ISAO ARITA WAS A BELIEVER. IN THE 1960s and 1970s, he was a crusader in the campaign against smallpox, the only disease ever eradicated. In 1990, he took on polio, directing the campaign that eliminated that scourge from the Western Pacific in 1997. Much of his long and distinguished career—at the World Health Organization (WHO) in Geneva, Switzerland, and the Agency for International Health in Kumanmoto, Japan—has been predicated on his faith in medicine’s ability to triumph over viruses.

So it is with great seriousness that he says that he no longer believes it is feasible to wipe out polio—not in 2006, and probably not ever.

And he is not alone. Like a handful of other longtime supporters of eradication, Arita has begun to go public with his doubts. On page 852, he and his colleagues write that the 18-year, $4 billion campaign has brought enormous public good, reducing polio cases from 350,000 in 1988 to just shy of 2000 in 2005. But the old adage about the last few percent being the hardest is coming true in spades.

Since polio exploded out of Nigeria in 2003, the virus has reinfected some 18 previously polio-free countries, many of them unforgiving, conflict-torn places such as Sudan and Somalia, where it is simply too dangerous to send in health workers. And despite “heroic” efforts to achieve the highest vaccination rates ever, the virus is hanging on in the slums of India and has seeded outbreaks in four countries, most recently Bangladesh. Nor does the virus show signs of budging from the shared reservoir between Pakistan and Afghanistan.

“However diligent they are, however much the staff does its best, there are very serious obstacles that militate against eradicating polio,” agrees Donald A. Henderson, the outspoken director of the earlier smallpox program and one of the few to question the feasibility of polio eradication from the start.

The skeptics, who include not only Henderson and Arita but also polio experts such as Konstantin Chumakov of the U.S. Food and Drug Administration and Vadim Agol of the Russian Academy of Medical Science’s Chumakov Institute for Poliomyelitis (named after Konstantin’s father), worry that the campaign is deluding itself and the world with its “ever-receding” deadline—originally 2000 and now reset at 2006. Says Henderson, who is now at the University of Pittsburgh’s Center for Biosecurity in Baltimore, Maryland: “It is always 12 or 18 months away from where we are.” And they contend that the program leaders are not paying sufficient attention to policies needed to control, rather than eradicate, polio over the long term—which would be a major accomplishment in its own right.

True, the case count looks bad, concedes David Heymann, another smallpox veteran who in 2002 was brought in to head the multiagency polio effort, headquartered at WHO. Global cases were higher in 2005 than in any year since 1999, and 2006 is shaping up to be even worse in Nigeria and India. But surveillance is also more sensitive, which could explain some of the increases, he says. He insists that overall, the campaign is racking up solid victories. Of the 22 countries reinfected with polio since 2003, outbreaks have been dramatically curtailed in all but nine. And the number of endemic countries—where transmission has never stopped—is down to four, an all-time low, he contends. Heymann, who runs the program with Bruce Aylward of WHO, extols the benefits of an improved, more targeted version of the oral polio vaccine. He and Aylward cite the enthusiasm and commitment of donors such as Rotary International, the G8, and the Gates Foundation—and of the polio-affected countries themselves. And they maintain that it is feasible to stop transmission of wild poliovirus in 2006 everywhere except Nigeria, which may take another year and a half, and perhaps one corner of India.

But optimism is no substitute for a contingency plan, counter the skeptics. And so the debate continues—respectful, increasingly public, and with no sign of resolution.

A reasonable target

Even now, most agree that the 1988 decision to eradicate polio made scientific sense. After all,
The Nigerian government is committed to eradicating polio, but the virus is still circulating out of control in the north.

The world had eradicated smallpox, and there seemed to be no overwhelming scientific obstacles to wiping out polio as well. The virus is spread from human to human, which means there’s no chance of it lurking in an animal reservoir. As with smallpox, there was an effective vaccine—two, in fact: the live oral Sabin polio vaccine (OPV) and the inactivated Salk polio vaccine (IPV). The World Health Assembly endorsed the concept in 1988, setting the world on a course to wipe out polio by 2000 and then, once the threat of the virus’s return was deemed negligible, to stop all control measures, as had occurred with smallpox.

It soon became clear, however, that polio would be even tougher to eradicate than smallpox, which Henderson has said was eradicated “just barely,” with a lot of luck. With smallpox, there was no question who was infected, as everyone developed a telltale rash. Polio, by contrast, circulates “invisibly,” causing paralysis in just one in every 100 to 200 people infected. Polio is caused by an enterovirus that replicates in the gut before sometimes invading the nervous system; it is excreted in the stool and predominantly spread by fecal-oral contamination.

And although the Sabin OPV adopted for the mass campaign proved very effective—it contains a live, attenuated virus that is also excreted in stool and thus confers immunity on people not directly vaccinated—it has decided drawbacks. The smallpox vaccine used in the Sabin vaccine can, in rare instances, regain its ability to circulate and trigger an outbreak. Scientists also discovered by chance that some immune-compromised people can shed virus for years—without showing any symptoms—and that the virus can be extremely virulent. “One man in England excreted virus for 20 years,” says Henderson. Given those dangers, the global campaign advocates that OPV use be discontinued when and if transmission of the wild virus is halted.

