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Polio Eradication: Strengthening The Weakest Links

Eradicating polio depends as much on improving the economics of vaccine manufacture as on vaccination itself.

by Scott Barrett

ABSTRACT: Polio eradication, like all eradication efforts, is a gamble. If it fails, much of the money spent will have been wasted. If it succeeds, the world will reap a dividend. Success or failure and the magnitude of the dividend depend on a long chain of “weakest links.” In this paper I identify these links and explain how the chain can be strengthened. A crucial vulnerability is the current plan to halt vaccination using the live-attenuated oral polio vaccine in the post-eradication era. This weakest link can be strengthened by efforts that lower the cost to poor countries of vaccinating with the inactivated poliovirus vaccine. [Health Affairs 28, no. 4 (2009): 1079–1090; 10.1377/hlthaff.28.4.1079]

Since the global polio eradication initiative was launched in 1988, the number of polio cases worldwide has declined more than 99 percent. This is a remarkable achievement in terms of control, but it falls one percentage point short of eradication. Eradication requires, as a first step, that incidence equal zero—exactly.

Eradication of wild polioviruses was supposed to have been achieved by 2000, but the effort is still ongoing. In 2001 the polio case count reached an all-time low—483 cases.¹ In 2006 it reached an all-time high in this century—1,997 cases. In 2008 there were more than 1,600 cases. Over these same years, the number of polio-endemic countries fell from twenty to four, but the number of countries reporting polio cases has gone up as well as down; in 2008 polio was identified in eighteen countries. Polio may yet be eradicated, but to this point at least, and notwithstanding the extraordinary efforts of eradication workers and their partners, polio has stood its ground in its last strongholds.

Why eradicate? The reason is not only to prevent illness. It is also to avoid the need to vaccinate in the future—the savings from which is sometimes called the...
“Eradication succeeds or fails depending on the ‘weakest links’ within each component of the eradication effort.”

“eradication dividend.” The dividend from smallpox eradication was huge. For polio the dividend is likely to be smaller, but it will be positive provided the chances of success are large enough and the risks of stopping vaccination post-eradication are low enough.²

Eradication is a high-stakes gamble. Indeed, it is important not to be misled by the success of the smallpox eradication campaign, for that effort barely succeeded; also, the ongoing effort to eradicate Guinea worm has stumbled for even longer than that for polio, despite being a much easier target.³

Eradication succeeds or fails depending on the “weakest links” within each specific component of the eradication effort. For polio, success depends on eliminating the wild viruses from the remaining four endemic countries, while ensuring that transmission continues to be interrupted everywhere else. Every endemic country and every other country that fails to sustain a critical level of population immunity is a weakest link in this section of the chain. Should we succeed in this phase, however, we will then need to confront a new set of challenges and many additional weakest links. These post-eradication challenges must be considered today, because if countries expect that any of these weakest links will fail, support for the current phase will fall away. Plans for the future must be integrated with current planning.

This paper summarizes all of these weakest links and explains how the chain of polio eradication can be strengthened.

Polio Eradication Basics

Polio is highly contagious, transmitted principally via the fecal-oral route in poor countries and by the oral-oral route in rich countries. Paralytic symptoms show in less than 1 percent of infected people, making surveillance very difficult. Polio can circulate sight-unseen.

There are three polioviruses, known as types 1, 2, and 3. Any one of these viruses can cause polio, and vaccination against one type does not provide immunity to the other types. There are two types of vaccine. The oral polio vaccine stimulates immunity using a live but weakened form of the virus, whereas the inactivated polio vaccine stimulates immunity using a killed form of the virus. The two vaccines have different advantages and disadvantages, which is why both vaccines are used. Most importantly, the oral vaccine is inexpensive, easy to administer, and especially helpful in halting spread. Unfortunately, in rare cases, mutations of the weakened live virus can cause vaccine-derived viruses to circulate in the community. Polio eradication requires the eradication of both kinds of virus: the wild viruses and those associated with the oral vaccine.
Weakest Link No. 1: Interrupting Transmission Of Wild Viruses

Eradication of wild polioviruses is technically and biologically feasible. We know this because type 2 wild poliovirus has not been detected anywhere since 1999. We also know this because types 1 and 3 have not been detected in most countries for a very long time. Why, then, has polio not yet been eradicated? There are three main trouble spots.

