Polio: Looking for a Little Luck

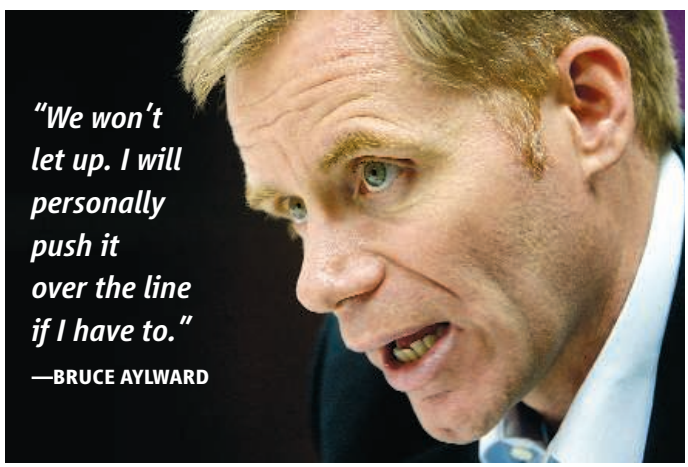
After another year of setbacks—and some real gains—the global polio eradication initiative continues with more support than ever

GENEVA, SWITZERLAND—Soon after she took office 2 years ago, Margaret Chan called an urgent meeting. The time had come, said the new director-general of the World Health Organization (WHO), to take a hard look at the global polio-eradication initiative, which by then was 6 years past deadline, a couple of billion dollars over budget, and facing increasing questions about its feasibility from scientists and tapped-out donors. She wanted no more grand promises of when the virus would be vanquished from the planet. Instead, Chan and the "major stakeholders"—the partner organizations, donors, and countries—launched an "intensified" 2-year program, setting measurable milestones by which to judge progress. The leaders of the global initiative, a collaborative effort based at WHO, were to report back in February 2009, at which time the world could reassess its massive investment in the biggest global health program ever.

That moment of reckoning is here, and the initiative has met only one of the milestones set 2 years ago. At 1643, global polio cases in 2008 were actually higher than the 1315 total in 2007, and the virus remains entrenched in the last four countries where, for reasons both social and biological, it refuses to budge.

Still, no one is talking about pulling the plug. If anything, the beleaguered program has garnered more support and more money than it did several years ago. Just last month, the Bill and Melinda Gates Foundation, Rotary International, and the U.K. and German governments pledged $635 million for polio eradication. "Polio *has* to succeed" is the widely voiced sentiment among Chan and other global health leaders, not only because of the huge investment—20-plus years and nearly $6 billion—but also because of the unsettling realization that there is no palatable way out (*Science*, 20 April 2007, p. 362). Stopping now, so close to the finish, would mean losing the spectacular gains of the past 20 years—a defeat that would certainly be the death knell for other potential global eradication projects, like those for malaria or measles, says Peter Wright, an infectious-disease expert at Dartmouth College who advises the eradication initiative. And that is a decision no one is yet ready to make.

That leaves the Global Polio Eradication Initiative (GPEI)—a collaboration led by WHO, Rotary International, UNICEF, and the U.S. Centers for Disease Control and Prevention—trying every trick in the book to beat the virus into submission. GPEI has a new 5-year plan that calls for reaching those unmet milestones—and far more. The program is investing heavily in research on improved vaccines that earlier program leaders swore would never be necessary; the virus would be gone by the time one could be developed. In a major departure, they are rethinking whether the world can ever safely stop vaccinating against polio, the fundamental assumption on which polio eradication was sold some 20 years ago (see sidebar, p. 705). And perhaps most of all, they are hoping for a little luck.



Stalemate

For a long time, it looked like the polio warriors had the virus licked. Soon after the program was launched in 1988, with the confident prediction that polio would be gone by 2000, the program began dispatching virus from more than 100 countries in quick succession, using the tried-and-true approach that had already eradicated polio in the Western Hemisphere: supplementing routine polio immunizations with huge countrywide campaigns several times a year to deliver drops of Albert Sabin's oral polio vaccine (OPV) to every child under age 5.