Still, it proved relatively easy to stamp out the disease in the United States and other countries with good hygiene and good health care systems. Developing nations were tougher, as the virus thrives in crowded, unsanitary environments; it is excreted in the stool and predominantly spread by fecal-oral contamination. It was clear that the Sabin vaccine wouldn’t even be tough enough to eradicate the virus in Pakistan, Afghanistan, and India. The polio-eradication team now thinks a sequential strategy, using new “monovalent” vaccines targeted against specific serotypes (Science, 28 October 2005, p. 625), might do the trick. “We want to get rid of type 1 first, then type 3,” explains Heymann.

Meltdown in Nigeria

Social and political problems are, however, overwhelming the campaign’s scientific strategy, the skeptics point out. Take the case of Nigeria, the most populous country in Africa, and one with an abysmal health care system. (Only about 13% of Nigerian children are routinely vaccinated against childhood diseases.)

In mid-2003, amid allegations that the polio vaccine was contaminated with the AIDS virus or tainted with hormones designed to sterilize Muslim girls, several states in the northern part of the country halted polio vaccination. The virus, which was already circulating in the region, found fertile ground in the growing number of unimmunized children. By the end of 2004, the number of known cases had doubled to about 800, and the virus quickly spread across Nigeria’s porous borders, taking root wherever it encountered a susceptible population (see map, left).

Although Nigeria resumed vaccination about a year later, after intense lobbying and repeated tests to confirm the vaccine’s safety, the virus still rages out of control. Nigeria poses any outbreak, the reasoning went, countries could boost immunity enough to knock out the virus. The last indigenous case in the Americas occurred 1991. Next was the Western Pacific region, where Arita led the effort, which interrupted transmission in 1997, followed by Europe in 1999.

In the process, almost inadvertently, the campaign knocked out one of the three serotypes of wild poliovirus—type 2—which has not been seen since 1999. “That is a big achievement,” says Eckard Wimmer, a virologist at Stony Brook University in New York. Since then, circulation of type 3 has also been considerably curtailed. It is now confined to small areas of four countries, albeit tough ones, given their crowding and poverty: India, Pakistan, Afghanistan, and Nigeria. The polio-eradication team now thinks a sequential strategy, using new “monovalent” vaccines targeted against specific serotypes (Science, 28 October 2005, p. 625), might do the trick. “We want to get rid of type 1 first, then type 3,” explains Heymann.

Stepping up. The number of polio cases dropped from 350,000 in 1988 to a low of about 500 in 2001. But a 2002 outbreak in India, followed by a disastrous setback in Nigeria in 2003–04, has sent cases climbing.
a “grave threat” to the world, says Heymann. Recent analyses suggest that in five northern states, the immunization campaigns are missing more than 40% of children, and incidence is four times higher than at the same time last year. “With such high levels of transmission, … an additional 12 to 18 months of intensive activities may be required to interrupt polio,” a 1 May update from the eradication campaign warned.

Outside Nigeria, the major problem is not so much opposition, although vaccinators still encounter it, as access. “In the Congo, between one-third and one-half [of the country] is just not accessible. You have roaming soldiers, lots of fighting in the eastern third, and it’s a huge area,” says Henderson. “Similarly, for Côte d’Ivoire, Angola, Afghanistan near Kandahar, … it is not possible to work there.”

“Security is a big issue,” concedes Heymann. Although the number of reported cases there is low, poliovirus remains entrenched in a corridor between Pakistan and Afghanistan. “The virus keeps going back and forth” between the two countries, notes Heymann, not far from where U.S. forces continue to hunt for Osama bin Laden. “Our external monitors can’t get in.”

Another “great risk” is Somalia, where the virus resurfaced around Mogadishu in July 2005. According to genetic sleuths at the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, one of the partner agencies in the campaign along with UNICEF and Rotary International, the virus came to Somalia from Nigeria, by way of Yemen.

Meanwhile, experience in India is suggesting that in some circumstances the virus can survive even saturation campaigns. Vaccination coverage in India has never been higher, says Heymann, who notes that the country is “pounding it,” conducting nine huge campaigns last year and three already this year, to the tune of $120 million. And for the past year, vaccinators have been supplementing the standard trivalent OPV with monovalent vaccine against type 1 and, more recently, type 3.

But still, cases are being reported in Uttar Pradesh and Bihar, areas of wrenching poverty. Monitoring has confirmed that vaccinators are reaching most children; many are getting six or seven doses of vaccine a year. Epidemiologists suspect that one reason the vaccine isn’t working is that the children are infected with other entroviruses that compete with the vaccine in the gut. And because many children have chronic diarrhea, the vaccine simply doesn’t stay in the body long enough to provide sufficient immunity.

