

# The Pfizer/IDCP Discovery Series

## *Turning Points in Infectious Diseases*

### Smallpox Eradication: A Saga of Triumph and Betrayal

by Donald A. Henderson

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Smallpox became for me a full-time preoccupation in June 1966. At that time, I was summoned to Washington D.C. and advised by Dr. James Watt, then the director of the Public Health Service's Division of International Health, that I was to be assigned forthwith to Geneva, Switzerland, to direct the World Health Organization's (WHO) global smallpox eradication campaign. I politely declined.

I was then working at the Communicable Disease Center (CDC), Atlanta, as chief of the Surveillance Section under Dr. Alex Langmuir, who was the director of the CDC's Epidemiology Branch. My expertise in smallpox was limited. I had seen some 15 cases in Argentina in 1957; a small unit in my section was then studying smallpox vaccine complication rates and a jet injector gun adapted for smallpox vaccination. In November 1957, however, the Agency for International Development (AID) had unexpectedly awarded a large contract to the CDC to undertake a smallpox eradication-measles control program in 18 countries of West and Central Africa [1] AID had been keen about the measles-control initiative; I had argued that smallpox vaccination be added. I was put in charge of the new program. Planning, recruitment, and training were just getting underway. It was AID's first major contract with the CDC, and it was a substantial

one. As I saw it, this was no time for a change in leadership. Besides which, as I pointed out to Dr. Watt, WHO was a complicated and fragmented bureaucracy that was unsuited for managing a global campaign.

Dr. Watt informed me that the Director General had specifically asked that I be assigned as program director and that I had no option but to go. It was agreed, however, that I could return to the CDC after 18 months. In November 1966, we placed most of our household goods in storage, and with three children, a wife, and two cats, I left for what I assumed would be a fairly brief stay. It turned out to be 11 years.


#### GENESIS OF THE SMALLPOX ERADICATION PROGRAM

WHO's first director, Brock Chisholm, had proposed in 1953 that smallpox eradication be undertaken as a major initiative of WHO, a program which would benefit all member countries [2]. It was rejected by the World Health Assembly (WHA) as being unrealistic. In 1958 the subject was raised again, but this time by the then Deputy Minister of Health of the Soviet Union, Dr. Viktor Zhdanov. The Soviet Union had only just returned to active participation in the United Nations, and member states were anxious to be supportive of any constructive initiative that the Soviets might propose. An eradication program was agreed upon with little discussion.

An underlying problem was that in 1955, the WHA, at the urging of the United States, had embarked on a global program for malaria eradication, a far more difficult,

*Infectious Diseases in Clinical Practice*, 1999;8:445-448  
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costly, and complex undertaking than would be required for smallpox. More than one-third of all funds at the disposal of WHO were then being expended for malaria eradication. For an organization whose entire budget was little more than \$30 million, a second campaign posed a serious problem. There were echoes of the confrontational atmosphere of the Cold War with the United States pressing for more resources for malaria eradication and with the Soviet Union, for smallpox eradication.

WHO's Director General was convinced that smallpox eradication was unachievable because, as he understood it, all persons in the world would have to be vaccinated, and he knew that this was impossible because there were natives in the Amazon who hadn't been seen by outsiders in decades. From 1959 to 1966, a WHO smallpox effort based in Geneva with staff assigned to four small countries and an annual total expenditure of approximately \$300,000 was dwarfed by the malaria campaign, which had some 500–600 staff members and a budget of some \$13 million. Little progress was made.

Soviet delegates to the WHA annually argued for a greater effort, but to no avail. In 1965, however, the tide of events turned. First, the United States announced its decision to provide support to West and Central African countries, and second, it was becoming increasingly apparent that malaria eradication was technically impossible. At the 1966 WHA, the United States joined the Soviet Union in pressing for more resources to be given to smallpox eradication. A tumultuous debate followed, but finally a decision was made to support the global program with an annual budget of \$2.4 million. Programs would eventually be required in some 50 countries. Smallpox eradication was launched by a margin of just two votes in a body where decisions were customarily taken by consensus.

As I learned later, the Director General blamed the United States primarily for the WHA's decision to embark on the intensified program. He decided that if he was going to have to implement a program which, as he saw it, was certain to fail and discredit the WHO, he wanted the United States to share the onus of this failure. Thus, he requested that the director of the program be an American. It was not an auspicious beginning for a young, optimistic but internationally inexperienced epidemiologist.

### THE PROGRAM BEGINS: 1967

As the program began, we foresaw a comparatively straightforward two-part strategy for the campaign—mass vaccination and surveillance-containment measures. In principle, this was sound, but it soon became apparent that a number of our assumptions were in error. The first component, a mass vaccination campaign, was intended to reach at least 80% of the population and therefore diminish transmission so that outbreaks could be readily

contained. The target of 80% had no basis in epidemic theory. It was, quite simply, what seemed to be an attainable figure with a well-organized program. In fact, 90% turned out to be closer to the true figure. We had assumed that only a small proportion of the population in endemic countries would have been previously vaccinated. As we were to discover, every country had been performing some vaccinations simply because of the seriousness of the disease, and it was usual to find more than 50% of the population in all countries to be immune either through vaccination or natural disease.