By 2000, global cases had fallen 99% from 350,000 to 791, reaching an all-time low of 483 in 2001. In the process, one of the three wild poliovirus serotypes, type 2, was eradicated almost inadvertently—providing a proof of concept that the ambitious plan was indeed feasible. By 2006, type 1 and type 3 virus were cornered in just four "endemic" countries—India, Nigeria, Afghanistan, and Pakistan—where transmission has never been interrupted (*Science*, 26 March 2004, p. 1960).

But there the initiative stalled, with the four endemic countries periodically erupting and reinfecting other polio-free countries and the global case count hovering between about 1000 and 2000.

As skepticism mounted among scientists and weary donors, a few advocated throwing in the towel on eradication and concentrating instead on keeping the virus in check (*Science*, 12 May 2006, p. 832). Meanwhile, Bruce Aylward, the peripatetic and unfailingly optimistic M.D./MPH who has led the effort since 1998, kept insisting that success was just around the corner—just another year away.

That was the context in which Chan launched the intensified program, pouring in more money and resources to determine once and for all whether eradication could be achieved. The answer, everyone agreed, depended on progress in the four endemic countries.

India seesaws

In India, more than in any other country, the polio fighters were banking on a win in 2007–08. The plan was to deal a "mortal blow" to poliovirus type 1, considered the worst player because it causes more paralytic disease and spreads faster than the other remaining wild virus, type 3. Once type 1 was dispatched, mopping up type 3 in India would be easy, they predicted, and would show the world the program was on track.

"If we can do it in India, the toughest place in the world, we can do it anywhere," says Aylward. Early on, polio experts realized India was different; instead of the three to four

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doses of OPV that had sufficed to stop poliovirus transmission elsewhere, in some parts of northern India, children needed eight or 10 doses to be protected—and still some became paralyzed. In the other endemic countries, GPEI says the problem is "a failure to vaccinate"; in India, by contrast, the problem is compounded by "a failure of the vaccine." The country's huge population, explosive birthrate, and crowded, squalid conditions combine to create an ideal environment for the virus, which is transmitted by feces.

To tackle this "pernicious transmission," as Aylward calls it, in early 2005 GPEI helped rush into use a new, more immunogenic version of OPV—a monovalent form that focused all its firepower on just type 1 (mOPV1). Later that year, mOPV3 was introduced (*Science*, 14 January 2005, p. 190). With the new vaccines in hand, northern India launched its sequential strategy, vowing to wipe out type 1 by the end of 2008.

Volunteers flooded the country with oral polio drops, upping rounds from every 2 months to every 4 weeks and focusing on the toughest districts in the crowded, impoverished states of Uttar Pradesh, outside Delhi, where circulation was most intense, and Bihar, some 800 kilometers east.

The results were stunning. Type 1 cases across the country dropped from 648 in 2006 to 73 in 2008. Most remarkable, Uttar Pradesh, which Aylward calls the wellspring of polio in the country—"every virus in India since 1999 has been linked to that area," he says—went 12 months without a case. "It is really a hallmark [achievement]," says Samuel Katz, a polio expert at Duke University in Durham, North Carolina, who directs GPEI's newly reconstituted research advisory committee.

But in early 2008, India was blindsided by a walloping epidemic of type 3 polio. Although the program had continued to use occasional rounds of mOPV3 and the trivalent formulation, tOPV, to forestall just such an event, "we didn't get the balance right," concedes David Heymann, who oversees the polio program as WHO's assistant director-general for infectious diseases.

Then in June 2008, type 1 came back to Uttar Pradesh. Genetic analyses showed it wasn't a local Uttar Pradesh virus, with its distinct genetic signature—instead, it was "imported" from Bihar. To scientists, the distinction was important—it meant transmission in Uttar Pradesh had indeed stopped for the first time ever—but that still left the country battling an epidemic on two fronts, with cases in 2008 down from 2007 but still, at 556, alarmingly high.

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Backsliding. Nigeria again has a runaway polio epidemic.

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At a November 2008 meeting, the India Expert Advisory Group, which oversees the country's effort, vowed to continue the fight into 2009, again focusing on type 1 but adding more doses of mOPV3 to keep that serotype in check. As a contingency plan, WHO and partners are testing a higher potency mOPV1, and the country is exploring whether adding doses of inactivated polio vaccine can help boost immunity in young children.

All bets are still on India to be the first of the four endemic countries to stop transmission of the wild virus. India is the "key to donor confidence," says Heymann. "We need a victory."

