemmesen developed a method to treat patients with barbiturate poisoning which involved artificial positive pressure ventilation through tracheotomy for respiratory failure as well as treatment of shock. In 1949, he opened a centralised unit at Bispebjerg Hospital in Copenhagen [18].

Defining Surrogate Serologic Tests with Respect to Predicting Protective Vaccine Efficacy: Poliovirus Vaccination

ROLAND W. SUTTER,[a,b]
MARK A. PALLANSCH,[c] LEIGH A. SAWYER,[d]
STEPHEN L. COCHI,[b]
AND STEPHEN C. HADLER[b]

[b] *National Immunization Program, and*
[c] *Division of Viral and Rickettsial Diseases*
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

[d] *Division of Viral Products*
Center for Biologics Evaluation and Research
United States Food and Drug Administration
Bethesda, Maryland 20852

INTRODUCTION

During the early 20th century, poliomyelitis became an epidemic disease in the United States. Epidemics of ever-increasing magnitude culminated in 1952, when more than 50,000 cases of poliomyelitis were reported.[1] The use of inactivated poliovirus vaccine (IPV), later replaced by oral poliovirus vaccine (OPV), led to the virtual elimination of poliomyelitis from the United States and most developed areas of the world,[1,2] and to the control of this disease in many areas of the developing world.[3,4] This represents one of the truly great achievements of public health in the 20th century. In the United States, the last two outbreaks of poliomyelitis due to wild poliovirus occurred in 1972[5] and 1979[6] among members of religious groups objecting to vaccination.

Inactivated poliovirus vaccine developed by Dr. Jonas Salk was licensed for use in 1955 in the United States after the Francis field trial reported efficacy of IPV in preventing paralytic disease.[7] Inactivated poliovirus vaccine, a combination vaccine, contains each of the three serotypes of formalin-inactivated poliovirus. To maximize seroconversion following IPV, the antigen content for each poliovirus serotype required careful adjustment. From 1959 to approximately 1968, two combination vaccines of

[a] Address for correspondence: Roland W. Sutter, M.D., M.P.H. & T. M., National Immunization Program (E61), Centers for Disease Control and Prevention, Atlanta, Georgia 30333.

IPV and diphtheria and tetanus toxoids and pertussis vaccine (DTP) were available: Quadrigen, with the preservative benzethonium chloride (phemerol), produced by Parke-Davis[8] and Tetra-Solgen by Eli Lilly.[8] In 1987, an enhanced-potency IPV was licensed in the United States[9] and has since replaced the previously formulated IPV.

In the early 1960s, monovalent oral, live attenuated poliovirus vaccines developed by Dr. Albert Sabin were licensed; two years later, after high seroconversion rates were reported with use of a "balanced formulation" trivalent OPV, this formulation was licensed in the United States.[10,11] Shortly after licensure, trivalent OPV replaced IPV as the vaccine of choice for poliomyelitis control in the United States and most of the rest of the world.[1] Based on rapid progress towards regional elimination of poliomyelitis from the western hemisphere,[12,13] the World Health Assembly in 1988 adopted the goal of global poliomyelitis eradication to be accomplished by the year 2000.[14]

In spite of the extraordinary success of poliomyelitis control programs relying exclusively on OPV, the vaccine has two major shortcomings: vaccine-associated paralytic poliomyelitis (VAPP) and low immunogenicity in children in developing countries. In this communication, the following questions will be addressed: (1) is there a need for an improved poliovirus vaccine or better utilization of the two existing vaccines, OPV and IPV? (2) what qualities should be sought in improved poliovirus vaccines? (3) how do humoral and mucosal immunity relate to predicting vaccine efficacy? (4) what serologic tests should be used as surrogates for protection to evaluate the protective efficacy of poliovirus vaccines? and (5) what are some current approaches for combining IPV and DTP?

RATIONALE FOR IMPROVEMENT OF POLIOVIRUS VACCINE

Despite the tremendous success in controlling and eliminating poliomyelitis from many areas of the world, the currently used OPV has two major shortcomings. The first major shortcoming of OPV is safety—a concern that has evolved predominantly in developed countries where poliomyelitis has been controlled for many years. Rarely, OPV can cause poliomyelitis indistinguishable from the disease caused by wild poliovirus.[1] While this small risk was acceptable to society when cases due to wild poliovirus were common, today, when the only form of poliomyelitis in the United States is VAPP, the policy of relying primarily on OPV has come under review by the Institute of Medicine in 1977[15] and again in 1988.[16]

The second major shortcoming of OPV is the low immunogenicity in children in developing, particularly tropical countries.[17] The median of seroconversion rates reported from available trials in developing countries were recently summarized in a comprehensive review article.[18] The median rates of seroconversion/seroprevalence following three doses of OPV were 72% for poliovirus type 1, 95% for type 2, and 65% for type 3. These rates are substantially lower than those achieved in the developed world, where three doses of OPV induce virtually 100% seroconversion for each of the three serotypes.[19] Although reasons for the lower than expected seroconversion rates are not well characterized, several hypotheses other than potency of the vaccine, dose, and schedule have been proposed. These hypotheses include: interference by concurrent infection with other enteroviruses, diarrhea, maternally-derived antibody, nonspecific inhibition, breast feeding, and nutritional factors.[18]

DESIRED QUALITIES OF AN IDEAL POLIOVIRUS VACCINE

An ideal poliovirus vaccine (after a primary series of ⩽3 doses) should induce high levels of seroconversion (>95%) to all three serotypes among young infants in both developed and developing countries and provide effective mucosal immunity. Circulating antibody associated with individual protection against paralytic disease should persist for life. Local secretory antibody should preclude or limit replication of the virus after infection, and thus decrease the circulation of the virus in the population. In addition, a reduction in the number of doses of such a vaccine would be desirable. And finally, such an improved poliovirus vaccine should be safe; ideally, it should not cause vaccine-associated disease.

Oral poliovirus vaccine and IPV, in addition to providing individual protection against clinical disease by circulating antibody, induce some degree of mucosal immunity that can be measured by secretory IgA and/or resistance to challenge doses of vaccine-related poliovirus.[20] Mucosal immunity is believed to be responsible for a shorter duration and decreased quantity of poliovirus shedding and excretion from the pharynx and intestine. These latter effects are believed to reduce poliovirus exposure among the remaining susceptible population. Although both IPV and OPV appear equally effective in decreasing pharyngeal excretion, OPV is clearly superior in decreasing intestinal replication and excretion compared to IPV. An optimal program to control poliomyelitis would attempt to maximize both humoral and mucosal immunity.

END POINT MEASURES FOR VACCINE TRIALS

What outcome measures should be used to predict protection? or what specific assays may be used as surrogates for predicting efficacy in preventing paralytic disease? Theoretically, poliovirus vaccine induces humoral, mucosal, and cell-mediated immunity. Humoral immunity can be assessed by measuring circulating antibody. Mucosal immunity can be assessed directly by measuring secretory antibody or indirectly by challenging subjects with vaccine-related poliovirus and evaluating the degree of resistance to virus replication by measuring the duration and titer of poliovirus excretion in stool or pharynx. Currently, no standardized methods have been developed to measure cell-mediated immunity to poliovirus.

Neutralization Assays

The "gold standard" method available to assess humoral antibody responses following vaccination or natural infection is the neutralization assay.[21] The assay has excellent sensitivity, specificity, positive predictive value, and negative predictive value, and can also be used to assess the long-term persistence of antibody. Although both the complement fixation and the IgM enzyme immunoassay are useful in certain instances, these assays are more dependent on the exact timing of specimen collection than the neutralization assay, and cannot be used to evaluate the long-term persistence of antibody. Other assays have been reported by several groups.[22–25] However, despite some encouraging findings, alternative methods have not been adopted by many laboratories.

