AGRON DRAGAJ

Female vaccinators — often the only ones allowed to speak to mothers or enter a child's home — wait outside a house in Afghanistan.

POLIO

The eradication endgame

Researchers are developing a strategy that could put an end to polio forever.

BY CASSANDRA WILLYARD

In 1988, scientists around the world launched a massive effort to eliminate polio, a disease that can cripple and kill. The Global Polio Eradication Initiative (GPEI) has since made great progress: the number of polio cases has fallen by more than 99%, from an estimated 350,000 cases in 1988 to around 400 in 2013. And in January, India, once a stronghold for polio, celebrated an important milestone: three years with no new cases. Yet poliovirus stubbornly persists in Nigeria, Afghanistan and Pakistan, where violence, politics and mistrust have hampered eradication efforts. Indeed, in early 2014, Kabul saw its first case of polio since 2001. In 2012, the GPEI issued a dire warning: "Polio eradication is at a tipping point. If immunity is not raised in the three remaining countries to levels necessary to stop poliovirus transmission, polio eradication will fail."

In chess, the final moves must be carefully planned, as one mistake can let your opponent gain the upper hand. It's the same with the polio endgame. Violence has made delivery of the vaccine nearly impossible in some regions. In others, fear and mistrust have led parents to refuse to have their children vaccinated. But there is another, seldom discussed, obstacle to eradication: in rare cases, the live, attenuated (weakened) virus in the oral polio vaccine (OPV) can mutate and spark polio outbreaks.

In April 2013, the GPEI presented a new strategy to wipe out polio — not only the wild virus, but also polioviruses derived from OPV. The plan is to introduce inactivated polio vaccine (IPV), which contains killed virus, in the 124 countries that rely on OPV by 2015. A more effective oral vaccine will then be used to eliminate the last pockets of virus. Once the world is free of polio, the oral vaccine can be phased out entirely. Introducing IPV in so many countries will pose a "major challenge", says Elizabeth Miller, an epidemiologist who chairs the polio working group of the Strategic Advisory Group of Experts (SAGE) on Immunization. "On the other hand, it offers huge rewards in terms of progress towards eradication."

SABIN VS SALK: THE REMATCH

Poliovirus replicates in the human gut and spreads through sneezes or coughs, or when someone comes into contact with infected faeces. Most people who contract polio develop only mild symptoms, if any. But in roughly 1 out of 200 infected individuals, the virus invades the nervous system and causes permanent paralysis. If the muscles that control breathing are paralysed, the disease can be fatal.

The fight against polio hinges on the two vaccines, IPV and OPV. IPV, an injectable vaccine invented by Jonas Salk and introduced in 1955, contains virus that has been bathed in a formaldehyde solution; this killed virus cannot replicate or cause paralysis. OPV, developed by Albert Sabin and approved in 1961, contains virus that has been weakened by growing it in monkey kidney cells. This live virus, delivered as oral drops, can replicate in the guts of vaccinated children for several weeks and spread — still weakened — through their faeces to unvaccinated children, allowing immunity to travel through the community. Because it is cheap and easy to administer, OPV has become the polio vaccine of choice, especially in developing countries.

But OPV has a major drawback: the live viruses in the vaccine can mutate, regaining their deadly characteristics. Roughly one

in every 2.7 million children who receive OPV will become paralysed. In those regions where large swaths of the population remain unvaccinated, vaccine-derived polioviruses can regain their ability to circulate and cause outbreaks. "There have been quite a few vaccine-derived poliovirus outbreaks in the past few years," says Nicholas Grassly, who heads the vaccine epidemiology research group at Imperial College London. One recent study[1] estimates that vaccine-derived virus infected 700,000 people between 2005 and 2011, although only a small number of these would have developed paralysis. And these viruses continue to circulate. In 2013, about 60 people were paralysed as a result of circulating vaccine-derived poliovirus, most in a remote region in Pakistan. Eliminating vaccine-derived polio will require an end to the use of OPV. The GPEI advocates not a sudden withdrawal but rather a phased removal of Sabin's vaccine.

All polioviruses fall into one of three groups, or serotypes, and standard OPV contains a weakened version of all three. Types 1 and 3 circulate worldwide, but type 2 wild virus hasn't been seen since 1999 — and viruses derived from the type 2 Sabin strain account for most vaccine-related polio outbreaks. Type 2 is therefore the first to be eliminated from the vaccine. "The continued use of type 2 in the trivalent oral polio vaccine is causing more problems than it is preventing," Miller says.

However, eliminating type 2 from OPV will leave children vulnerable to type 2 vaccine-derived infection. So before making the switch to bivalent OPV — which contains only type 1 and type 3 virus — the plan is to introduce a single dose of IPV, which protects against all three types. Miller says the combination "would protect the population should there be an emergence of a type 2 vaccine-derived strain."

"This is an elegant strategy," says Bruce Aylward, who has led the polio eradication programme at the World Health Organization for the past 15 years.