Nightmare in Nigeria

In contrast, few expected much progress in northern Nigeria, where opposition, apathy, political instability, and corruption have stymied the program for years. But even realists didn't necessarily expect an outbreak of the magnitude that struck in 2008, in which cases in some areas were 10 times higher than in 2007. "Polio in Nigeria remains a nightmare," says Oyewale Tomori of Redeemer's University near Lagos, head of the country's expert polio advisory group.

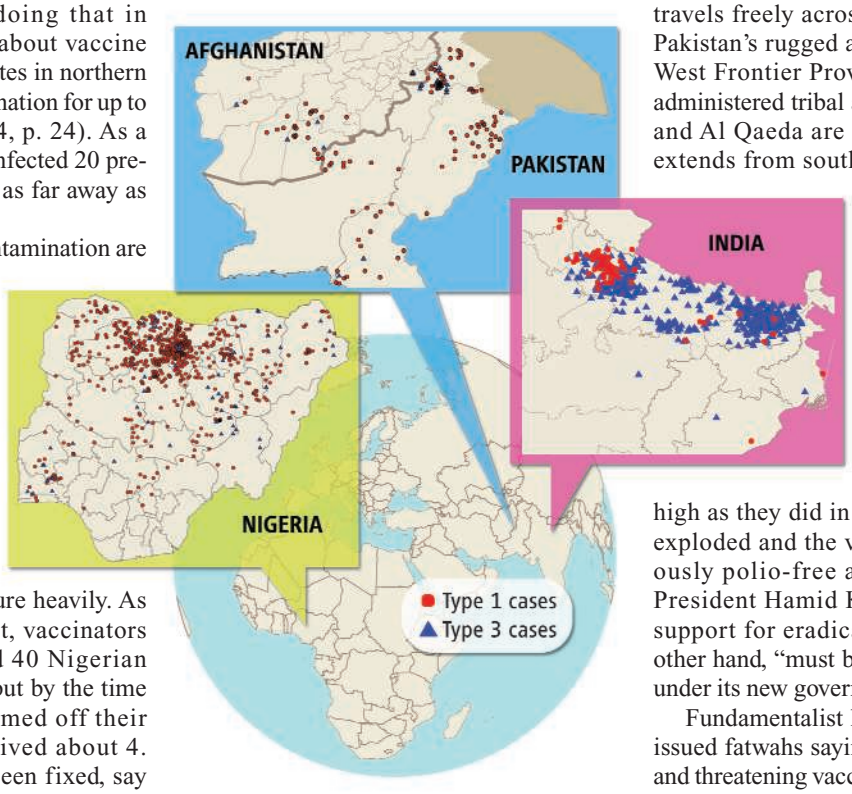
In May 2008, WHO issued a blunt warning that Nigeria posed a risk to the rest of the world, threatening to derail the entire global effort. It came close to doing that in 2003–04, when suspicions about vaccine safety led several Muslim states in northern Nigeria to stop all polio vaccination for up to a year (*Science*, 2 July 2004, p. 24). As a result, virus from Nigeria reinfected 20 previously polio-free countries, as far away as Indonesia.

Rumors about vaccine contamination are no longer the major impediment to eradication; instead, Nigeria's problems are largely "operational," say GPEI officials, citing a lack of political will and the government's failure to provide even the most rudimentary health services. Others more bluntly refer to "gross incompetence" and say graft and corruption figure heavily. As Tomori explains, in the past, vaccinators might have been promised 40 Nigerian nairas a day for their work, but by the time government officials skimmed off their share, each may have received about 4. Those problems have now been fixed, say GPEI officials.

At the epicenter of the epidemic in Kano state, 68% of all children have received fewer than three doses of OPV, and up to 30% are "zero-dose." With 791 cases in 2008, Nigeria accounted for almost 50% of the global total. That number is especially frustrating to polio experts because stopping transmission in Nigeria should be a cinch compared with India. Studies by Nicholas Grassly and colleagues at Imperial College London have shown that vaccine efficacy is high there; that means that transmission of the virus should stop when population immunity reaches roughly 80%.

Now, as in 2003, WHO and world leaders are trying to shame Nigeria into action. Last May, the World Health Assembly passed a resolution singling out Nigeria and calling on the country to quickly stop its runaway outbreak.