- **Afghanistan and Pakistan.** People move back and forth across the porous border separating Afghanistan and Pakistan, both sides of which are variously un-governed or under the control of antigovernment, Taliban, Al Qaeda, or tribal groups. To initiate a vaccination campaign in this conflict zone requires a cease-fire, but getting one hinges on the consent of every warring party. Making matters worse, polio can persist in, and spread from, even small populations, and not all groups are friendly to the polio eradication effort. After being warned by religious leaders that polio vaccination “was an American plot to sterilize innocent Muslim children,” many parents refused to vaccinate their children. Doctors associated with the polio eradication effort have been killed—targets of roadside bombs and suicide attacks.

- **Northern Nigeria.** As in the Afghanistan-Pakistan border area, too few children in northern Nigeria receive even a single dose of vaccine (four doses of the live oral polio vaccine are recommended). The reasons, however, are somewhat different than in Afghanistan and Pakistan.

The most important single event in the history of the global polio eradication effort was the suspension of vaccination in northern Nigeria, especially Kano State, in late 2003. The suspension was urged by political and religious leaders claiming that “the vaccine could be contaminated with anti-fertility agents..., HIV, and cancerous agents.” The suspension triggered an epidemic that spread polio to numerous formerly polio-free countries. The Global Polio Eradication Initiative (GPEI) was eventually able to turn things around; vaccination resumed in Kano in 2004, and supplementary immunization succeeded in interrupting or greatly curtailing outbreaks in all but one of the polio-importing countries. But the Kano crisis diverted resources at a critical time. It also showed how vulnerable the entire enterprise could be to local mischief.

The suspension was a dramatic event, but immunization was low before the boycott. The main problem has been distrust by the people in this region in their national government, in the motives of the West, and in the vaccine itself. To some people living in northern Nigeria, polio eradication seems a misdirected priority. Why should they be urged to vaccinate their children for polio, and be given the vaccine for free, when their children are dying of other diseases, for which no help is being offered? To address this concern, Nigerian health authorities adopted new tools and tactics in early 2006, replacing national immunization days with “immunization-plus days,” during which “a range of childhood vaccinations and
other health interventions are offered along with the oral poliovirus vaccine.\textsuperscript{8} Immunization improved in some places, but not everywhere. Population immunity remains dangerously low in Kano.

\textbf{Uttar Pradesh and Bihar, India.} The GPEI has also tried to improve the efficacy of the vaccines it is able to administer, by replacing the normal, trivalent oral poliovirus vaccine, which protects against all three types of polio, with monovalent versions, which are more effective at immunizing for individual types.\textsuperscript{9}

The monovalent vaccines are crucial to the eradication effort in Uttar Pradesh and Bihar, two northern states of India characterized by rapid population growth, high population density, and poor sanitation—ideal conditions for spread. Here, coverage with multiple doses of trivalent vaccine has been high, but the vaccine often fails to stimulate immunity, probably because of the high prevalence of other enteroviruses and diarrhea. According to one study, the efficacy of trivalent oral vaccine in stimulating immunity to types 1 and 3 polio is just 9 percent in Uttar Pradesh.\textsuperscript{10} Ordinarily, four or five doses of live oral vaccine should be sufficient to guarantee immunity, but in northern India some children have been paralyzed by polio after receiving ten or more doses. The use of monovalent oral vaccine will help, but the protective efficacy of the type 1 vaccine in Uttar Pradesh is just 30 percent.\textsuperscript{11} To boost immunity even more, the GPEI is now considering additional options, including the introduction of bivalent vaccines (to offer protection in areas with both types 1 and 3 polio) and the inactivated (or killed) polio vaccine.

\textbf{Other trouble spots.} These are not the only trouble spots. Polio has circulated uninterrupted for more than a year in several formerly polio-free countries, including Sudan, Chad, the Democratic Republic of Congo, Angola, and Niger. So, as we try to eliminate polio in its last endemic holdouts, we need simultaneously to keep polio out of, or to drive it out from, every other country. Another country could easily replace today's endemic countries as the weakest link.

