Hot spot: the Dominican Republic recently played host to an outbreak of polio caused by rogue viruses from the oral polio vaccine.

Polio's last stand

Does an outbreak of poliomyelitis in the Caribbean caused by a mutated vaccine mean that plans to complete the disease's eradication must be reworked? Tom Clarke considers the evidence.

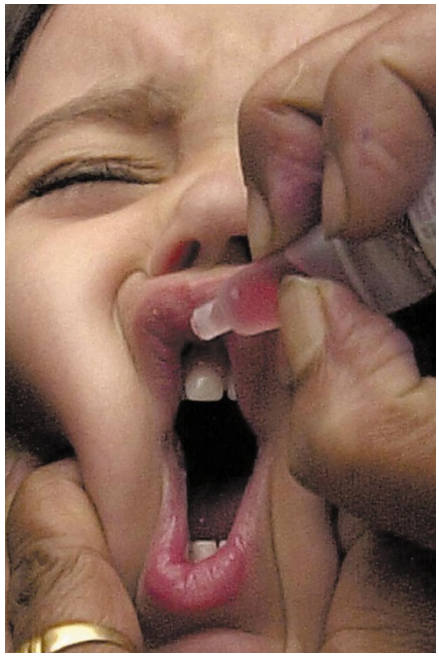
Initially, pesticide poisoning was the suspected cause. But epidemiologists investigating reports last summer that children in the Constanza region of the Dominican Republic were suffering from a mysterious paralysis discovered something a little more sinister. The researchers, from the Pan American Health Organization (PAHO), found that the children's lifeless limbs bore all the hallmarks of polio — a disease that the PAHO had certified as being eradicated from the Americas in 1994.

If the epidemiologists were surprised at polio's apparent return to the Caribbean, it was nothing compared with what was to follow. In late October, laboratory analysis confirmed that the virus infecting the Dominican children was polio, but it was not a wild strain. Instead, it was a mutant form of a live virus from the oral polio vaccine (OPV), used to stamp out the wild strains in the first place[1]. This virus, deliberately weakened for use in the vaccine, had regained the ability to cause an outbreak of disease — something never previously seen in almost four decades of field experience.

This unexpected discovery is causing soul-searching among public-health officials working towards the global eradication of polio. In the same month that the Caribbean polio cases were confirmed, the World Health Organization (WHO) had declared the entire western hemisphere free of wild poliovirus. The OPV's unquestioned success had allowed the WHO to begin planning its polio 'end-game' — the final stage in its global polio eradication initiative.

The idea was carefully to withdraw OPV from use. Once the weakened viruses in the vaccine died out, poliomyelitis would join smallpox on the roster of conquered infectious diseases. But if the viruses from the OPV circulating in the environment can revert to a disease-causing form, this strategy might be dangerous. Indeed, some experts are now wondering whether it will be necessary to use another vaccine, incapable of such reversion, to eradicate the OPV viruses.

In the 1960s, when doctors first began dropping the OPV into the mouths of children, they knew that a vaccine made from live, weakened polioviruses could survive in the environment and spread from person to person. Indeed, this attribute is one reason why it has been so effective. Children given



AFP

Into the mouths of babes: the oral polio vaccine has been key in the fight to eradicate the disease.

the OPV continue to excrete the vaccine's viruses into the environment for some time after they are vaccinated. By infecting people who are later exposed to these excreted viruses, the vaccine confers some immunity to individuals missed by vaccination efforts — a real benefit in developing countries, where vaccination coverage can be poor.

Mutant manoeuvres

Cases of polio caused by the vaccine are not unknown. About one in every 750,000 people vaccinated with the OPV becomes ill — mostly people with weakened immune systems. Virologists also know that, under selective pressure in the harsh environment of the gut, viruses in the OPV can mutate into more virulent strains[2]. But in nearly 40 years of experience, these excreted mutant viruses had never been shown to start an outbreak of polio.

At the latest count, seven cases of vaccine-derived polio have been confirmed in the Caribbean — six in the Dominican Republic and one in neighbouring Haiti. An eighth case, from the Dominican Republic, is awaiting laboratory confirmation at the US Centers for Disease Control and Prevention (CDC) in

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Atlanta. After analysing the gene sequences of the viruses found in the victims, PAHO epidemiologists are certain that all but one of the cases in the Dominican Republic are epidemiologically linked. This means that not only has one of the OPV viruses become virulent, but that it has recovered the ability to spread.