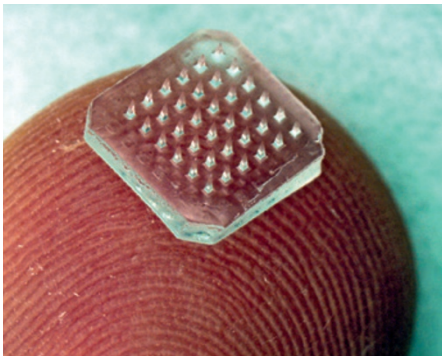
AT THE SHARP END

Elegance does not necessarily translate into ease or economy of implementation, however. OPV typically costs just US$0.14 per dose. But producing IPV requires more virus, and, because it is produced from virulent wild strains, its production demands expensive biosafety measures. It is therefore significantly more expensive. "The best price you can get for IPV is between US$2 and US$3 a dose," says Stephen Cochi, senior adviser at the US Centers for Disease Control and Prevention's Global Immunization Division in Atlanta, Georgia.

The cost of IPV will fall as demand grows — Miller and Aylward hope the poorest countries will be able to secure the vaccine for about US$1 a dose — but it is likely to remain more expensive than OPV. And funds used to purchase IPV won't be available to buy other vaccines for diseases far more common than polio. "A country like Uruguay will have many cases per year of diseases such as pneumonia, meningitis and hepatitis, but may go for 20–30 years without a single vaccine-related case of polio," says Ciro de Quadros, executive vice-president of the Sabin Vaccine Institute in Washington, DC. Such lopsided statistics, he says, will influence investment priorities.

Administering IPV is more problematic, too. Unlike oral drops, injections require trained professionals and sterile syringes. There's also the thorny question of acceptance. In parts of Pakistan and Nigeria, some people are already suspicious of the vaccine. Now health officials must convince parents that their children need not one but two different kinds of polio vaccine.

Researchers are working to help health officials overcome these barriers. Aylward and his colleagues are investigating cost-cutting measures, such as using adjuvants to reduce the amount of virus needed. They have also found that the dose can be reduced if the vaccine is injected under the skin instead of into the muscle[2]. Mark Prausnitz, a chemical engineer at the Georgia Institute of Technology in Atlanta, is working on a version of IPV that could be applied like a band-aid, eliminating the need for syringes and trained medical professionals. The patch contains 100 microneedles, each less than a millimetre long, affixed to a flexible pad smaller than a postage stamp. When the patch is in place, the needles puncture the skin and dissolve in 5–10 minutes, releasing the inactivated virus. Prausnitz recently tested the polio patch in rhesus macaques and found that it raises an immune response just as effectively as the standard injectable vaccine. He and his colleagues are seeking funding to conduct a clinical trial of the patch.



JEONG-WOO LEE

A dissolving microneedle patch on a finger.

SILENT SPREAD

The challenges posed by IPV extend beyond economics and logistics. IPV is good at protecting against paralysis, but it doesn't evoke a strong immune response in the gut, where polio replicates, so people who are vaccinated with IPV can still spread the virus. Israel made the switch from OPV to IPV in 2005. The country hasn't had a case of paralytic polio since 1988, but authorities continue to monitor the country's sewage for signs of the virus. In the spring of 2013, they found it in the sewers of Rahat in southern Israel. By August the virus had been detected in 91 sewage samples from 27 sites in southern and central Israel, and in faecal samples from 42 people in those regions. "It spread throughout Israel and to the West Bank and Gaza," Cochi says. Because roughly 94% of children in Israel have been vaccinated, not a single child developed the disease. But the continued circulation of the virus puts other countries with lower rates of vaccination at risk.

It is theoretically possible that, once the world begins using bivalent OPV, type 2 vaccine-derived outbreaks could emerge and undergo a similar silent spread because children who had received IPV would probably not develop paralysis[3]. "In Israel they have the most intensive environmental sampling — looking for poliovirus and other pathogens — in the world," Cochi says. But in regions without intensive sampling, the virus could go undetected much longer.

Aylward considers that scenario unlikely, however. He and Grassly recently developed a model to examine the risk and found that, under most conditions, IPV will hasten the virus's demise[3]. But when vaccine coverage is high and the virus has a high reproductive rate, "you could see the situation you see in Israel: persistent circulation," Aylward says. Fortunately, he adds, "not many settings mimic that environment." What's more, the GPEI aims to introduce only a single dose of IPV, so children will have some immunity but won't be fully protected, making it less likely that an outbreak will go undetected. Aylward acknowledges the potential risk of this approach, but he emphasizes the perils of continuing to use an oral vaccine containing all three strains of virus. "The error," he says, "is thinking the current situation is a safe one."

The GPEI's optimistic timeline sees the world certified polio-free in 2018, a result that would allow the complete withdrawal of the oral vaccine. But even if the many obstacles to introducing IPV can be overcome, it may be difficult to introduce it into enough countries in 2015 to prepare for a coordinated withdrawal of type 2 vaccine in 2016. As de Quadros points out, such a rapid rollout would be unprecedented. "The way they are planning the introduction is very ambitious," he says. "It will be interesting to observe what will happen."

That's the problem with endgames. Even with only a few pieces left on the board, it's still not entirely clear how to win the game. ■

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