Standardization of Neutralizing Assays

Recently, standard procedures for conducting neutralization assays were adopted in a meeting sponsored by the World Health Organization (WHO).[26] The most significant of these standards are the adoption of Hep 2 (Cincinnati) as the preferred cell line, the use of vaccine-related virus instead of wild poliovirus as challenge virus, and the use of a uniform standard starting dilution of 1:8.[26] These standardized procedures will allow direct comparison of antibody titers reported from poliovirus clinical trials. Adoption of these recommendations would eliminate the large reservoir of wild polioviruses (Mahoney [type 1], MEF-1 [type 2], and Saukett [type 3]) that are currently used in many laboratories conducting neutralizing antibody testing around the world,[21] a concern of the global poliomyelitis eradication program. If the WHO protocol for neutralization assays is not used, serum specimens should be tested in parallel with control sera,[27] since the reported titer of neutralizing antibody is dependent on incubation period[28] and other factors.

Assessment of Mucosal Immunity

Mucosal immunity can be assessed directly or indirectly. Specific secretory IgA or neutralizing antibodies in the pharynx or the intestine can be measured directly,[20,29] while challenge with vaccine-related poliovirus provides an indirect assessment of mucosal immunity in terms of decreasing replication and virus excretion. However, no standardized methods have been developed to measure mucosal secretory IgA.

EVIDENCE THAT NEUTRALIZING ANTIBODIES PROTECT AGAINST POLIOMYELITIS

Although direct evidence that neutralizing antibodies induced by natural infection, OPV, and/or IPV are protective against paralytic disease is limited, several lines of *indirect* evidence support this hypothesis:

1. Low titers of neutralizing antibodies (1:2) appear to prevent poliovirus viremia following vaccination in humans.[30] Viremia appears to be necessary to permit central nervous system invasion and paralytic disease.[31]
2. Studies in household contacts of poliomyelitis cases suggest that a neutralizing antibody titer of 1:8 may be protective.[32]
3. Challenge studies in humans are not feasible on ethical grounds. However, experimental challenge with wild poliovirus in monkeys suggest that moderate levels of neutralizing antibody (i.e., 1:20) may be necessary to protect against paralytic disease,[33] although an exact threshold level of antibody for protection may be higher than the antibody level required in humans.[32] However, antibody titers depend on assays used;[27] therefore, titers reported in previous studies may not be exactly comparable with titers reported in the more recent studies.
4. Passive immunization with immune globulin preexposure reduced the risk of paralytic disease in the 1950s prevaccine era[34,35] despite low titers of poliovirus-neutralizing antibody.[36,37] However, administration of immune globulin treat-

ment in preparalytic stage of poliomyelitis is not effective in aborting or modifying the course of paralytic disease.[38] These findings strongly stimulated poliovirus vaccine development in the early 1950s, because they supported the hypothesis that neutralizing antibody can protect against paralytic poliomyelitis if induced prior to poliovirus infection.

5. Persons with agammaglobulinemia or hypogammaglobulinemia are clearly at highest risk for poliomyelitis due to wild- or vaccine-related poliovirus.[1,39]
6. Fully vaccinated persons appear to be at very low risk for vaccine-associated paralytic poliomyelitis. Only one VAPP case with a history of three doses of OPV in childhood has been described in the literature. This adult case had contact with his recently vaccinated son.[40]
7. Newborns rarely contract poliomyelitis during the first three to six months of life, presumably due to maternally derived antibody.[41]
8. Evidence from investigations among isolated populations suggest that previous exposure to poliovirus is protective against paralytic disease from subsequent poliovirus exposure (of the same serotype); this protective immunity could be quantified by assessing neutralizing antibody.[42,43] In addition, a close correlation was observed between vaccine efficacy and seroprevalence from several outbreak investigations.[41,44,45] Furthermore, ecological studies from many countries including the United States suggest that the incidence of poliomyelitis decreased dramatically following introduction of poliovirus vaccines, and that the seroprevalence levels correspond in general to the degree of control (and population immunity levels).[1,46,47]

RECENT POLIOVIRUS VACCINE TRIALS WITH CDC PARTICIPATION

The Centers for Disease Control and Prevention (CDC) are currently collaborating with universities, ministries of health, and the WHO to complete a series of randomized poliovirus vaccine trials that will directly assist poliovirus vaccination policy development in the United States and potentially expedite achievement of the goal of global eradication of poliomyelitis (TABLE 1). These studies have generally determined both humoral and mucosal responses to the vaccines being studied.

The first study aimed to improve the immunogenicity of OPV in developing coun-

TABLE 1. Major Poliovirus Vaccine Trials in Progress or Recently Completed

Study	Country	Major Outcome Measures[a]
OPV formulation	Brazil, Gambia	Seroconversion
Combined OPV-IPV	Gambia, Oman, Thailand	Seroconversion, mP1 challenge
IPV, mP3, US-OPV	Oman	Seroconversion, titer rises, mP3 challenge, IgM EIA
IPV at 9 mo	Ivory Coast	Seroconversion, titer rises
Sequential schedules	United States	Seroconversion, TOPV challenge, SIgA

[a] Seroconversion assessed by neutralizing antibody; mP1 (monovalent type 1); mP3 (monovalent type 3), EIA (enzyme immuno-assay); TOPV (trivalent OPV).

tries (TABLE 1). A formulation study carried out in Brazil and The Gambia evaluated the optimal relative as well as absolute content of each poliovirus serotype of OPV.[49] The study expanded upon an earlier trial in Brazil that suggested that the seroconversion rate to poliovirus type 3 could be improved by increasing the poliovirus type 3 content in the vaccine from 300,000 median tissue culture infective dose ($TCID_{50}$) to 600,000 $TCID_{50}$.[50]

The second study has attempted to better utilize the existing poliovirus vaccines (i.e., OPV and IPV). Both vaccines were administered simultaneously according to the OPV vaccination schedule advocated by the Expanded Program on Immunization. Oral poliovirus vaccine was given at birth, followed by doses of both vaccines at 6, 10, and 14 weeks of age. These vaccines were evaluated in a multicenter study conducted in three countries, The Gambia, Oman, and Thailand. The field and laboratory work of these studies has been completed, and the collected data are currently being analyzed.

Rather than changing the formulation of OPV or adding multiple doses of IPV to the current vaccination schedule, the following two studies, one in Abijan, Ivory Coast, and the other in Oman assessed the potential usefulness of adding a dose of IPV at 9 months of age–the age when the routine measles vaccination is offered to infants in developing countries–to the usual schedule of four doses of OPV in infancy. The rationale for these studies is to improve the seroconversion rates to poliovirus in infants who have received a primary series with OPV. The trial in Abijan has reported encouraging results that have recently been published;[51] the study in Oman will be completed in the fall of 1993.

Several studies are also ongoing or nearing completion in the United States, the most important of which is a trial conducted by the Johns Hopkins University (with funding from Connaught Laboratories, Inc. and CDC) that compares different sequential schedules of IPV followed by OPV. Sequential schedules of IPV followed by OPV should decrease the risk of vaccine-associated paralytic disease in the United States. Three sequential schedules are compared to groups receiving IPV only or OPV only (for a total of five study groups) (TABLE 2). The first and second study groups received two doses of IPV followed by one or two doses of OPV, while the last study group received one dose of IPV, followed by doses of IPV and OPV administered simultaneously, and two more doses of OPV. All study groups were challenged at the end of the study with OPV to assess mucosal immunity. Preliminary findings of the study were recently reported[52] and, together with the findings from earlier published reports,[53–55] should provide a basis for determining which sequential schedule may be adopted for use in the United States.

