Lessons Learned from the Smallpox Experience

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On 8 May 1980, the 33rd World Health Assembly, in a specially convened plenary session, passed unanimously a resolution which:

- "Declares solemnly that the world and all its peoples have won freedom from smallpox ...."

and recommended that:

- "Smallpox vaccination should be discontinued in every country, except for investigators at special risk"
- "No country should now require vaccination certificates from international travelers."

Five years have ~~now~~ elapsed since October, 1977, when a 23-year-old hospital cook in Merka, Somalia, became ill with smallpox. He represented the last known case in the continuing human-to-human chain of infection extending back perhaps 10,000 years. ~~Two further cases occurred in 1978 as a result of a tragic laboratory accident.~~ So concluded a chapter in medical history - the first successful deliberate extinction of a species - smallpox.

I welcome the opportunity today to reflect upon the program and on some of the lessons learned from this experience. Before doing so, I believe it would be helpful to recall briefly for you the history of smallpox and its impact on history and to recapitulate briefly the highlights of the eradication program.

Smallpox had no animal reservoir and, in man, there was no human carrier state. Therefore the virus, to persist, had to infect person after person in a continuing chain of transmission. Its origins are thus assumed to date back no more than 10,000 years, to the time of the first agricultural settlements - to a time where there was a sufficient concentration of population to permit the chain of infection to be sustained. Most likely it began as a mutant of one of the large family of animal poxviruses. The earliest definitive evidence of its presence dates back more than 3,000 years. The mummy of Ramses V, who died in 1160 B.C. bears unmistakable, characteristic lesions of smallpox.

Throughout history, few diseases have proved so devastating. Twenty to forty percent of those who developed smallpox died. Most who survived were permanently scarred and some were blind. The disease could spread in any climate - in any area. Like measles, essentially everyone eventually contracted the disease. There was [illegible] - no treatment. So feared was smallpox that deities consecrated to this disease are known in many cultures. Throughout India, there were temples to Shitala mata. In other cultures, there were other deities such as Shapona in Western Africa.

From India, or perhaps Egypt, smallpox spread across Asia and Africa, becoming endemic over an ever-wider area, as population densities increased.

In the Middle Ages, it became established in increasingly populated Europe. In the 17th century Lord Macauley wrote:[8] "That disease was then the most terrible of the ministers of death ... smallpox was always present, filling the churchyard with corpses ... and making the eyes and cheeks of the betrothed maiden objects of horror to the lover." Nor was royalty exempt. During the 18th century alone, smallpox killed five reigning monarchs, ended the Royal House of Stuart, and shifted the Hapsburg line of succession four times in as many generations.

In the New World, smallpox is estimated to have killed 5 million Incan and Aztec Indians, precipatating the collapse of both civilizations. ~~Of North America, George Catlin wrote:[9] "I would venture the assertion ... that of the numerous tribes ... each one had had this exotic disease (smallpox) in their turn, and in a few months have lost one-half or more of their numbers."~~ Smallpox thus played an important role in colonizing the Americas.

9 In 1796, ~~Just 14 years after the founding of the Harvard Medical School~~, Edward Jenner demonstrated that an infection induced with cowpox virus could prevent smallpox. This was hailed as one of history's most important advances. ~~Indeed, in 1803, only 5 years after the event, Harvard conferred on Jenner his first honorary degree.~~ Folklore of the

time attributed the celebrated unblemished complexion of dairymaids to their acquisition of cowpox. Jenner took material from a cowpox lesion on the hand of a dairymaid, Sarah Nelms, and inoculated it into the arm of one James Phipps. He later showed that Phipps was protected from smallpox, and that material could be taken from the pustule on his arm and successfully transferred to the arm of another person. In less than five years, Jenner's cowpox had been carried around the world. ~~In the United States, Benjamin Waterhouse, the first professor of medicine at Harvard, performed the first vaccination in July 1800 and subsequently played a leading, if controversial, role in popularizing its use.~~

Propagation of cowpox, or vaccinia as it was later called, by arm to arm transfer permitted only small numbers to be inoculated. Extensive vaccination was not possible until late ~~in the 19th century~~ when large amounts of virus were grown on the flank of a calf. ~~However, such vaccine, after harvest, became inactive within days~~. With increasing refrigeration, countries in the more temperate areas began to control smallpox.