We had assumed that it would be necessary to periodically revaccinate persons of all ages because of the prevalent belief that vaccination immunity waned sharply over a 5–10-year period. However, we soon discovered in endemic areas that vaccine efficacy ratios were 90% or greater at 20 years. Subclinical infections in vaccinated persons served to boost immunity, much as is the case with measles today. Thus, it was possible to focus the mass campaigns on children, a group which was far more accessible than adults, with the objective of ensuring that everyone bore a vaccination scar.

The second part of the strategy was surveillance and containment, as it came to be known. Basically, this consisted of establishing a weekly smallpox reporting system from all health centers and hospitals. When cases were reported from a village, they were to be investigated to trace the source of infection, to discover other cases, and to vaccinate family and neighbor contacts so as to provide a barrier of immunity against further spread. With a continuing epidemiologic analysis of cases, progress could be monitored, resources more effectively deployed, and strategies adjusted. This was a direct outgrowth of the concept of surveillance that Alex Langmuir had developed at the CDC in the 1950s. Although the concept seemed simple and obvious, it proved to be surprisingly difficult to implement. Both country and even WHO staff questioned devoting resources to simply "finding cases and containing outbreaks" when, as they saw it, they could be more productively engaged in vaccinating the unvaccinated.

The program was launched in January 1967. That year, 46 countries reported cases of smallpox, in 31 of which the disease was endemic. It was later possible to estimate that there had been some 10–15 million cases that year and 2 million deaths. A 10-year time target was assigned. Delegates at the WHA reasoned that if a man could be placed on the moon in 10 years, we should expect to eradicate smallpox in 10 years. In fact, we missed this goal, but by only 9 months and 26 days.

### THE SOVIET ROLE

The Soviet delegate to the WHA, the Deputy Minister of Health, initially expressed keen disappointment that a

Russian had not been appointed as director of the program. Given the Soviet Union's advocacy for the program and its pledge to provide some 25 million doses of the vaccine annually, this was a not unreasonable expectation. The vaccine commitment was critical, as this was a quantity far beyond the production capacity of any other country. If the Soviets would not supply it, it was unclear as to who would or could. In meetings with the Deputy Minister, I expressed my concerns that the donations continue. At the 1967 WHA, he took me aside, informed me that his people had checked me out and had decided that I was a serious scientist and not some type of political operative. He pledged his full support and that of his country. Besides, as he pointed out, in a centrally planned economy, once some level of production of a commodity is established, it is difficult to change it. The Soviet Union eventually provided more than 298 million doses of vaccine, nearly two-thirds of all of the vaccine doses received by the WHO. The Soviet Union was to contribute much more than this, however. Dr. Marennikova and her colleagues at the Institute of Virus Preparations in Moscow undertook numerous important scientific studies pertaining to smallpox and the smallpox vaccine; they provided consultation and advice to laboratories in many countries. Her center served, with the CDC, as a principal WHO Collaborating Center to provide confirmatory laboratory diagnosis on specimens from the field. Indeed, throughout some of the most difficult times of the Cold War, there was a generally warm and friendly collaboration between Soviet, American, and other staff working in the program.

### LESSONS FROM THE PROGRAM

The most important of the lesson is the fact that, under the leadership of a United Nations organization, a worldwide effort could be successfully conducted, which no single country or group of countries could have achieved. The fact that the smallpox program dealt a fatal blow to the most serious of all pestilential diseases made the achievement all that more meaningful. It provided courage to WHO and member countries to undertake more ambitious schemes. The success of the smallpox program led us to propose expanding the smallpox program to embrace DPT, measles, polio, and BCG vaccines as well, a program later called the "Expanded Program on Immunization" (EPI). It is now reaching some 80% of the world's children and has been the departure point for the global polio eradication effort.

There was much that we learned which is broadly applicable to other public health programs in terms of strategic planning, implementation, and monitoring, and this has been extensively documented [2,3]. I focus on only three points as having special relevance: staffing, communication, and research.

The quality of a program is primarily contingent on the quality of its staff, and this was clearly apparent with smallpox eradication. Eventually, some 812 international staff from 73 countries were to serve in the program, although never more than 100 at any given time. Many served for periods of only 3–6 months; others served for the duration of the effort. An early decision was to ignore as a qualification any past experience with smallpox and to focus on recruiting those with a high degree of motivation and basic intelligence who were prepared to work in the field. Not surprisingly, they tended to be young, often idealistic, and of a somewhat different mold than the long-time international civil servants. During lunch one day at the WHO, a thoroughly scruffy, long-haired individual wearing an Indian dhoti plodded across the room as a colleague turned to me and said, "One of yours, perhaps?" I studied him carefully and quietly answered, "One of ours. In fact, one of our best!" Many did not fit in particularly well at conventional embassy cocktail parties.