TABLE 2. Sequential Study of IPV and OPV in the United States, Johns Hopkins University (Connaught and CDC)

Group	2 mo	4 mo	6 mo	15 mo	18 mo
1	IPV	IPV		OPV	OPV challenge
2	IPV	IPV	OPV	OPV	OPV challenge
3	IPV	IPV		IPV	OPV challenge
4	OPV	OPV		OPV	OPV challenge
5	IPV	IPV/OPV	OPV	OPV	OPV challenge

USE OF COMBINATION DTP-IPV VACCINE

A combination of IPV and DTP vaccine is under clinical evaluation in the United States. This vaccine consists of two previously licensed products: DTP, licensed by Connaught Laboratories, Inc. and IPV, licensed by Pasteur Merieux, packaged in an innovative bypass dual-chambered syringe. Inactivated poliovirus vaccine is stored in a chamber separated from DTP so that mixing of these vaccines occurs only briefly prior to injection and deposition into the muscle to minimize the detrimental effect of thimerosal, the preservative in DTP vaccine, on IPV. Thimerosal was shown to be detrimental to IPV as early as in the 1950s.[56]

Recently, experiments performed by Sawyer *et al.*[57,58] confirmed the instability of IPV in the presence of thimerosal at 4°C for all three types of poliovirus measured by ELISA using monoclonal antibodies. The instability was greatest for type 1, and was confirmed by studies in mice. In addition, a change in the antigenicity of one type 2 epitope, which is sensitive to thimerosal, occurred within five minutes of mixing in the dual-chambered syringe. Using an ELISA with monoclonal antibodies, potency studies of IPV held at 37°C in the presence or absence of thimerosal suggested that all three polioviruses were sensitive to elevated temperatures and that this effect was enhanced in the presence of thimerosal.[57,58]

These and earlier studies may have implications for the proposed DTP-IPV combination vaccine. Preliminary findings of a trial with the dual-chambered syringe combination vaccine have been presented previously,[59] and suggest comparable seroprevalence rates following the administration of the combination vaccine at 2 and 4 months of age compared with the separate but simultaneous administration of IPV and DTP. However, geometric mean titers (GMT) were significantly lower after two doses for the group receiving the combination DTP-IPV vaccine. Additional data provided by Dr. Fritzell at the workshop suggested that, after a booster dose of OPV or IPV at 15–18 months of age, the GMT differences were no longer apparent.

CONCLUSIONS AND PROSPECTS FOR THE FUTURE

In conclusion, the primary surrogate serologic test currently available that correlates well with individual protection against paralytic disease is the neutralization assay. Assessment of mucosal immunity provides additional information that may predict the performance of a vaccine or a vaccination schedule in limiting transmission within a population. Improved poliovirus vaccines or sequential schedules using existing poliovirus vaccines should, ideally, induce comparable humoral and mucosal immunity as does the currently recommended vaccination schedule relying on OPV alone.

Efforts to combine IPV with other vaccines should be expanded, and application of sequential vaccination schedules of IPV followed by OPV to be used in the United States appear feasible and desirable.

While some groups are attempting to improve poliovirus vaccines, one option that could be implemented at this time is to improve utilization of the two existing vaccines. After extensive review of the poliovirus vaccination policy options in 1988 for the United States, the Institute of Medicine[6] recommended that a sequential schedule of IPV followed by OPV should be considered when combination vaccines containing IPV and other antigens (e.g., DTP) were available. This schedule could re-

duce the risk of vaccine-associated disease (presumably because immunity induced by IPV would prevent disease due to OPV)[48] and would not increase the number of injections given to infants, leading to greater acceptability of IPV by parents and providers. Although it is difficult to precisely estimate the proportion of vaccine-associated disease that could be prevented with a sequential schedule, a Delphi panel convened recently at the CDC suggested that approximately 50% of VAPP cases could be prevented. However, few or no cases could be prevented in contacts of OPV vaccinated infants or in immunodeficient persons. The lack of availability of such a combination vaccine has to date inhibited implementation of a sequential schedule in the United States.

What are some of the prospects for the future? In France (and other countries), the licensed combination vaccine of IPV/DTP contains 2-phenoxyethanol as a preservative in place of thimerosal; this preservative does not appear to affect IPV potency and thus eliminates the need for the dual-chambered syringe. Ideally, the safety and immunogenicity of IPV containing this preservative should be examined in the United States. Another potential improvement would be the addition of acellular pertussis vaccine instead of the whole-cell pertussis vaccine currently available in some countries or suggested for use in the combination of IPV and DTP for the United States; however, use of such a vaccine must await licensure of acellular pertussis vaccines for infants. In addition, several approaches to combination vaccines are currently being evaluated; one promising approach may be the reconstitution of *Haemophilus influenzae* type b (Hib) conjugate vaccine with a combination IPV-DTP vaccine.[60] Other vaccines that combine DTP and/or Hib and/or hepatitis B with IPV appear feasible but require further investigation. The recent licensure of a product combining DTP and Hib conjugate vaccine perhaps lessens the need for an IPV/DTP combination vaccine. Nevertheless, until global eradication of poliomyelitis is accomplished,[14] poliovirus vaccination options must continue to be critically evaluated in the United States.

SUMMARY

Inactivated and trivalent oral poliovirus vaccines contain either formalin-inactivated or live, attenuated poliovirus, respectively, of the three serotypes. Interference among the three attenuated poliovirus serotypes was minimized with a "balanced-formulation" vaccine, and serologic responses after IPV were optimized by adjusting the antigenic content of each inactivated poliovirus serotype. Seroconversion is dependent on both the relative content as well as the absolute quantity of virus in the vaccine. The "gold standard" method to assess humoral antibody responses following vaccination is the neutralization assay. Any detectable titer of neutralizing antibody against poliovirus is considered protective against clinical paralytic diseases. Recently, standard procedures were adopted for conducting neutralization assays. Efforts are being undertaken now to develop a combined diphtheria and tetanus toxoids and pertussis vaccine and IPV vaccine in the United States using a dual-chambered syringe that mixes the content of both vaccines at the time of injection; this approach is necessary to overcome the potential detrimental effect of thimerosal on IPV (the preservative in DTP). Other vaccines that combine DTP and/or *Haemophilus influenzae* type b and/or hepatitis B with IPV appear feasible but require further investigation. New combination vaccines should induce similar or superior levels of neutralizing antibody in serum for individual protection against paralytic disease and mucosal immunity that effectively

decreases viral replication in the intestine and pharynx for population protection against transmission of poliovirus.

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Article

Long-Term Immunogenicity of Inactivated and Oral Polio Vaccines: An Italian Retrospective Cohort Study

Angela Maria Vittoria Larocca [1], Francesco Paolo Bianchi [2], Anna Bozzi [1], Silvio Tafuri [2,*], Pasquale Stefanizzi [2] and Cinzia Annatea Germinario [2]

[1] Hygiene Department, Bari Policlinico General Hospital, 70124 Bari, Italy
[2] Interdisciplinary Department of Medicine, Aldo Moro University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy
* Correspondence: silvio.tafuri@uniba.it; Tel.: +39-80-5478473; Fax: +39-80-5478472

Abstract: Oral and inactivated poliovirus (PV) vaccines have contributed toward the global eradication of wild PV2 and PV3, as well as the elimination of PV1 in most countries. While the long-term (>5–10 years) persistence of protective antibodies in ≥80% of the population vaccinated with ≥3–4 doses of oral poliovirus vaccine (OPV) has been demonstrated, the duration of immunity in people vaccinated with the inactivated poliovirus vaccine (IPV) is still unclear. This study evaluated the seroprevalence of anti-PV neutralizing antibodies and the long-term immunogenicity conferred by OPV and IPV in a sample of medical students from the University of Bari (April 2014–October 2020). The levels of neutralizing PV1, PV2, and PV3 antibodies in blood samples taken during the assessments were evaluated. Neutralizing antibodies against PV1, PV2, and PV3 were present in >90% of the study participants, with rates of >99%, >98%, and ~92–99%, respectively. IPV resulted in a higher immunological response than OPV against PV3. Protective antibodies against all three viruses persisted for at least 18 years after administration of the last vaccine dose. Until PV1 is completely eradicated, maximum vigilance from public health institutions must be maintained.