“Some pockets [of transmission] are damn near impossible,” says Ellie Ehrenfeld, a polio expert at the U.S. National Institutes of Health in Bethesda, Maryland, who also advises WHO on its program. “We really don’t understand why mop-ups don’t knock out the virus in these areas.”

Meeting in Delhi in early May, India’s expert advisory group decided to pound the virus even harder with monthly vaccination campaigns in the worst-afflicted parts of Uttar Pradesh and Bihar. Health workers in Uttar Pradesh will also test the feasibility of delivering a dose of OPV to all newborns in the most resilient areas of transmission within 72 hours of birth—before they become infected with competing viruses—to see whether that boosts seroconversion rates.

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**Redefining success**

In light of these setbacks, as well as disconcerting evidence that the virus can circulate undetected even longer than people feared, prospects for stopping transmission seem grim indeed, say the skeptics. Henderson notes that last year in Sudan, surveillance turned up a strain that had been circulating silently for 5 years—while the country was labeled “polio-free.” No one is ready to say emphatically that eradication is impossible, but Arita and his colleagues write that the goal is “unlikely to be achieved.”

“I have no way to predict what will happen in the next 5 years, but I don’t think polio will disappear,” says Wimmer.

Ehrenfeld has become increasingly worried in the past few years but says she is not ready to abandon all hope. “At what point do you say we are going to give up on polio? I don’t know,” she asks. “Maybe these problems can be solved,” she adds, noting that there was a “fair amount of progress this past year. … But it would take a very long time, much longer than anyone now expects. … And the world is tired.”

And since the 2000 deadline has passed, costs have skyrocketed. It’s “mind-boggling” what these massive mop-ups are costing, Ehrenfeld says. The global initiative spent almost $700 million in 2005, nearly double what it spent in 2000, and up from $600 million in 2004. One reason the world bought into the huge eradication program in the first place was the promise of money to be saved by stopping vaccination, Ehrenfeld notes—a prospect that looks increasingly unlikely. Several of the skeptics suggest that some of the vast amounts of money and energy going toward wiping out every last case of polio might be better spent increasing routine immunization against all vaccine-preventable diseases.

Unfortunately, says Chumakov, there seems to be no inclination among the program leadership to reassess whether an eradication campaign still makes sense. They “press on as if nothing had happened, as if it were 1988,” says Chumakov, who calls them “captive of their own advertising. … Every year is the final one. This can’t continue forever.” He adds that the program should be proud of what it has achieved, and the world should “declare victory now.”

In his Policy Forum in this issue, Arita urges that the reassessment begin. “The time has come for the global strategy for polio to be shifted from eradication to effective control,” he writes. Henderson agrees. “Let’s create a program to keep it [polio] under moderate control and say that is the best we can do.”

The experts differ, however, on what, exactly, such a control strategy would consist of.
A Cure for the Common T

A new journal aims to alleviate bias in clinical trials reporting, but some question whether it’s the remedy the field needs.

On the excitement spectrum, results from the LOTIS trial rank right alongside “New soil fungus identified.” In the study, a Dutch team takes 402 85-year-olds and gives half access to an occupational therapist, who teaches them how to use walkers and apply for household help. The point is to see whether such interventions slow the onset of age-related disabilities. They do not.

Ordinarily, a study with negative results like this wouldn’t see the light of day in a medical journal—at least not a top-tier one. But the Public Library of Science (PLoS) aims to be different. It’s using the LOTIS study to launch its new journal, PLoS Clinical Trials, which begins publishing on 19 May.

The journal’s credo is simple: Disappointing results can still be good news. Its editors have explicitly stated that all clinical trials submitted—regardless of outcome or significance—will be published, as long as they are methodologically sound. The policy takes aim at a pervasive problem in the clinical trials literature: a heavy skew toward studies with positive outcomes. Some say there’s a “black hole” where studies with negative or ambiguous outcomes should be.

This bias can cost lives. In a particularly lethal example, a 1980 clinical trial that indicated that a prophylactic heart attack drug did more harm than good went unpublished because the drug was abandoned. Thirteen years later, the researchers involved in the trial published the study to illustrate the warning it might have provided. Estimates suggest that—in the intervening years—hundreds of thousands of people may have died prematurely from effects associated with this class of drugs, known as antiarrhythmics. More recently, industry-sponsored trials of Paxil and Vioxx have also highlighted the dangers of not reporting negative results (Science, 14 January 2005, p. 196).

“Science has been letting the public down very badly by not getting to grips with this problem,” says Iain Chalmers, a clinical trials expert and editor of the James Lind Library in Oxford, U.K. “PLoS Clinical Trials is sending a message that it won’t contribute to this bias.”

Still, Chalmers and others wonder how effective such “catch-all” journals can be—especially given that much of the bias seems to be coming from the authors. And some worry that flooding the literature with negative or ambiguous studies could itself do more harm than good.

Leveling the field

The PLoS Clinical Trials philosophy is hardly unique. Several medical journals, including The New England Journal of Medicine

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