\textbf{Weakest Link No. 2: Financing Eradication}

The success of these efforts, and others discussed later, depends on rich countries' and other donors' continuing to finance the initiative. Should they stop contributing, many poor countries will abandon the effort.

\textbf{Money raised; money needed.} So far, the GPEI has raised more than $6 billion from international sources. This is much greater than the amount raised to eradicate smallpox, but it is not enough. More than $2 billion of additional money will be needed through 2013 (of this total, some money has already been pledged; a gap of about $870 million remains).\textsuperscript{12}

The willingness to pay for eradication depends on donors’ believing that the effort will succeed. After the Nigerian boycott, donations by the European Union stopped.\textsuperscript{11} It was only after vaccination resumed in Nigeria that the money flowed once again. If donors believe that eradication will fail, funding will dry up; then the donors’ expectations will be self-fulfilling.
Free riding. Donations are also vulnerable to free riding. If countries gain whether or not they contribute financially to the effort, why should they contribute? A belief that polio eradication will succeed is thus only a necessary condition for full financing; it is not sufficient.

Finding the right motivation. The motives for financing are also important. Rich countries gained tremendously from smallpox eradication; it was in their collective self-interest to finance this effort. If they cannot expect to gain also from polio eradication, financing will have to rely on a different motive, like compassion, and we know that self-interest is usually the more reliable impulse. For polio eradication, the compassion motive is especially fragile. This is because the current plan for the post-eradication era exposes developing countries to a serious risk.

Weakest Link No. 3: Circulating Vaccine-Derived Polioviruses And Synchronized OPV Cessation

When smallpox was declared eradicated, countries could decide independently whether or not to stop vaccinating. For polio, this approach could prove disastrous. This is because the weakened live virus strains in oral vaccine can evolve to reacquire the ability to cause paralytic disease and to spread. Outbreaks of circulating vaccine-derived polioviruses have occurred before (since 2000 in the Dominican Republic/Haiti, the Philippines, China, Madagascar, Indonesia, Cambodia, Niger, Burma/Myanmar, Nigeria, Ethiopia, and the Democratic Republic of Congo); more are virtually inevitable. Unless steps are taken to limit such outbreaks, and to extinguish those that cannot be prevented, the gains to eradicating wild polio will shrink. Indeed, if the vaccine-derived viruses evolve to resemble the wild viruses, as many virologists believe is likely, and if these strains cannot be eradicated, then the gains from interrupting wild polio transmission will be lost; the entire effort will only have succeeded in replacing one set of viruses with another. The risk is real. Although wild type 2 polio was eradicated long ago, type 2 vaccine-derived polioviruses have circulated in Nigeria for years.

How likely is it that new vaccine-derived virus outbreaks will occur after the wild polioviruses have been eradicated? According to one modeling study, there is a 65–90 percent chance that at least one outbreak will occur within a year of coordinated cessation of vaccination. After that, the annual probability is expected to decline. By the third year the probability may be only 1–5 percent. Note, however, that the impact of such an outbreak will increase over time. The longer the live oral vaccine continues not to be used (and inactivated polio vaccine not used in its place), the greater will be the pool of susceptible people in the population. The risk of a vaccine-derived virus outbreak could rise even as the probability of an outbreak declines.

To secure the gains from eradicating the wild viruses, the GPEI has proposed that all countries synchronize their cessation of oral vaccination after transmission has been interrupted. Here is why: if all countries stop vaccinating at pre-
“Should even one country insist on continuing to vaccinate with live oral vaccine, other countries may have to continue also.”

cisely the same moment, the period of time during which vaccine-derived viruses could emerge, anywhere, would be minimized. If, in addition, vaccination were stepped up immediately prior to cessation, the number of susceptible people worldwide would be minimized (although, worryingly, the volume of viruses derived from oral vaccine entering the environment would at the same time be maximized). Both efforts combined would probably give eradication of all polioviruses its best chance.

Unfortunately, this strategy also creates another weakest link. Should even one country insist on continuing to vaccinate with live oral vaccine, other countries may have to continue also. In this case, a World Health Assembly resolution will be required to assure every country that every other country will cease oral vaccination.