This disturbing outbreak is a dark cloud on an otherwise bright horizon. Since the WHO's global polio eradication initiative was launched in 1988, the number of cases of polio worldwide has fallen by over 99% — from 350,000 in that year to about 2,000 last year. The WHO officially declares a region polio-free when no cases of polio caused by wild virus strains have been recorded for three years. The Western Pacific joined the Americas in being certified polio-free in October 2000, completing the disease's eradication from the western hemisphere. The WHO European region, which includes the former Soviet Union, has not seen a new case of polio since the end of 1998. And although countries in Africa and Asia still play host to annual epidemics, the WHO expects to rid the world of polio by 2005. "We're very, very close," says Bruce Aylward, who coordinates the eradication initiative from the WHO's headquarters in Geneva.

Triple whammy

The WHO's success with polio is largely attributable to the OPV, developed in the 1950s by Albert Sabin, then at the University of Cincinnati College of Medicine in Ohio. Sabin's OPV replaced Jonas Salk's famous vaccine, which was made using dead poliovirus. Sabin patiently created the OPV by passaging each of the three types of naturally occurring poliovirus through different non-host tissues under various culture conditions. After each passage, he screened the surviving viruses for their ability to cause disease in monkeys. By selecting the weakest strains of each virus and continuing the passaging regime, Sabin managed to produce a live vaccine containing weakened viruses that would confer immunity to all three types of polio.

The OPV stimulates the production of antibodies in the blood, protecting the nervous system from the neurotoxic effects of the virus should infection occur. But because the vaccine is given orally, it also produces a local immune response in the intestine's mucosal membranes, causing the production of both antibodies and T cells, which destroy infected cells. This attacks the virus as soon as it gains an initial foothold in the gut, rapidly shutting down person-to-person transmission of wild polio strains if enough of the population is vaccinated. "In terms of eradicating wild-type polio viruses, there's no question that the OPV works," says David Wood, a polio expert at Britain's National Institute for Biological Standards and Control in Potters Bar, near London.

The potential for OPV viruses to revert to a dangerous form has always been there. But to the encouragement of WHO officials, this reversion did not seem to be happening in the real world. Studies of children in Cuba, who all receive the vaccine at the same time of year, indicated that although the OPV is excreted and circulates in the population, it disappears within three months[3].

Analyses carried out by Roland Sutter, chief of the polio eradication branch at the CDC, suggested that OPV viruses are slow to mutate. In an unpublished study of isolates taken from vaccinated populations across the Americas between 1995 and 1997, Sutter and his colleagues have found that gene sequences from the viruses were 99.5% identical to those from a sample of the OPV straight from the shelf. "The isolates suggested we didn't have a problem," says Sutter.

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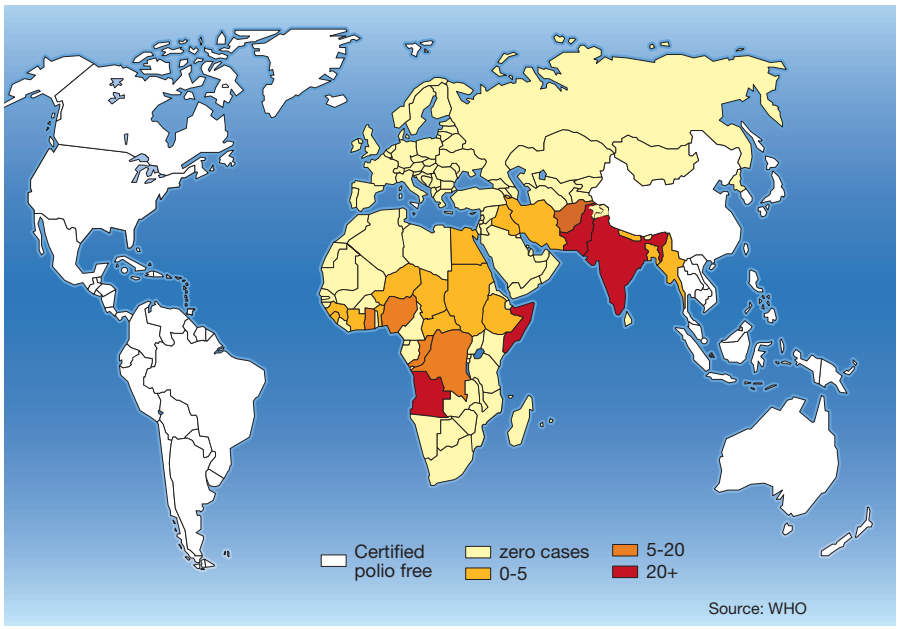
Devastating results: the neurotoxic effects of polio can leave its victims paralysed.

