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RESEARCH AND SMALLPOX ERADICATION

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In 1966, just 25 years ago, the World Health Assembly voted to commit \$2.4 million for a program of smallpox eradication. The program began in January 1967. Hope was expressed that the eradication goal could be achieved in 10 years. However, most delegates were skeptical of success at all and their doubts were understandable. The disease was widely prevalent over four continents. Moreover, it was fact that no disease had ever before been eradicated. Many believed that, through evolution, man and his microbial environment were so related and interdependent that eradication of an organism could not be achieved, however many resources were made available. Moreover, as was pointed out, the smallpox vaccine had been available for 160 years since Edward Jenner's time. What possibly could be done with an investment, on average, of an additional \$50,000 per country that was not already being done?

Smallpox at that time was then endemic in 34 countries with a population of more than one billion persons. Many of the countries were among the world's poorest and most densely populated. In all, there were between 10 and 15 million cases each year of whom 2 to 2.5 million died. Every country conducted vaccination programs because of the fear of imported cases. In the U.S., smallpox vaccination was required for school entry. To imagine that all countries which were endemic for smallpox could work cooperatively and effectively together to achieve any common objective seemed most unlikely. Even with universal goodwill, the problems of war and civil strife, as well as natural disasters would inevitably have to be overcome.

As we began the program, we made perhaps the most critical policy decision we were to make. We decided that we had to have a research program. Almost no one agreed. It was pointed out that we had available a highly protective, thermostable vaccine, that smallpox had been extensively studied in the field and that there was simply nothing that could be learned or developed which could help the program. As they saw it, our problem was administrative and operational -- to vaccinate one billion people and, "Voila," the task would be finished.

In candor, I was not certain then what the research agenda would be. It seemed to me that we had to be certain there was no naturally occurring animal reservoir but with no knowledge of what we might find when we went to the field, I could not then identify what else we needed to know.

Why then a research program? Only 12 years before, a global malaria eradication scheme had been launched when it was discovered that residual DDT, sprayed on walls, served to kill mosquitoes and so interrupt transmission. The decision had been made then, in 1955, to cease support for research. It was decided that since the tools were in hand -- it was simply an administrative task to employ them well. Malariologists vanished. Ten years later with insecticide resistance emerging and programs foundering, new answers and new approaches were needed but the research base was gone. As the great Ian Macgregor said: "We didn't eradicate malaria but we did eradicate the malariologists." This was an important lesson to me.

For smallpox we established a budget of \$40,000 (yes, you heard the number correctly) which permitted us to make a few grants of \$5,000 to \$10,000 each, to support a small field team and to convene a meeting of investigators once every two years.

It was a modest effort by any standards but by the time the program was over, our scientific understanding of smallpox and smallpox control had radically changed. All vaccine strains in use were evaluated -- and there were many -- and the best one supplied to production laboratories; a new device for vaccination -- the bifurcated needle -- was field tested and was soon universally in use; new methods for vaccine production and vaccine assay were tested and introduced; vaccine protection, widely "known" to extend only 3-5 years, was found to extend for 20 years or more. Thus, we were able to stop revaccinating so many and to concentrate on primary vaccination. The prevalent wisdom when we began was that the virus spread rapidly, sometimes by aerosol; as we discovered, the virus almost never spread by aerosol and that it spread slowly -- one infected person seldom infecting more than 2 to 5 others. And, finally, in the course of searching for a reservoir, we identified a new human disease, called monkeypox, with similar clinical findings to smallpox but with little capacity to spread from human to human. There were many other observations -- in part because we actively encouraged field staff to explore all manner of questions. As these were answered, the strategy and tactics of the program changed. About the sixth year of the program, I was asked to revise the chapter on smallpox for Cecil's Textbook of Medicine. Thinking this could be quickly done, I accepted and set aside a weekend only to discover that the entire chapter had to be totally rewritten, so much of what was established knowledge was simply wrong.