Keywords: eradication; healthcare workers; poliomyelitis

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1. Introduction

The eradication of polioviruses remains a major global public health goal. The introduction of the inactivated poliovirus vaccine (IPV) and trivalent oral poliovirus vaccine (OPV) in official vaccination schedules worldwide has led to the eradication of wild PV2 (in 2015) and wild PV3 (in 2019); moreover, since 2017, wild PV1 cases have only been reported in Afghanistan and Pakistan [1–4]. Nonetheless, the WHO's strategy to eradicate polio might slow down in situations of conflict (i.e., in which socioenvironmental and hygienic conditions are disrupted) [5].

In 1964, the Italian Ministry of Health developed a mass vaccination campaign in which the Sabin vaccine was offered free and actively to all children between the ages of 6 months and 14 years [6]. Between 1964 and 2000, vaccinations with OPVs resulted in a small number of cases of vaccine-associated paralytic poliomyelitis. Due to ethical concerns and the favorable epidemiological context, in 2000, a sequential schedule (IPV–IPV–OPV–OPV) was introduced. In 2003, the use of a live attenuated vaccine was suspended and IPV was introduced exclusively for polio vaccinations during childhood [6]. Since 2002, the vaccination schedule in Italy has consisted of the first three doses of IPV to infants at 3, 5, and 11 months of age using a hexavalent formulation (IPV–hepatitis B–Haemophilus influenzae type b–tetanus–diphtheria–acellular pertussis), with a fourth dose administered as a tetravalent formula (tetanus–diphtheria–acellular pertussis–IPV) at 5–6 years of age. In 2017, a fifth dose administered during adolescence was recommended. Moreover, in 2017, the Italian government made vaccinations against polio mandatory for infants

and children [7]. With the success of vaccination campaigns carried out since 1964, Italy (together with the entire European region) was certified as polio-free in 2002 by the Regional Commission for the Certification of Poliomyelitis Eradication; in fact, no case of polio had been recorded since 1983 [8].

Serologic studies have shown that seroconversion rates—following three doses of either IPV or OPV—are nearly 100% for all three viruses [9]. However, while the World Health Organization (WHO) reported strong scientific evidence for the long-term (>5–10 years) persistence of protective antibodies in ≥80% of the population vaccinated with ≥3–4 doses of OPV [10], the duration of immunity conferred by IPV is unclear [11].

The aim of this study was to evaluate the seroprevalence of anti-poliovirus neutralizing antibodies in a sample of medical students and residents from the medical school of the University of Bari who had been fully vaccinated with the IPV. The long-term immunity of participants who received OPV was also determined and compared with that of the IPV group. The study was carried out in Apulia (southern Italy, with ~4,000,000 inhabitants).

2. Materials and Methods

This was a retrospective cohort study.

The study population was composed of students and residents who attended the Hygiene Department from April 2014 to October 2020. Inclusion criteria were: vaccinated with four doses of IPV or all OPV, according to the Italian schedule that was in effect until 2017 (3 doses during the first year of life and the fourth dose at age 5–6 years). Individuals without available vaccination histories, who were never vaccinated, who lived for more than a year in a highly endemic country, vaccinated with both the IPV and OPV, were vaccinated with another formula, or who had been vaccinated with less or more than four doses of IPV or OPV at baseline were excluded from the study. None of the study candidates reported a history of poliomyelitis.

From April 2014 to October 2020, 6105 medical students and residents were tested; a blood sample was taken during the first access to the clinic. The immunization status, downloaded from Apulia's Regional Immunization Database (GIAVA), was available for 4661/6105 (76.3%). From this group, 123/4661 (2.6%) had received four doses of IPV and were included in the study; the other subjects were vaccinated as follows: 1408 (30.2%) vaccinated with four doses of trivalent OPV, 945 (20.3%) received a mixed schedule (IPV–OPV), 2036 (43.7%) received less or more than four doses of trivalent OPV and 149 (3.2%) with less or more than four doses of IPV. Those included participants were matched with a control group consisting of individuals who attended the same biological screening program and had been vaccinated with four doses of trivalent OPV. An allocation ratio of 1:3 was used to improve the statistical analysis power. The two groups were matched for age and sex using STATA MP16 software, resulting in a final sample of 492 individuals: 123 who had been vaccinated with four doses of IPV and 369 with four doses of trivalent OPV.

2.1. Laboratory Analysis

The neutralization test was conducted in microtiter plates according to the guidelines of the WHO/Expanded Program on Immunization (EPI). Titers ≥ 1/8 were considered positive, as recommended by the WHO/EPI [12]. Two-fold dilutions of inactivated sera (from 1/8 to 1/1024) were incubated in duplicate with suspensions of each of the three reference Sabin strains (PV1/Mahoney strain, PV2/MEF-1 strain, and PV3/Saukett strain) corresponding to a 100 TCID50/0.025-mL challenge. After a 3-h incubation at 36 °C, 5% CO_2, a human heteroploid Hep-2 cell suspension (1–2 × 104 cells/0.1 mL; MEM Earle's salts 10% FBS; 37 °C, 5% CO_2) was added to each well containing the virus–serum mixtures. A titration of each viral strain and cell controls were included. The plates were incubated at 36 °C for 5 days and then examined for the appearance of cytopathic effects (CPE) using an inverted microscope. The neutralizing antibody titer (expressed as reciprocal) was determined using the Karber formula, based on the highest dilution of serum that protected

50% of the cultures against a 100 TCID50 viral challenge and inhibited CPE. Titers $\geq 1/8$ were considered positive, as recommended by the WHO/EPI.

2.2. Statistical Analysis

The data were analyzed using STATA MP16 software. Continuous variables were reported as the mean ± standard deviation and range, and categorical variables as proportions, with 95% confidence intervals (95%CIs) when appropriate. Protective antibody titers were classified as low (1/8–1/32) or high (1/64–>1/256) and compared by group (IPV vs. OPV) and age class. Skewness and kurtosis tests were used to evaluate the normality of the continuous variables, but none of them were normally distributed or normalizable. Wilcoxon's rank sum test was used to compare continuous variables between groups and chi-squared or Fisher's exact tests to compare proportions with respect to group and age class. To assess the seroprotection determinants at the time of enrollment (seroconversion after the vaccine basal cycle, which is three doses during the first year of life and the fourth dose at age 5–6 years), multivariate logistic regression models were created for each type of poliovirus, in which the seroprotection determinants were the outcome and group (IPV vs. OPV), sex (male vs. female), age at enrollment (years), and immune-related chronic disease (yes/no). Adjusted odds ratios (aORs) were calculated together with their 95%CIs. Protective antibody survival (PAS), defined as the time elapsed from the last dose of the routine vaccine to the evaluation of the antibody titer (years), was determined and then analyzed using Kaplan–Meier curves. The log-rank test was used to evaluate differences between groups. The loss of seroprotection per 1000 person-years and the 95%CIs were calculated. The incidence rate ratio (IRR), in which the value for the OPV group was the denominator and that for the IPV group the numerator, was also calculated together with the 95%CIs. For all tests, a two-sided p-value < 0.05 was considered statistically significant.

The study was carried out in accordance with the Declaration of Helsinki. All healthcare workers (HCWs) who were screened provided written consent regarding the use and scientific publication of data collected for clinical purposes.