The public humiliation may be having the desired effect. In July, President Umaru Yar'Adua vowed to redouble the effort. The ineffective head of the national polio program has been replaced, the third such change in 3 years. "This time it is different; the president is on board," asserts Aylward. Tomori is more circumspect, saying he will wait to see whether this high-level commitment actually translates to action on the ground. Meanwhile, in 2008, poliovirus from Nigeria spread to seven West African countries. Other war-torn countries, including Chad and Sudan, are still grappling with epidemics sparked by earlier "importations" from Nigeria.



Mixed bag. Despite significant advances, polio cases in 2008 remained high in the four endemic countries.

SOURCE: WHO

Perils in Afghanistan and Pakistan

In the other two hot spots, Afghanistan and Pakistan, violence, political turmoil, religious opposition, and the fierce autonomy of local leaders render eradication all but impossible. Large swaths of both countries are "no-go" zones where WHO and other United Nations personnel are not allowed to operate. National polio teams can still get in but are justifiably leery of doing so. Even in "accessible" areas, a "climate of fear" prevails, and vaccination teams may report going more often than they actually do, says epidemiologist Rudi Tangermann, who oversees efforts in the two countries from Geneva.

In mid-2007, GPEI thought it had made significant headway; a "third party" had brokered an agreement with the Taliban to let polio vaccinators work unimpeded. Despite that agreement, in March 2008, two polio workers and their driver were killed by a suicide bomber in southern Afghanistan, where they were traveling to prepare for a vaccination campaign.

Surveillance and monitoring are compromised as well. "We are peering in from the outside," concedes Aylward. The countries constitute one epidemiologic block, with two transmission zones where the wild virus travels freely across the border. One is in Pakistan's rugged and inhospitable North-West Frontier Province and the federally administered tribal areas, where the Taliban and Al Qaeda are resurgent. The second extends from southern Afghanistan, near Kandahar, through Baluchistan, and then stretches all the way to northern Sindh in central Pakistan.

Of the two, Pakistan is the bigger worry, says Tangermann. The number of cases rose in Afghanistan in 2008, but nowhere near as high as they did in Pakistan, where type 1 exploded and the virus spread into previously polio-free areas. In Afghanistan, President Hamid Karzai has pledged his support for eradication; Pakistan, on the other hand, "must become more committed under its new government," says Heymann.

Fundamentalist leaders in Pakistan have issued fatwahs saying the vaccine is unsafe and threatening vaccinators. "Refusals" have risen considerably. In February 2007, a Pakistani doctor and his driver were killed by a

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RETHINKING THE POLIO ENDGAME

One of the toughest conundrums for the long-running Global Polio Eradication Initiative has been whether and when it would be safe to stop vaccinating once they deem the virus gone. Now, the thinking is undergoing a major shift.

The first big complication came in 1999 when scientists realized that the weakened virus used in the live oral polio vaccine (OPV) could revert to its neurovirulent form in rare cases and spark an epidemic. Thus was born the "OPV paradox": OPV was necessary to eradicate the virus, but as long as OPV was in use, eradication could never be achieved. As a solution, World Health Organization (WHO) scientists proposed a plan: After the world was certified polio-free, all countries would stop using OPV simultaneously, as if at the stroke of midnight.

Some scientists dismissed the idea as folly and instead advocated universal use of the inactivated polio vaccine (IPV), already widely used in developed countries. That would be the only way to ensure the world was really safe, they argued, and the only way to prevent a gross inequity in which poor countries bore all the risk of polio.

"The world will be a much safer place if more countries use [inactivated polio vaccine]" when the virus is deemed gone.

—ROLAND SUTTER

For years, WHO maintained that such a switch wasn't feasible: IPV was too expensive for poor countries, it must be injected, and its effectiveness is unproven in tropical settings. Now, experts such as Roland Sutter, who heads WHO research in Geneva, Switzerland, concede that IPV does have a role after all. "The world will be a much safer place if more countries use IPV," he says.

To make that possible, WHO is now dusting off some earlier studies and investing heavily in new research into a cheaper, more effective version of IPV. WHO is looking at "dose sparing" strategies that could bring down the cost. In Cuba and Oman, it is testing the efficacy of using one-fifth the normal dose, delivered intradermally with an injection gun instead of intramuscularly with a needle. Other projects are trying to "stretch" the antigen with new adjuvants.