We began the program with a two-fold strategy. First was to vaccinate 80% of the population in all endemic countries. The second was to establish a comprehensive reporting system which would detect cases of smallpox when they occurred and to investigate and to contain outbreaks by isolation of the patient and vaccination of his contacts.

The strategy was quite different from that which had been employed before 1967. Until 1967, progress in smallpox control had been measured in terms of millions of persons vaccinated. Nothing had been done to improve the reporting of cases. Incredible but true, no effort was being made to determine whether or not the vaccination programs were having any effect on the occurrence of disease.

We estimated a need for more than 250 million doses of vaccine each year. If purchased, this would have exceeded our entire budget. And so, we sought donations while, at the same time, we worked with developing countries to help them produce their own vaccine. A Canadian and Dutch laboratory agreed to test batches of vaccine intended for use. As we later discovered, this proved to be the first international quality control system ever to be established for a biological product, but all countries cooperated. Initially, most vaccine was donated by the U.S.S.R. and the U.S.A. but within six years, 80% of the vaccine was able to be produced in the developing countries themselves.

In 1968, we field tested a remarkable new invention -- the bifurcated needle. The needle was dipped into the vaccine. By capillarity, vaccine was held between the tines and 15 rapid strokes implanted sufficient vaccine virus to assure successful vaccination. Vaccinators could be trained in 10 to 15 minutes. The needles were inexpensive and could be sterilized and reused many times. With a bifurcated needle, a 25 dose vial of vaccine was enough to vaccinate 100 persons.

During vaccination campaigns, we organized assessment teams to visit a sample of the areas which had been vaccinated to verify that at least 80% had been vaccinated and that the vaccinations were successful. This approach was a revolutionary idea for many countries and often accepted reluctantly. National health officials thought it wasteful to assign valuable staff only to check the work of others. This, of course, represented nothing more nor less than "quality control," much as is practiced in industry. Wherever assessment was implemented, the performance of the vaccination teams improved.

The most important strategy in the campaign, however, was the addition of surveillance for cases. Our target was "0" cases of smallpox. To measure progress, we had to know how many cases were occurring. By continually determining which groups of individuals were most afflicted with smallpox, we were able to alter our strategy to assure vaccination of those with the highest rates of infection and to stop outbreaks by isolating patients and vaccinating their contacts. Roving teams visited health centers and hospitals to ask that they report cases each week. They visited schools and markets to show a WHO Recognition Card and to ask if anyone had seen cases of smallpox. When cases were reported, the teams promptly investigated them and contained the outbreaks. In Africa and South American, we found that a surveillance team of only two to three persons could control smallpox in an area inhabited by as many as five million persons.

Between 1967 and 1969, programs began in most infected countries and by 1971, all were in operation. Progress in most of Africa and the Americas was rapid. By 1970, the number of endemic countries had decreased from 33 to 17. By 1973, smallpox was confined to the Indian subcontinent and to Ethiopia whose program had just begun.

The Indian subcontinent, however, proved to be a formidable challenge. Efforts such as we had made in Africa had little impact. In the endemic Asian areas, nearly 700 million people lived in the most densely populated regions on earth. They traveled frequently and for long distances by trains and buses. Many smallpox patients, infected in cities, returned to their villages to recover or to die. The disease spread rapidly and widely. There were many then who knowingly assured us that in Asia, the traditional, ancient home of smallpox, eradication could never be achieved. More than once we wondered if they might not be right.

During the summer of 1973, a special campaign was planned. All health workers, during one week each month, would visit every village in India -- later every house -- in search of cases. When cases were discovered, special teams moved in to contain the

outbreaks. The logistics were formidable -- 120,000 workers were assigned to visit over 100 million households. Assessment teams visited a 10% sample to verify the work. Additional teams searched for cases at markets and schools. More than 8 tons of forms were needed for each search, and hundreds of vehicles, as well as tens of thousands of bicycles, boats and rickshaws.