3. Results

The study population included 492 subjects, of which, 472 were students (95.9%; mean age: 21.1 ± 2.6 years) and 20 were residents (4.1%; mean age: 29.1 ± 1.9 years). A total of 344 (69.9%) subjects were female; there was no significant difference between the OPV group (n = 258/369; 69.9%) and the IPV group (86/123; 69.9%; p = 1.000). The average age at study enrollment was 21.4 ± 3.1 years (range = 18.0–33.0), with no difference between the groups (OPV: 21.5 ± 3.0; range = 18–33 vs. IPV: 21.2 ± 3.2; range = 18–33; p = 0.126). The average PAS time was 19.0 ± 3.1 years (range = 9–31), specifically 19.1 ± 3.0 (range = 12–30) for the OPV group and 18.6 ± 3.5 (range = 9–31) for the IPV group.

3.1. PV1

The prevalence in the study population of the absence of PV1 neutralizing antibodies was 0.20% (95%CI: 0.01–1.12; n = 1/492); the difference between the OPV and IPV groups was not significant (p = 1.000; Table 1). A high titer was measured in 91.5% (n = 449/491) of the study participants, with no significant difference between the two groups (OPV vs. IPV: $p > 0.05$ for each PV; Table 1, Figure 1).

Table 1. Proportion of study participants without poliovirus (PV) neutralizing antibodies and the distribution of the titer (low–high) between groups with respect to vaccination and PV type.

Variable	PV1				PV2				PV3			
	OPV	IPV	Total	*p*-Value	OPV	IPV	Total	*p*-Value	OPV	IPV	Total	*p*-Value
Susceptible; n (%; 95%CI)	1 (0.27; 0.00–1.50)	0 (0.00; 0.00–2.95)	1 (0.20; 0.01–1.12)	1.000	4 (1.59; 0.43–4.01)	1 (1.08; 0.03–5.85)	5 (1.45; 0.47–3.35)	1.000	29 (7.85; 5.33–11.09)	3 (2.44; 0.51–6.96)	32 (6.50; 4.49–9.06)	0.022
Protective titer; n (%)												
low	31/368 (8.4)	11/123 (8.9)	42/491 (8.6)	0.859	72/248 (29.0)	20/92 (21.7)	92/340 (27.1)	0.179	144/340 (42.4)	57/120 (47.5)	201/460 (43.7)	0.328
high	337/368 (91.6)	112/123 (91.1)	449/491 (91.4)		176/248 (71.0)	72/92 (78.3)	248/340 (72.9)		196/340 (57.6)	63/120 (52.5)	259/460 (56.3)	

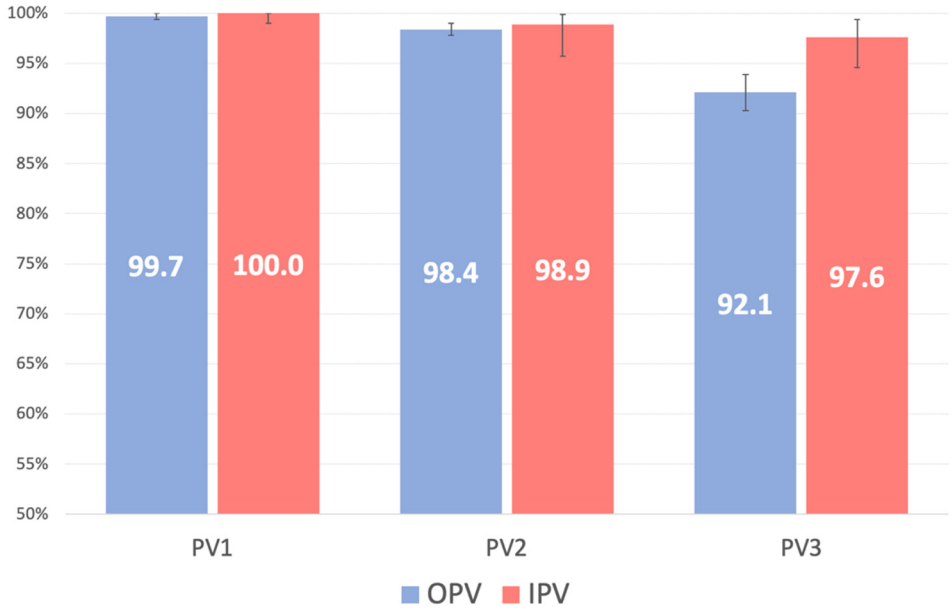

Figure 1. Prevalence (%) among the study participants of neutralizing antibodies, per poliovirus (PV) type.

In the OPV group, the titer of neutralizing antibodies decreased significantly with increasing age (p = 0.027), whereas in the IPV group, the titer of neutralizing antibodies was slightly lower but remained relatively constant among age classes (p = 0.782; Figure 2).