Even with such an assurance, might a country be willing to “break from the pack,” as it were? The possibility must be considered, not least because the rich countries are expected to continue to vaccinate with inactivated polio vaccine so long as major risks remain. Why, the leaders of a poor country might ask, should their country be expected to accept the risk of vaccine-derived viruses (and other risks discussed later) when the rich countries refuse to accept it?

Weakest Link No. 4: Immunodeficiency-Associated Vaccine-Derived Polioviruses

People with primary immunodeficiency disorders, when given live oral vaccine, may excrete vaccine-derived polioviruses for years. One person is known to have excreted immunodeficiency-associated vaccine-derived polioviruses for more than two decades. Slightly more than thirty such virus sources have been identified so far. But how many more might there be? The answer is uncertain, because it is difficult to identify such people against a background of high population immunity. When immunity wanes after oral vaccination has ceased, we may discover more spreaders of immunodeficiency-associated viruses.

In 2005 an immunocompromised infant living in an Amish community in central Minnesota was discovered to have vaccine-derived poliovirus. Further investigation showed that she had passed the virus on to at least four other children. No one knows how the child became infected, but the virus she carried was traced to vaccine administered more than a year before her birth and years after the United States and Canada stopped oral vaccinations. Because neither the infant nor her family had traveled outside the United States, the virus must have been imported. Normally, circulating vaccine-derived polioviruses recombine with other enteroviruses in the environment, but this virus was “pure,” suggesting that it was prob-
ably transmitted by another immunocompromised person. However, the virus that infected this girl was unrelated to any of the known immunodeficiency-associated viruses. The risk from such viruses in the post-eradication era could thus be very serious indeed.

Weakest Link No. 5: Inactivated Polio Vaccine Manufacture

Rich countries will continue to rely on the inactivated polio vaccine well into the post-eradication era, partly to guard against the risk of circulating vaccine-derived polioviruses. In doing so, however, they will expose the countries that stop using the oral vaccine, and that don't replace it with inactivated polio vaccine, to another risk. The potent wild seed viruses used to make the inactivated polio vaccine can escape. Accidents have happened before. In 1994 an infant was infected with a wild poliovirus reference strain traced to the inactivated polio vaccine plant in the Netherlands where the child's father worked.19

- **Protecting workers at production facilities.** How to prevent transmission from vaccine workers to the population? Vaccinating workers at inactivated vaccine production facilities with the vaccine will offer only incomplete blocking protection. Vaccination with live oral vaccine would make spread by plant workers of the wild viruses less likely, but it would make transmission of vaccine-derived viruses more likely.20 The GPEI is thus exploring another possibility: replacing the wild strains used today for making inactivated polio vaccine with attenuated (Sabin) oral vaccine strains.21 This would improve matters, but it would not eliminate the risk of vaccine-derived viruses’ emerging and spreading.

- **Standards for maintaining immunity.** Currently, inactivated polio vaccine is manufactured only in rich countries, but in a world in which live oral vaccination is prohibited and inactivated polio vaccine is very expensive, it seems inevitable that poor countries will want to produce their own supplies. Indeed, since they could probably do so more cheaply than rich countries, this could be an advantage for the world. To be sure that the world gains, however, standards are needed, not only for inactivated polio vaccine manufacture, but also for the maintenance of immunity in the countries that produce the vaccine. The manufacturing plant with the poorest standards, operating in the most vulnerable environment, will be another weakest link.

Weakest Link No. 6: Laboratory Samples

Stocks of wild poliovirus are held in hundreds of laboratories all over the world.22 If the virus were to escape from any of these labs, either by accident or through negligence or bioterrorist action, polio would be reintroduced into the environment. All it would take is for one laboratory to slip up.

Escapes have occurred in the past. During 2002–2003 seven polio cases were traced to a laboratory reference strain.23 Smallpox also escaped from a lab after it had been eradicated. More recently, severe acute respiratory syndrome (SARS) es-
escaped from a lab that met the same safety standard as is being planned for polio: biosafety level 3.