The first search took place in October 1973. The results were appalling. In the northern Indian State of Uttar Pradesh, whose population was 100,000,000 persons, two years of intensive work had already been devoted to improve the reporting system. Several hundred cases were then being reported each week. During the first one-week search, nearly 7,000 unreported cases were found. However, with the search program, more outbreaks were found, and more rapidly. Once found, they could be contained. The quality of the searches steadily improved. More rigid control measures were used. House guards were posted at each infected house on a 24-hour schedule to prevent patients from leaving, and to vaccinate all visitors. As cases decreased, a reward was offered to the villager who reported each new case. Techniques employed in India were soon adapted for use in Pakistan, Nepal and Bangladesh. By the summer of 1974, we knew that eradication in Asia could be achieved. In October 1974, the last case occurred in Pakistan; in May 1975, in Nepal; a month later in India; and, finally, in October 1975, in Bangladesh.

Only Ethiopia remained to be conquered. Ethiopia, however, was a challenge unto itself. It was a country of 25 million people scattered across desert and highland plateau in an area equivalent to all U.S. states on the Eastern seaboard. It is a country where half the population lived more than a day's walk from any accessible road. Health staff were few; for smallpox we had less than 100 for the entire country. Insurrection and fighting were widespread. Our smallpox staff were periodically kidnapped and fired upon; one of our helicopters was destroyed by a hand grenade and others damaged by bullets. In 1971, during the program's first year, 26,000 cases were recorded, probably one-tenth the actual number. Gradually an intrepid team of national and volunteer staff eliminated the disease from the northern highland areas. Smallpox remained only among nomads of the vast southern Ogaden desert. Here, it proved difficult even to find the nomads, who often traveled 20 or 30 miles in a night. To solve that problem, we hired and trained the nomads themselves as vaccinators and searchers. In August 1976, the last outbreak was contained.

There was, however, one last chapter. Somali guerrillas, then fighting Ethiopian forces, brought the disease back to Somalia. The first cases were reported in September 1976. For yet another year a smallpox campaign was waged throughout Somalia. But, at last, the final chains of transmission were severed. Ali Maalin, a cook from Merka, Somalia, proved to be the last case in a continuing chain of infection extending back at least 3,000 years. The 10-year time target had been missed, but only by 9 months and 26 days.

Variola virus is now confined to glass vials in just two laboratories.

The possibility that there might be a natural reservoir of the virus had been a continuing concern to us. Wide-ranging studies were undertaken to try to discover such a reservoir. None was found. The best evidence came from epidemiological observations. All smallpox outbreaks which were detected in smallpox-free areas were able to be traced to other known human cases. If there were an animal reservoir or if the virus could persist in nature, what would appear to be "spontaneous" outbreaks should have been discovered. None were. Thus, barring improbable circumstances, a human case of smallpox will never again be seen.

The savings to be realized because of the cessation of vaccination and quarantine measures are estimated to be two billion dollars each year. In comparison, international assistance to the program amounted to an average of only \$8 million per year.

The program illustrated how inexpensive and effective prevention could be. It did not require large numbers. At WHO headquarters, we never had more than six professionals and never more than 100 professional staff in the field at any given time. Smallpox eradication was achieved primarily by national health staff. WHO built on the smallpox program to launch a global Program of Immunization to protect the 100 million newborns each year against six major infectious diseases. Today, 80% of all children receive vaccines against diphtheria, pertussis, tetanus, poliomyelitis and measles -- a marked change from 1975 when only 2% did. A global polio eradication program is in progress and, as yet little known to Americans, is the fact that nearly 8 months have now elapsed since the last case was detected in the whole of the Western Hemisphere.

Smallpox eradication may now seem to have been comparatively straightforward but there were innumerable times in which the program balanced on a knife edge between success and disaster, decided by an unexpected change of government, a cessation of hostilities, or an heroic exhibition of dedication and courage by field staff.

A small but important step has been taken in a long and difficult journey toward better health but in taking that step, we have renewed confidence that other successes in prevention and public health are possible -- provided that we assure that, as with smallpox, research is a foundation stone of that effort.