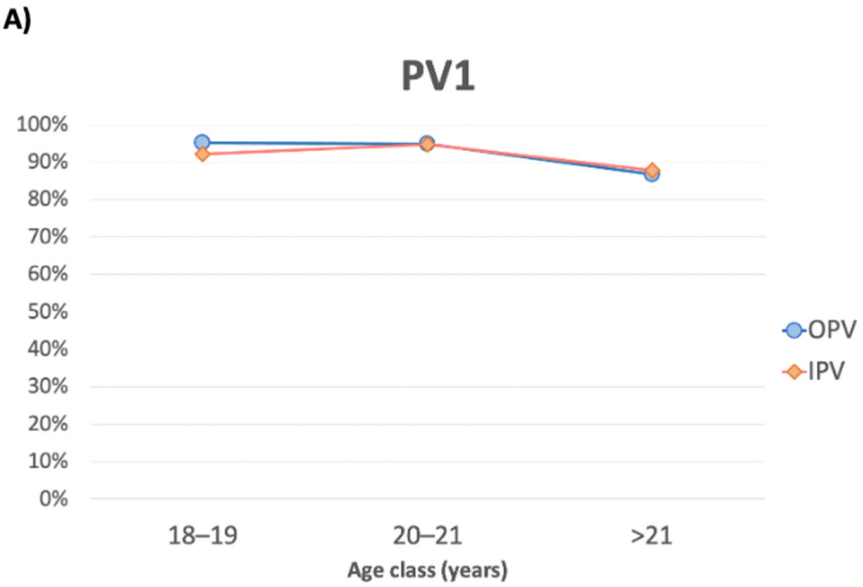

Figure 2. *Cont.*

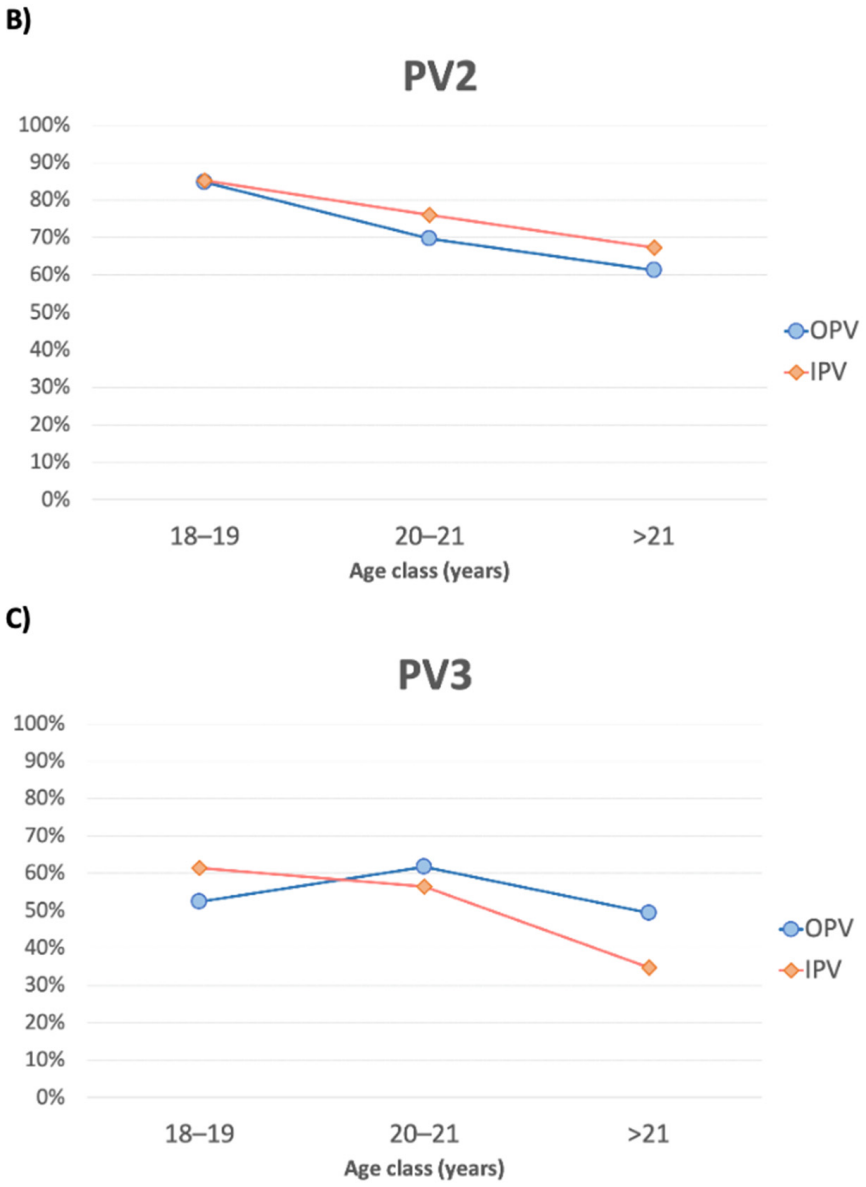

Figure 2. Prevalence (%) among the study participants of high protective titer of neutralizing antibodies against PV1 (**A**), PV2 (**B**), and PV3 (**C**), per age class.

In the multivariate logistic regression, there was no association between the seroprevalence of anti-PV1 antibodies and any of the analyzed determinants ($p > 0.05$; not shown).

The incidence of seronegativity in the whole sample per 1000 person-years was 0.10 (95%CI: 0.01–0.74). The incidence of seronegativity in the OPV group was 0.14 (95%CI: 0.01–0.98), but due to the small number of events in the IPV group, neither seronegativity nor the IRR could be calculated. There was no significant vaccine-based difference in the PAS (log-rank *p*-value = 0.594; Figure 3).

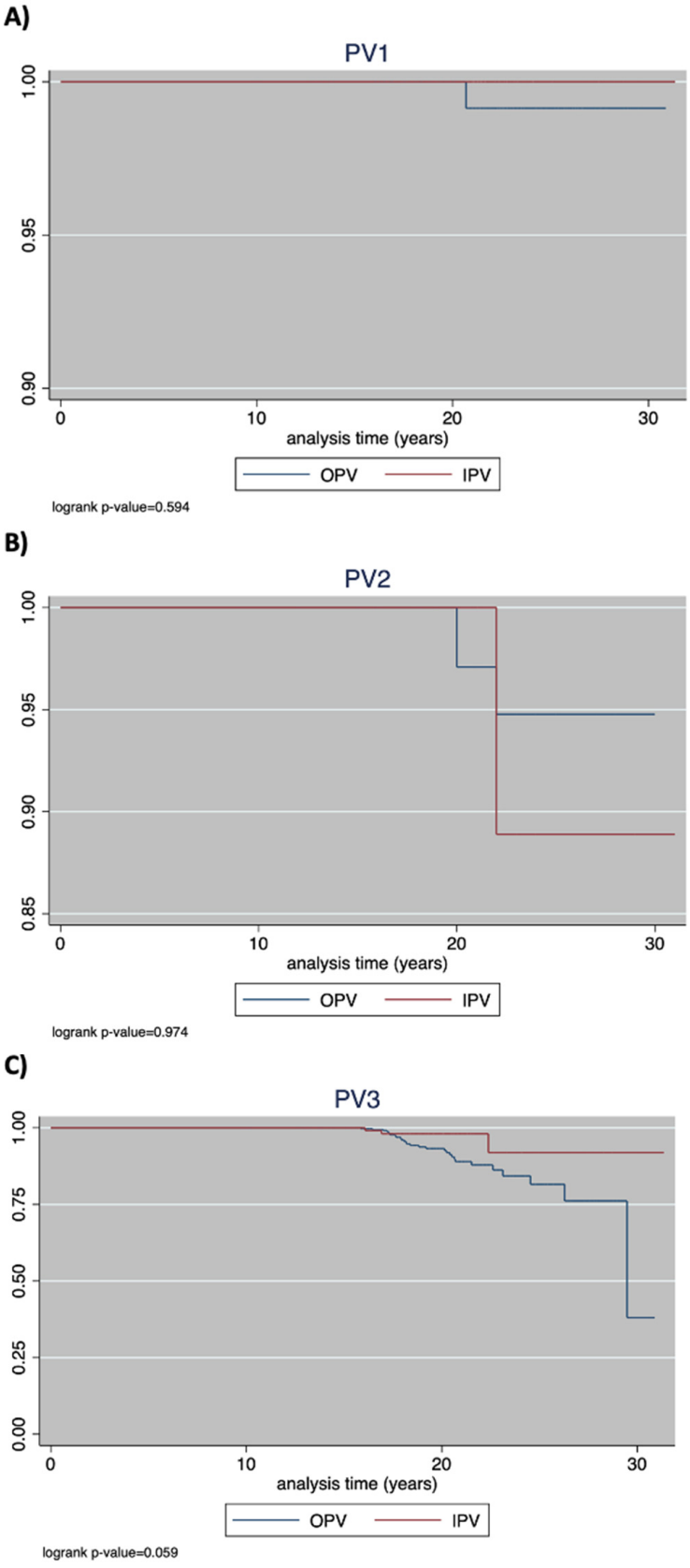

Figure 3. Kaplan–Meier estimates of protective antibody survival, per group (IPV vs. OPV) for (**A**) PV1, (**B**) PV2, and (**C**) PV3.

3.2. PV2

The prevalence in the study population of the absence of PV2 neutralizing antibodies was 1.45% (95%CI: 0.47–3.35; n = 5/345), with no significant difference between the OPV and IPV groups (p = 1.000; Table 1). A high titer was detected in 72.9% (n = 248/340) of the study population, with no significant difference between the groups ($p > 0.05$; Table 1). In the OPV group, the titer of neutralizing antibodies decreased significantly with age (p = 0.002); in the IPV group, the titer was slightly higher but also decreased with age, albeit not significantly (p = 0.186; Figure 3).

In the multivariate logistic regression, there was no association between the seroprevalence of anti-PV2 antibodies and the analyzed determinants ($p > 0.05$; not shown).

The incidence of seronegativity per 1000 person-years was 0.79 (95%CI: 0.32–1.85) and was lower in the IPV group (0.59; 95%CI: 0.01–4.18) than in the OPV group (0.83; 95%CI: 0.31–2.22), with an IRR of 0.71 (95%CI: 0.01–7.15; p = 0.830). The PAS did not differ as a function of the group (log-rank p-value = 0.974; Figure 3).

3.3. PV3

The prevalence in the study population of the absence of PV3 neutralizing antibodies was 6.50% (95%CI: 4.49–9.06; n = 32/492), with a statistically significant difference between the OPV and IPV groups (92.1% vs. 97.6%; p = 0.035; Table 1). A high titer was detected in 56.3% (n = 259/460) of the study population, without a difference between groups ($p > 0.05$; Table 1). The titer of neutralizing antibodies decreased significantly with age in the IPV group (p = 0.027) but, although similar, largely remained constant in the OPV group (p = 0.185; Figure 2).