How can the possibility of another escape be limited? Under the WHO’s Global Action Plan for containment, biomedical labs are being surveyed worldwide to identify existing stockpiles of wild polioviruses. But what is the chance of identifying every single stock? Some samples containing polioviruses do not say “polio” on the label. A sample of coxsackievirus B1 (an enterovirus), for example, was once discovered to contain poliovirus.24 The laboratory with the poorest inventory control will be the weakest link in this section of the chain.

Weakest Link No. 7: Bioterrorism

Securing existing stocks will not only prevent accidental escapes; it will also help keep polio out of the hands of terrorists. Unfortunately, terrorists could obtain polio another way. Unlike most other viruses, polio can be synthesized in the laboratory. Polio may not be the ideal bioweapon, but terrorists might turn to it simply because it is easier to obtain than the alternatives. The probability of their doing so may be small, but it is not zero.

Weakest Link No. 8: Surveillance

Knowing whether the wild polioviruses have been eradicated, or a new outbreak (say, of circulating vaccine-derived polioviruses) has occurred, requires effective surveillance. However, surveillance can only confirm the presence of polioviruses; it cannot prove conclusively that polioviruses no longer circulate. For polio, surveillance is particularly difficult. Symptoms only show in about one in 200 infected people. Moreover, “acute flaccid paralysis” has other causes than polio. Evidence of polio circulation cannot be proved in the field; it must be confirmed by clinical diagnosis.

The discovery, in 2004, of a case of wild type 3 poliovirus in Sudan illustrates the nature of this challenge. Previous to this discovery, the last case in Sudan was detected in 1999. The criterion for certification of eradication is the failure to discover wild poliovirus for at least three years in countries with certification-quality surveillance. Genetic sequencing of the wild virus found in 2004 showed that it might have circulated undetected in Sudan for more than three years—a time when surveillance in Sudan was thought to be satisfactory.25 Surveillance probably was satisfactory at the national level, but it must also be of an acceptable standard within every local district. Conflict zones pose the greatest challenge: these areas are likely to be the weakest links for global polio surveillance.

“Surveillance is of value only if the information obtained is reported to the world.”
Weakest Link No. 9: Reporting
Surveillance is of value only if the information obtained is reported to the world. National pride can be a barrier to rapid reporting. Officials in Somalia suppressed information about smallpox cases in the final months of that eradication campaign, not wanting their country to bear the stigma of being the last to harbor the virus. More recently, China kept information about its SARS outbreak secret. Can we be sure that a polio outbreak will be reported without delay, particularly in the post-eradication phase?

Weakest Link No. 10: Outbreak Preparedness And Response
The willingness of countries to stop oral vaccination will depend not only on the probability of a post-eradication outbreak but also on its consequences. These will depend on our ability to respond to an outbreak, which will depend in turn on our preparedness. Under the WHO plan, outbreaks of wild or vaccine-derived viruses are to be extinguished in the post-eradication era using a stockpile of live oral vaccine maintained exclusively by the WHO. The WHO hopes that the World Health Assembly will pass a resolution “ensuring that the global polio vaccine stockpile managed by WHO will be the only [oral vaccine] stockpile and countries will not keep their own” (emphasis added).26 Why limit the availability of live oral vaccine in the post-eradication era? This vaccine is more effective than inactivated vaccine in smothering outbreaks, but its use will increase the chance of a future outbreak of vaccine-derived virus. Response to an outbreak in the post-eradication era thus requires a delicate balance. Enough oral vaccine must be used to snuff out an outbreak, but no more should be used than is necessary. Limiting its use will be difficult, however; since only a small fraction of infected people show symptoms, polio outbreaks must be controlled by mass vaccination.

Recalling the consequences of the Nigerian outbreak from late 2003, countries in unaffected areas may also want to vaccinate with live oral vaccine for prophylactic reasons. As more countries do so, however, the chance of a future outbreak of vaccine-derived virus will increase. This in turn will make yet more countries want to resume oral vaccination. A future outbreak could thus trigger a cascade of oral vaccinations. If the process cannot be stopped, the world may end up where it began after transmission of wild polioviruses was first interrupted. That means starting the whole process again. But having experienced one episode of backsliding, some countries may be unwilling to stop using oral vaccine again. The country least inclined to stop the second time around would be another weakest link.