Another big push is for what is called a "Sabin IPV." One of the drawbacks of the standard Salk IPV is that production starts with the dangerous wild virus, which is then killed. To reduce the chances of an accidental release, IPV is manufactured only in facilities that operate under strict biocontainment procedures and only in countries that maintain a very high population immunity against polio. Both requirements rule out transferring the technology to developing-country manufacturers, which would bring down the cost.

A Sabin IPV would use the less infectious attenuated strain from the oral vaccine as its seed stock, providing "a margin of safety" should an accident occur, says Sutter. Several clinical trials of a Sabin IPV are ongoing; if all goes well, it could be introduced within 5 to 8 years.

Ultimately, says Bruce Aylward, who runs WHO's eradication initiative, "I want something much better than Sabin IPV." Several groups are working on manipulating the virus to make safer seed strains that could be handled under less stringent safeguards. It's still early days, but there are several promising leads, including a virus that can't survive at body temperature.

Sutter and Aylward say each country will decide whether to continue vaccinating. But if countries do choose to continue, they want to have in place a "cost neutral" vaccine that delivers the same protection as OPV at the same price—without the risk. **–L.R.**

remote bomb while they were returning from a village where they were trying to persuade parents to let their children be vaccinated.

Equally unsettling, the Geneva team suspects that the program in Pakistan is weaker than they imagined and that the viral foe may be tougher. Earlier reports that vaccination teams reached 95% of the target children seem to have been fabricated, says Tangermann. And recent studies by Grassly and colleagues at Imperial suggest that viral transmission is much more efficient in Pakistan than previously believed, closer to that of India than that of Nigeria. "Pakistan is the only place we really have questions about what we are dealing with," says Aylward.

To get a better fix on the biology, WHO and Pakistani partners are planning studies to measure antibodies to the virus in children in Karachi, Peshawar, and Lahore. "We have to see how effective the vaccine is and how well the program is working," says Aylward.

On the political front, Aylward has been trying to work his magic. At a high-level meeting last December in Islamabad, he and other partners got assurances from Minister of Health Mir Aijaz Hussain Jakhrani that Pakistan would make eradication a priority.

For now, says Heymann, the most the program can hope to achieve there is to show it can stop transmission in conflict-free regions, like Punjab, where despite repeated campaigns, circulation remains intense. For the other areas, they wait. "We may be quite slow in areas with security problems," he says.

Vote of confidence

Despite the upsurge of cases in 2008, Aylward insists that the world is much closer to eradication than it was a year ago. Chan has declared polio eradication WHO's "top operational priority," saying in a speech in June, "The credibility of not just WHO but of many other health initiatives is on the line." She is organizing an independent review to figure out what went wrong in each country and what the program could do better.

The global oversight body, the Advisory Committee on Polio Eradication, is on board as well; in December, it endorsed GPEI's strategic plan for 2009 to 2013. Although Aylward is leery of firm deadlines, the plan calls for interrupting type 1 transmission in India by the end of 2009 and type 3 the following year. They hope to wipe out both types in Afghanistan and Pakistan in 2010, but Nigeria might take a year longer. All that depends, of course, on donors keeping their checkbooks open and countries putting their mind and muscle behind eradication.

The donors have stepped up. With the $635 million infusion from Gates and others, funding looks better than it has in years. The $255 million Gates grant is the largest single donation since Rotary International kicked off the effort in 1988 with $240 million.

Aylward keeps up his unrelenting schedule, visiting endemic and reinfected countries to spur or prod them into action. For the toughest spots, the big guns go too, such as Chan, Heymann, and the newest advocate, Bill Gates, who is also championing malaria eradication and who visited India in December 2008 and Nigeria just last week.

For now, the global health community seems willing to give the eradication initiative more time. There are still skeptics who say it will never be finished. But most agree with Wright. "It's terribly hard," he says. "All the models suggest it is not a good idea to give up on the program."

"We won't let up," said Aylward in an interview from the noisy Brazzaville airport in Congo en route to Islamabad. "I will personally push it over the line if I have to. We still have very long sleeves and lots of tricks up them if we need them." **–LESLIE ROBERTS**

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