In the multivariate logistic regression, an association at the limit of statistical significance was determined between the seroprevalence of anti-PV3 antibodies and the group (aOR = 3.34; 95%CI: 1.00–11.20; p = 0.050). There were no significant associations between any of the other analyzed determinants ($p > 0.05$; Table 2).

Table 2. Analysis of the determinants of neutralizing anti-PV3 antibodies in a multivariate logistic regression model.

Determinant	aOR	95%CI	*p*-Value
Group (IPV vs. OPV)	3.34	1.00–11.20	0.050
Sex (male vs. female)	0.97	0.44–2.12	0.934
Age (years)	1.00	0.89–1.13	0.979
Immune-related chronic disease (YES/NO)	1.83	0.80–4.18	0.152

aOR: adjusted odds ratio; Hosmer–Lemeshow X^2 = 11.8; p = 0.162.

The incidence of seronegativity per 1000 person-years was 3.34 (95%CI: 2.36–4.72) and was lower in the IPV group (0.13; 95%CI: 0.41–3.97) than in the OPV group (4.00; 95%CI: 2.78–5.76), with an IRR of 0.32 (95%CI: 0.06–1.03; p = 0.037). The PAS did not differ as a function of the group (log-rank p-value = 0.059; Figure 3).

4. Discussion

Our study showed that neutralizing antibodies against all three types of poliovirus were present in >90% of the study participants, regardless of their vaccination with IPV or OPV, with rates of >99% for PV1, >98% for PV2, and ~92–99% for PV3. A higher immunological response to PV3 was obtained with IPV than with OPV (98% vs. 92%), as was also determined in the logistic and semiparametric Cox regression models. Tafuri et al., in a 2008 Italian study [13], determined seropositivity rates of >99% for all three viruses in a group of Apulian children (vaccination status unknown) and adolescents (the data are similar to data reported in studies set up in other countries) [14–16].

Over time, both vaccines seem to trigger an immune response that leads to high levels of neutralizing antibodies for PV1 (87–94%), lower levels for PV2 (62–85%), and even lower

levels for PV3 (46–60%). The levels of neutralizing antibodies decreased with increasing age but without substantial differences between the OPV and IPV groups. This decline is a proxy for the real risk factor, which is the time elapsed since the last vaccine dose. Similar to other vaccines [17–20], the role of age (or time elapsed since the last dose) in the response to polio vaccines has been demonstrated in several studies [13,21–23].

The PAS analysis showed that protective antibodies against all three viruses persist for at least 18 years after the administration of the last dose of OPV or IPV; a longer duration of immunity against PV3 was provided by IPV than by OPV. Although the long duration of OPV immunization is well established [9], to our knowledge, ours is the first study to quantitatively evaluate a large study population vaccinated with four doses of the oral vaccine during childhood and to compare the two vaccine formulations that have long been in use. Our findings should be considered in light of the absence of natural boosters in Italy, where, in the last 30 years, no case of polio has been reported (or use of supplementary immunization activities (SIAs)). In addition, in the Apulia region, analyses of blood and stool samples from emigrants arriving mostly from the Middle East and Africa have likewise been negative for poliovirus [24,25].

In summary, the time between the last vaccination and the antibody titer evaluation is a determinant of the levels of persisting neutralizing antibodies. While the antibody titer decreases over time, immunity against PV1 and PV2 can possibly be considered life-long; on the other hand, a challenge dose of IPV or trivalent OPV may strengthen the long-term persistence of protective immunity, especially against PV3. There were no significant differences between IPV and OPV, although IPV may provide a higher immunological response against PV3.

The strengths of our study are in its evaluation of the long-term immunogenicity of IPV vs. OPV and the comparisons of antibody titers over time. Moreover, to our knowledge, this is the first study that compared the two formulas and one of the most important experiences in the literature regarding subjects vaccinated with IPV. Our data showed the overall higher effectiveness of the IPV formula considering the duration of immunity and prevalence of neutralizing antibodies; nevertheless, the OPV formula remains crucial in the prevention of the transmission and, therefore, it is a valid option in countries where the virus circulations are still highly probable. Nonetheless, a major limitation involved the age distribution of the study participants, which was mostly <25 years old; indeed, only 53 subjects were >25 years old (but this was expected, as our population consisted of students in medical school). This may have distorted the results since young adults have enhanced durable immune memories. Furthermore, the investigation of rare events, such as the absence of neutralizing antibodies, especially among people vaccinated with IPVs, requires studies with larger numbers of participants. Moreover, the neutralization antibody titer measurement does not value the vulnerabilities of the subjects to mucosal intestinal infections with PV and subsequent transmissions; indeed, adequate humoral immunogenicity assessments are relevant to protect against paralysis, but not against intestinal replication and transmission of poliovirus. Future studies should expand the sample size and the observation time to evaluate critical issues that may place an individual or population at risk in the event of wild virus reintroduction.

In conclusion, the basal vaccination scheme for IPV induces long-lasting protection against paralytic poliomyelitis. Wild PV2 and PV3 have been eradicated, and protection against paralysis from polio against PV1 remains close to 100% even after many years. Considering the efficacy of four doses, a fifth booster IPV dose, as recommended by the Italian immunization plan, will likely be sufficient to ensure life-long protection. As pointed out by Lopalco PL in a 2016 study [26], the global use of OPV has led to the eradication of wild PV2 and PV3, but the burden caused by vaccine-derived cases of polio is becoming increasingly problematic. These data support the use of IPVs to maintain high levels of seropositivity, particularly to PV3, accompanied by high-level clinical and environmental surveillance. Indeed, in Italy, there is active surveillance for cases of acute

flaccid paralysis [27] and a high level of IPV coverage is part of the most recent Italian immunization plan [28].

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INVITED COMMENTARY

Understanding and Improving Vaccine Effectiveness Estimates in the Age of Widespread Background Immunity: A Step Toward Improved Science Communication

Edward Nirenberg[1] and Eli N. Perencevich[2,3]

[1]Independent Scholar; [2]Center for Access and Delivery Research and Evaluation (CADRE), Iowa City VA Health Care System, Iowa City, Iowa, USA; and [3]University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

Medical decision making and scientific communication around coronavirus disease 2019 (COVID-19) vaccines and booster doses requires proper understanding of how vaccine effectiveness estimates are determined and the potential biases inherent in current estimates. The importance of background immunity from prior infection is reviewed along with ideas for improving the vaccine effectiveness estimates.

Keywords. Vaccine effectiveness; COVID-19; correlates of protection; vaccination policy.

The costs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in terms of lives, quality of life, economic hardship, and heartache are immeasurably vast. Despite this, the circumstances of the pandemic have produced extraordinary advances in vaccinology. The messenger RNA (mRNA) vaccines first reported exceptionally high vaccine effectiveness (VE) against symptomatic COVID-19 (~95%) and severe COVID-19 (~100%) [1,2]. However, current SARS-CoV-2 variants have contributed to declines in VE prompting the use of booster doses [3]. The protection seen in randomized controlled trials shows boosters exceed 2-dose efficacy against the Delta variant and greatly enhance protection against Omicron as well; boosters have furthermore proved particularly critical for high-risk patients [4–6]. Despite this, recovery of 95% effectiveness against symptomatic infection has proved elusive. The facile explanation is that the pace of evolution of SARS-CoV-2 is faster than our innovation, regulatory apparatuses, and immune system—yet this is incomplete and, indeed, may not even be the main reason for such findings.