Polio’s Post-Eradication Strategy Reconsidered
Eradication involves risks. So does sustaining the eradication dividend. Today the world is more vulnerable than ever to a smallpox outbreak. Eradication has enabled countries to stop vaccinating, but at the cost of reducing population im-
“If poor countries could acquire inactivated vaccine more cheaply, this weakest link would fall away.”

community. In recent years the terrorist threat changed perceptions about vulnerability. The United States, for example, ordered the production and stockpiling of vaccine—one dose for every American. This was costly; it reduced the magnitude of the dividend. But it also reduced vulnerability to a post-eradication outbreak. The challenge is to find the right balance between the risk and the reward.

■ Balancing cessation with eradication. Does the current post-eradication strategy for polio get the balance right? Vaccination cessation increases the reward, but it also increases vulnerability. Rich countries will continue to vaccinate with inactivated vaccine in the immediate post-eradication era. In doing so, they will forgo an eradication dividend, but they will also be shielded from a post-eradication risk. It is the poorest people living in the poorest countries who will be vulnerable in the post-eradication era under this plan. If even one poor country refuses to go along, the entire post-eradication plan may be in jeopardy and the rewards to eradication lost to the world.

■ Substituting inactivated for live oral vaccine. If poor countries could acquire inactivated vaccine more cheaply, this and other post-eradication weakest links would fall away. Suppose poor countries could protect their populations as cheaply using inactivated as live oral vaccine. Then they would have nothing to lose by stopping oral vaccination. The likelihood of a post-eradication outbreak of vaccine-derived viruses would be unchanged, but the consequences of such an outbreak would be less dire, because countries could maintain population immunity at no additional cost (relative to continuing to oral vaccination), and without making other states more vulnerable. Post-eradication outbreak preparedness and response would also improve (countries would be less concerned about not having their own stockpiles of live oral vaccine). A lower price for inactivated polio vaccine would thus strengthen polio’s post-eradication weakest links.

How costly would it be to substitute inactivated for live oral vaccine? According to one estimate, the incremental cost to all poor countries of switching from live oral to inactivated vaccine is about $317 million per year.27 This is less than the amount spent each year on polio eradication since 2000; it is less than half as much as has been spent in recent years.28

Rich countries might be willing to pay for this cost, at least for a period of time (say, five years). Recall that the probability of a post-eradication outbreak of vaccine-derived virus will decline over time. If the risks of such outbreaks can be greatly reduced, then the risk-reward balance will tilt in favor of vaccine cessation, for both poor and rich countries. This would yield the world a return on its eradication investment.

■ Reducing the cost of using inactivated polio vaccine. Reductions in the
cost of stimulating population immunity using inactivated polio vaccine would help even more. Shifting production to developing countries could lower production costs, not least by increasing competition among producers, although the risks associated with manufacturing inactivated polio vaccine in developing-country settings would have to be reduced for this to be an advantage overall. Costs will also fall with product and process innovation. The product could be improved by changing the vaccination schedule, to reduce the number of required doses; by using fractional doses; and by using an adjuvant (a substance added to a vaccine to improve the immune response so that less vaccine is needed) to stimulate immunity. Another idea is to spread the fixed costs of needle injection by combining inactivated poliovirus with other antigens. Alternatively, use of intradermal injection would allow inactivated vaccine to be administered with almost as much ease as oral vaccine. Finally, years ago the Netherlands developed a number of process innovations for the manufacture of inactivated polio vaccine, and more process improvements may be possible.29

The GPEI is exploring all of these possibilities. Although the world’s attention today is understandably focused on eradicating the wild viruses, the ultimate success of the initiative will depend as much on the steps being taken now to improve the economics of inactivated polio vaccination. These steps will strengthen what is perhaps the most critical weakest link in the post-eradication chain.

NOTES


9. Ibid.


15. An empirical investigation of an outbreak of circulating vaccine-derived poliovirus on Madura Island in Indonesia concluded that this virus was “not clinically or epidemiologically different from that caused by [wild virus].” See C.F. Estivariz et al., “A Large Vaccine-Derived Poliovirus Outbreak on Madura Island—Indonesia, 2005,” *Journal of Infectious Diseases* 197, no. 3 (2008): 347–254.


23. Dowdle et al., “Will Containment of Wild Poliovirus?”