For those who worked in the field, one of the most frustrating of all experiences was the problem of communication with headquarters. Unanswered correspondence, telephone calls which were not returned, and queries which were not resolved were all too common. To keep communications open, we followed the policy of endeavoring to respond to all communications within a matter of 48 hours, even if meant saying that we had no answer and would have to get back to the correspondent. Every 3 weeks, we sent a special summary report on the program and copies of relevant scientific papers to all WHO staff and national program directors to facilitate the rapid transfer of experience. A stockpile of vaccine, kept in storage in Geneva, could be dispatched with bifurcated (vaccination) needles within 48 hours wherever needed.

Research played a critical role. It led to an entirely new vaccination instrument that found worldwide acceptance, to more potent and safer vaccines, and to frequent changes in the program's strategy and tactics as we learned from practical experience how smallpox actually behaved and which approaches did and did not work. Indeed, the program would never have succeeded without the continuing flow of new ideas and approaches that continuously altered concepts and strategies. In contrast to this was the failing malaria eradication program, which at its inception declared, "We have the tools; we know what to do; all that is needed is to administer the program in a competent manner." Program directors effectively terminated research efforts, only later to have to resurrect some sort of effort as both drug and insecticide resistance developed. By then it was too late. As we had begun the smallpox program, I was similarly told, "You don't need research; you have a good vaccine; the only problem is administering it to everyone." They could not have been more wrong.

## THE ULTIMATE BETRAYAL

As the program concluded, our Soviet colleagues expressed great pride in the achievement. Rightly, they took credit for initially launching the program, for providing the hundreds of millions of doses of vaccine that were so critically needed, and for producing a rich array of significant research findings, including the first isolation of monkeypox virus from a human.

With the declaration on May 8th that smallpox had been eradicated, I believed that a chapter in my life had closed. However, there was another Soviet agenda of which we were innocent until the mid-1990s and of which I am persuaded our Russian colleagues were innocent.

After the eradication, the WHO Committee on Orthopoxviruses was created to advise on measures to be taken in the posteradication era. These included measures to limit the number of centers in which the smallpox virus was kept. A worldwide inventory of all laboratories that had or might have had the virus was prepared, and then one by one, country by country, laboratories were persuaded to destroy their stocks of smallpox virus or to transfer them to a WHO reference laboratory. Eventually, known stocks of the virus were limited to just two laboratories: the Centers for Disease Control and Prevention in Atlanta, Georgia, and the Institute for Virus Preparations in Moscow. They were regularly inspected by WHO consultants to provide assurance that proper security precautions were being followed to ensure that the virus would not escape. Escape of the virus seemed unlikely, especially in view of the fact that from the early 1980s, essentially no research using the smallpox virus was known to have been performed, and none was contemplated.

In 1986, in response to requests from many member governments of WHO, the committee took up the question of whether the smallpox virus stocks should be destroyed. After careful review, the committee agreed in principle that the virus should be destroyed, but proposed that first, various steps should be taken to preserve as much of the genetic information as possible. Thus, libraries of cloned fragments of representative strains were prepared and later sequenced. A number of scientific societies were formally consulted as to their views on destruction; all concurred. Thus, in 1994, the committee proposed in a formal report to the WHA that the virus be destroyed. Vaccinia, the related smallpox vaccine virus, would be retained, of course.

It was about this time that the deputy director of the Soviet Union's bioweapons program defected. He reported that beginning in the early 1980s, the Soviet Union had set out to weaponize the smallpox virus and had successfully done so [4]. A manufacturing facility capable of pro-

ducing 80-100 tons of virus per year had been established under the auspices of the military, a facility which, even today, is closed to visitors. Meanwhile, the virus stocks at the Moscow center were transferred to a laboratory called VECTOR in Novosibirsk, Siberia, one of the principal bioweapons research and development facilities and the one which had weaponized the smallpox virus. These dismaying revelations came as Russia was experiencing serious economic problems and when many scientists were leaving their laboratories for employment in other countries. It raised the question of whether other countries might now acquire the technology as well as the weapons themselves. Thus, the stage has been set for the possible release of the most dangerous of all biological weapons and, potentially, a global catastrophe in a now-unvaccinated world in which few stocks of vaccine remain and in which there are today no remaining vaccine production facilities.

If ever there was a time to take all possible measures to diminish the risk of a smallpox release, this would seem to be it. However, expectations that the 1999 WHA would concur with a 1996 resolution to destroy smallpox virus stocks were thwarted by arguments advanced by the United States and by Russia. Both countries completely reversed long-held official positions which advocated destruction at the earliest possible time. They intimated, in fact, that they would retain their virus stocks this June irrespective of what the WHA requested. They argued that the virus was urgently needed for research purposes, specifically for the development of antiviral drugs and new vaccines. It was a curious argument, given the fact that essentially no research of this type had been conducted by either country for 20 years or more.

Whatever the merits of the arguments for special research initiatives—and there are many who consider the proposed initiatives as unworkable, impracticable, and scientifically doubtful—the virus will now be kept at least until 2002. An opportunity to limit the likelihood of any further dissemination of the smallpox virus has been lost. Meanwhile, a concerned world which ceased vaccination 20 years ago watches anxiously, knowing that the limited stocks of the vaccine now available will be unlikely to stop even a modest epidemic should someone choose to release the virus.

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