But the OPV-derived polio outbreak in the Caribbean throws that comforting view into question. If problems with the OPV were ever going to emerge, the island of Hispaniola, shared by the Dominican Republic and Haiti, was a likely venue. It is an area where there has been no wild polio for several years, so natural immunity is low. In addition, continued vaccination coverage was poor. In the Constanza region, only about 20% of children in 2000 had received one of the three doses of OPV needed to give adequate immunity. "Essentially it was a totally susceptible population," says Ciro de Quadros of the PAHO, who has led the campaign against polio in the Americas. Unpublished analysis of the gene sequence of the rogue OPV virus carried out by the CDC suggests that it had been replicating for as long as two years — long enough to turn nasty.

Back to the drawing board?

Now the WHO faces some difficult questions in planning its polio eradication end-game. Optimists had hoped that this would comprise a relatively simple — albeit difficult to organize — *coup de grâce*: a coordinated withdrawal of OPV on the same day worldwide. Provided all populations had been adequately vaccinated, the OPV viruses should just disappear from the environment as they have been seen to do in Cuba. Now the WHO cannot be sure that this will happen.



Close to extinction: the incidence of polio caused by the wild virus in 2000 shows that the programme to control the disease is close to success, but the figures do not include vaccine-induced cases.

"Not only does the OPV revert to neurovirulence and paralyse people, but it also looks as if it is really transmissible," says Sutter.

First on the list of priorities is to figure out just how likely another OPV-derived outbreak will be. "My assumption is that this is an unusual event," says Donald Henderson of Johns Hopkins University in Baltimore, who led the WHO's successful effort to eradicate smallpox. "It can't be occurring with great frequency otherwise we would have seen it a long time ago." But polio experts freely admit that, because they did not suspect the OPV in the past, they may have missed previous vaccine-related outbreaks. In fact, a retrospective analysis of isolates from sporadic polio cases in Egypt between 1989 and 1998 indicates that at least some of the cases there may have been due to vaccine-derived polio[4]. This was not noticed at the time because Egypt is still host to wild virus strains.

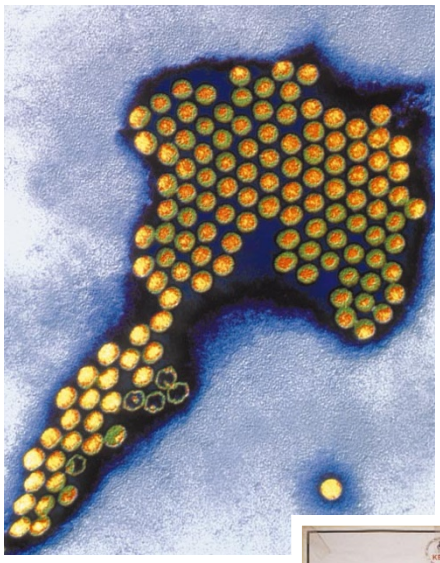
One key step towards determining the likelihood of future vaccine-derived outbreaks is establishing how thin the vaccination coverage must be before the frequency of mutant viruses begins to rise from the low levels seen in the Americas by Sutter. The cases in Hispaniola and Egypt occurred in areas where vaccination coverage was very poor, meaning that a greater number of people with no immunity were exposed to potentially virulent OPV viruses. But how patchy a vaccination effort can be before a crisis occurs is not known.

Gaining a better understanding of the genetic determinants of viral transmissibility will also be important. Although the basis for neurovirulence in polio is fairly well understood — for example, point mutations in the gene for the virus' protein coat alter its ability to paralyse its victims[5] — Wood describes the molecular basis of polio transmission as "one of the key unknowns". If this information could be gleaned, he points out, it would be possible to identify quickly mutants that have the potential to cause outbreaks.