Vaccine effectiveness (or efficacy in randomized controlled trials) is a commonly misunderstood metric [7], defined as the relative risk reduction in a given outcome among vaccinees compared with non-vaccinees, as written in Equation (1) [8]:

$$\begin{aligned} VE_{outcome} &= \frac{attackrateunvaccinated_{outcome} - attackratevaccinated_{outcome}}{attackrateunvaccinated_{outcome}} \times 100\% \\ &= 1 - RR_{vaccination} \times 100\% \end{aligned}$$

VE can decline from either an increase in the attack rate in the vaccinated or a decrease in the attack rate in the unvaccinated (ie, the unvaccinated acquire immunity via infection). Convalescent individuals have robust protection against symptomatic reinfection, typically for approximately 1 year (subject to variation based on SARS-CoV-2's evolution) [9]. When vaccination began, "unvaccinated" largely meant "lacking immunity." Thus, the vaccinated were much better protected. Now, "unvaccinated" typically means "convalescent." As more unvaccinated acquire immune protection, the vaccinated—even if they are also well protected—no longer have such a large relative advantage. VE, which measures that relative advantage falls, via the depletion of susceptibles bias [10].

It takes substantial immunity in the unvaccinated group for this bias to have significant effects on VE estimates, but, in the span of 10 weeks, the BA.1 subvariant of Omicron was estimated to have infected approximately half of the United States, and it is estimated that by 9 November 2022, 94% of the United States had been infected by SARS-CoV-2 at least once [11,12]. This depletion of susceptibles bias is readily apparent when examining COVID-19 VE in regions that had, to that point,

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Correspondence: E. Perencevich, Clinical and Health Services Research, University of Iowa Carver College of Medicine, CADRE, Iowa City VA Health Care System, 601 Highway 6 West, Iowa City, IA 52246, USA (eli-perencevich@uiowa.edu).

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very few infections, such as the BA.2 wave in Hong Kong, which reported continually high vaccine effectiveness against severe disease for the Bnt162b2 vaccine and Coronavac, and significant protection even from mild to moderate disease from BA.2 after 3 doses [13].

Protection from the less severe spectrum of outcomes diminishes more quickly than does protection from the worst outcomes; thus, many reported positive tests in hospitalized patients reflect incidental diagnoses, speciously lowering the apparent effectiveness of the vaccines. Correcting for this may require careful chart review by relevant specialists, ideally blinded to the vaccination status of the patients. Notably, when this is done, vaccine effectiveness substantially improves to levels similar to pre-Omicron epoch values [14]. However, extensive review of all inpatient charts at scale in the aforementioned manner is labor-intensive, so some states have used proxies such as dexamethasone use in conjunction with a positive test in their hospitalized patients to report vaccine effectiveness metrics against severe disease [15]. Indeed, protection against severe disease, per observational data, appears extremely robust and durable in immunocompetent individuals, and, although aided by a booster dose, plateaus at a still very high level of protection [16]. Note that Omicron, which had infection levels vastly exceeding those of prior waves, still had a substantially reduced risk of hospitalization, although some of this may reflect reduced intrinsic virulence [17,18].

These complicating epidemiological issues raise questions about how to best describe vaccine effectiveness. One fundamental challenge is that because vaccine effectiveness is only appropriately defined in terms of relative risk reduction, percentage changes can be misleading in the magnitude of their effect. For example, the decline from 95% VE to 90% VE may seem to be just 5% to the untrained observer, but this is a doubling of risk from a 20-fold reduction to a 10-fold reduction. Therefore, it is likely prudent to state explicitly the fold-reduction in risk, as this is more intuitive and reflective of real-world conditions. Conversely, a vaccine effectiveness of 50% reflects a halving of risk. We should bear in mind that ultimately when evaluating the effectiveness of a vaccine, the key decision to be made is whether or not the risks of taking the vaccine outweigh its benefits, rather than any specific VE number. A less fraught metric when considering additional vaccine doses beyond a primary series would be the relative VE (rVE) of the additional dose, explicitly describing additional benefit [5,19]. For example, Centers for Disease Control and Prevention (CDC) just reported an rVE of between 43% and 56% versus symptomatic disease for the updated bivalent booster compared to those who had only received ≥2 monovalent doses, which they admit may be "biased to the null" because of inability to control for infection-related immunity [20]. Even so, vaccines with this level of effectiveness can still have massive public health benefits when used at sufficiently large scale, as is seen with seasonal influenza vaccination, another respiratory virus wherein baseline immunity from prior year vaccination or infection is widespread and the vaccine is grappling for additional benefit over a very high rate of background immunity [19,21].

Still, a challenge with epidemiological evaluations of vaccine effectiveness in the presence of a protean, mutable pathogen with extensive presymptomatic spread is being proactive about vaccination efforts. This is particularly unfortunate because the impact of a booster campaign is likely to be greatest when a wave first begins or immediately preceding one [22]. To mitigate this, it is critical to establish outcome-specific correlates of protection and, in particular, absolute correlates [23].

More detailed immunogenicity data in the prelicensure phase of study would be helpful in this goal. For example, mucosal pathogens would be expected to require protection at the mucosal interface, yet no prelicensure evaluation of immune effectors at the respiratory tract, in particular resident memory T and B cells, was obtained. Insights into the durability of protection could be bolstered by evaluation of vaccine-elicited memory and effector cells within the plasma, lymph nodes, and bone marrow in a limited immunogenicity subset of willing participants [24–26].

Some correlates of protection against SARS-CoV-2 are at least partially defined. For example, it is robustly established that protection from symptomatic infection appears to be a function of neutralizing antibody titer, as passive antibody transfer is sufficient to protect animals, vaccine effectiveness against symptomatic disease is well predicted by these titers, and monoclonal antibody therapies given prophylactically show reduced incidence of infection [27]. This demonstrates serum neutralizing antibodies are correlates of protection from SARS-CoV-2 infection (further data with manipulation of neutralizing titer are needed to confirm that they are mechanistic correlates). Although no standardized absolute correlate is known, some prelicensure trials were able to establish a relationship between ID_{50} and vaccine effectiveness [28,29]. Additionally, generalizing a titer-protection relationship to novel variants may be challenging because of changes in tropism and kinetics, and because neutralizing antibodies in the upper respiratory tract correlate with protection more robustly than do serum antibodies [30]. Maintaining a large cohort of sera or nasal washings may allow for rapid insight on the propensity of that variant to cause a wave of infections. With widespread immunity, it is probable that the capacity to evade pre-existing protection from infection is a dominant factor in determining the evolutionary success of a variant [31].

Beyond infection, we urgently need correlates of protection against severe

disease. It has been speculated that this protection is the result of robust cellular immunity mediated by memory T cells and memory B cells, which are rapidly recalled to control the infection before it can progress to the lower respiratory tract, and that any reasonable combination of these factors is sufficient [32]. Nonetheless, quantitative metrics are lacking. Additionally, long coronavirus disease (COVID) is a much-feared outcome that, although likely reduced by vaccines, may occur despite vaccination [33]. A more precise definition of long COVID, along with clarification of disease endotypes are also desperately needed to enhance and define the role of vaccines and vaccine doses in prevention [33–35].

We still face a significant public health dilemma in that in an epoch where nearly everyone should have had at least 3 doses of COVID-19 vaccine, too many have received none [36,37]. The misperceptions of vaccine effectiveness driven by incomplete understanding of what vaccine effectiveness calculations currently estimate is directly harmful to the well-being of the unvaccinated and the general population. More precise communication and metrics of vaccine effectiveness that honestly reflect the value of vaccination is imperative. Our current vaccines are imperfect, and we look forward to seeing what improvements may occur with the next generation; however, it is undeniable that they are extremely effective against some of the most feared outcomes of COVID-19, and they are our most important tool for addressing its threat.

Notes

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