During the 1940s, ~~vaccination programs in~~ Europe and North America succeeded in eliminating smallpox. But for the tropical areas, heat stable vaccines were essential. ~~Finally~~, in the 1950s, a freeze-dried vaccine was developed which remained potent for a month or longer at temperatures of ~~98°F~~ 37°C.

Meanwhile, imported cases of smallpox continued to occur and spread in the smallpox-free countries. The cases were as severe and fatal as in the developing nations. All countries protected themselves by national vaccination programs, and required vaccination certificates of international travelers.

In 1959, the World Health Organization began a global eradication campaign. Mass vaccination programs were started in many countries, but few were successful. Countries which succeeded in stopping transmission experienced reinfection from their neighbors. Hoped for contributions of money and vaccine were not forthcoming. Most discouraging was that the strategy of mass vaccination did not seem to be working. In some areas of India, a larger number of vaccinations were reported than there were people - but still smallpox persisted.

Increasingly frustrated by failure, the 1966 World Health Assembly decided to make one further attempt, and voted to allocate $2.5 million for an intensified campaign. This may seem to be a substantial sum but, in perspective, provided an average of only $50,000 each for the 50 countries where programs were needed. Publicly, the delegates were enthusiastic, and proposed a 10-year goal for achievement. Privately, few believed eradication to be possible. The skepticism was justified, considering that the program would have to be undertaken in some of the most inhospitable parts of the world, and in some of the least developed countries. Moreover, no other disease had ever before been eradicated.

The program commenced on January 1, 1967. 11 Thirty-four countries were then endemic, 9 others experienced importations. There were estimated to be 10 to 15 million cases that year.

The belief that eradication of smallpox was theoritically possible was based, in part, on the practical demonstration that transmission had been interrupted in Europe and North America and in some developing countries as well, such as Central America and North Africa. Scientifically, the goal seemed reasonable. Man was the only known host for the virus. A person with smallpox could transmit infection only from the time when the rash first appeared, until the last scabs separated. Following recovery he was immune. ~~Thus, it was possible to know whether or not smallpox was present in an area, by searching for patients with a visible rash~~. The disease spread through face-to-face contact in a continuing chain of infection. By tracing the source of infection of the victim, and by identifying his contacts, other cases in the chain could be identified and outbreaks contained. Moreover, smallpox, when introduced into remote villages, soon depleted the susceptible population, and often died out even if nothing was done. This occurred even over extensive, sparsely populated areas. In Brazil, for example, the smallpox program began in the heavily populated coastal areas. When teams moved through the Amazon, no cases were found. Finally, the heat-stable vaccine conferred long-lasting protection.

For the intensified campaign, we needed each year more than 250 million doses of the heat stable, freeze-dried vaccine. 11c Donations from the

Soviet Union and the United States provided most of this need during the early years, but donations were eventually received from 26 countries. Meanwhile, we helped the developing countries to produce vaccine, and within six years, they were able to produce 80% of the needed vaccine and they, in turn, contributed vaccine to others.

12 In 1968, we tested a remarkable invention of Wyeth Laboratories - the bifurcated needle. The needle could be dipped into the vaccine. By capillarity, vaccine was held between the tines, and fifteen rapid strokes implanted enough vaccine to obtain a take. Only one-fourth as much vaccine was required as had been needed with older techniques. Vaccinators could be quickly trained. The needles were inexpensive, and could be reused many times. Vaccination was further simplified when it was shown that an alcohol saturated cotton sponge did little more than rearrange bacteria on the skin surface. Vaccinators were thus instructed only to wipe away caked dirt if present 13 With heat stable vaccine, a vaccinator could carry in his pocket all the equipment he needed for a month's work.