There is also a need to determine factors that might allow the OPV to persist in the environment for longer than anticipated. For instance, recent research has shown that people with severely impaired immune systems can remain host to the OPV viruses for many years — possibly serving as reservoirs once polio has been eradicated[6]. Although initial investigations have found no evidence for HIV/AIDS patients harbouring the OPV viruses, it could be an important factor for polio eradication in countries with high rates of HIV and low polio vaccination coverage[7].

But the problem is that, as the WHO's eradication campaign proceeded, research on polio slipped down the list of biomedical priorities. "The funding agencies are turning round to people and saying 'you should be moving on to something else'," says Wood.

It is too early to tell whether the Caribbean outbreak will lead to renewed funding for polio research. But officials with the WHO and the PAHO argue that Hispaniola provides an excellent arena for answering some of the important questions. "The investigation of this is hugely important," says Aylward. "It will help us figure out how to track the virus epidemiologically and virologically." Indeed, analysis of the RNA sequences of OPV isolates from Hispaniola are already allowing the CDC to track the course of the rogue virus' spread and may help reveal how it recovered its ability to cause disease outbreaks in the first place.



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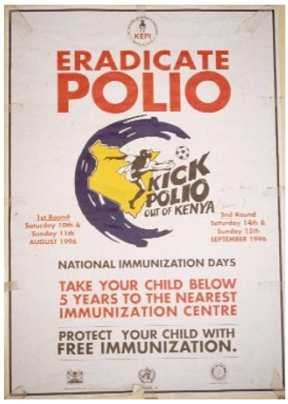

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Wipe out: after a twelve-year campaign, the poliovirus (above) is set to follow smallpox as a conquered infectious agent.

Under observation

Although a thorough evaluation of what went wrong on Hispaniola will yield information crucial to the WHO's polio endgame, other obstacles remain. According to Aylward, surveillance for vaccine-derived polio must be improved. Unlike the disfiguring rash of smallpox, polio's symptoms are tough to spot and must be confirmed in a well-equipped laboratory. This makes it difficult to identify outbreaks in remote parts of the world where there are few trained health workers.

More fundamentally, if it becomes clear that OPV-derived outbreaks are more likely than was thought, another vaccine may be needed to maintain people's immunity to polio while the OPV strains die out. Right now, the only available candidate is the Salk inactivated polio vaccine (IPV). This requires only one dose, confers immunity to all types of polio, and, because it is made from dead virus, cannot cause disease.

But the IPV has some serious drawbacks for use in developing countries. First, it does not trigger mucosal immunity in the gut and so does not stop transmission. Second, it must be injected, meaning that it must be administered by trained health workers, rather than unqualified volunteers. And there is currently no industrial capacity to produce the vaccine on the scale required. "The cost is going to be mind-boggling," says Henderson.

Another solution would be a totally new vaccine. Approaches based on subunits of the virus' protein coat, which work well against many diseases, do not look promising for polio. But it is now possible to use the techniques of genetic engineering to create live vaccines that lack genes for neurovirulence — which should be very unlikely to revert to a virulent form. But new vaccines take time and money to produce, and the WHO opted early in the eradication programme not to develop improved vaccines — a decision described in 1999 by Henderson, writing in the journal *Vaccine*[8], as "an extraordinary act of ignorance". Now, with polio on its way out, few vaccine manufacturers are likely to be interested in bringing a new vaccine to market. "This is going to be at best a vaccine with a very limited lifespan," says Aylward.

The good news is that on Hispaniola tests of all subsequent suspected cases of polio have proved negative — indicating that the brief epidemic is over. The authorities in Haiti and the Dominican Republic are determined not to get caught out again. "Both countries are very worried and are responding very seriously to the situation," says de Quadros. Last month the Dominican Republic held a massive campaign to vaccinate 1.2 million children with the OPV in three days. And earlier this month, Haiti began a similar effort, now being overseen by de Quadros.

But the WHO's polio experts face an anxious future, as they wait for the results of investigations into the Hispaniola outbreak. At best, it may come to be seen as a regrettable case of inadequate vaccination and surveillance, reinforcing the need to follow the WHO's recommended regime. At worst, it may mean that plans for the polio end-game need to be redrawn. "Clearly this is raising a red flag," says Sutter. "Whether it's a small one or a big one is something we need to worry about." ■

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