Between 1967 and 1969 programs began in most infected countries, and by 1971, all were in operation. The strategy initially called for nationwide systematic vaccination programs to be completed over two to three years. It was expected that by then an effective reporting system could be developed which would detect the remaining outbreaks. These then would be eliminated by isolating the patient, and vaccinating his contacts. We quickly found that ~~even in the poorest countries and least vaccinated areas~~, case detection systems could usually be rapidly

developed and outbreaks eliminated. Accordingly, the program strategy was altered to give greater priority to "surveillance and containment," rather than to mass vaccination. In most countries of Africa, a surveillance team of only 2 to 3 persons could control smallpox in an area inhabited by a population of 2 to 5 million. Each health center and hospital was visited and asked to send a report each week as to the number of smallpox cases seen. Schools and weekly markets were visited, to ask if any had seen smallpox cases. When cases were detected, the surveillance teams, with local health workers, contained the outbreak.

Progress in most of Africa and in the Americas was rapid.[14] By 1970, the number of endemic countries had decreased from 33 to 17.[15] By 1973, smallpox was confined to the Indian subcontinent, to Ethiopia, whose program did not begin until 1971, and to Botswana.

The Indian subcontinent, however, proved to be a more formidable challenge. Efforts such as we had made in Africa had little impact. In the endemic Asian areas, nearly 700 million people lived in one of the most densely populated regions on earth. Train and bus service facilitated extensive travel. Many smallpox patients, infected in cities, returned to their villages to recover or to die and, in so doing, to spread smallpox. The disease spread rapidly and widely. There were many then who knowingly asserted that in Asia, the traditional, ancient home of smallpox, eradication could not be achieved. We wondered if they might not be right.

During the summer of 1973, a new strategy was planned. It was decided that 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 contained 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 thousands of vehicles, as well as tens of thousands of bicycles, boats and rickshaws.

The first search took place in October. The results were depressing. In the northern Indian State of Uttar Pradesh, two years of intensive work had already been devoted to improve the reporting system. 16 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 being 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. ~~Vaccination teams lived in each infected village, to search and vaccinate in a wide radius around the village.~~ 17 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.

Only one year after the new strategy was implemented, in October 1974, the last case occurred in Pakistan; in May 1975, in Nepal; in June 1975, in India; and, finally, on 16 October, 1975, in Bangladesh.[18] This three-year-old girl, Rahima Banu, became the last victim of smallpox in Asia.

[19] Only Ethiopia remained to be conquered. Ethiopia, however, was a challenge of yet another type. It is a country of 25 million people scattered across desert and highland plateau in an area larger in size than France, Germany and Denmark.[20] It is a country where half the population lives more than a day's walk from any accessible road. Insurrection and fighting were widespread. Health staff were few in number and less than 100 could be employed for the program. The staff were periodically kidnapped and fired upon. Several were killed. A helicopter provided to the program 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 which included volunteers from the United States, Japan and Austria, eliminated the disease from the northern highland areas. Smallpox remained only among nomads of the vast Ogaden desert. Here, it was difficult even to find the nomads. To solve that problem, nomads themselves were hired and trained as vaccinators. In August 1976, the last outbreak was contained.

However, there was 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, the 23-year-old cook in Merka, Somalia, proved to be the last case. The 10 year time target had been missed, but only by 9 months and 26 days.

To confirm that eradication had been achieved, village by village and house by house searches continued over a two-year period. A reward was offered to anyone who reported a case which could be confirmed as smallpox. The announcement of the reward brought a flood of reports of persons with rash. All were checked and specimens examined. No cases were found.

Finally, to provide assurance that eradication had been achieved, international commissions were appointed to visit each previously infected country after at least two years had elapsed since the last case. The commission reviewed detailed reports of each program and then spent two to three weeks in the field to verify the work. In all, 10 different International Commissions visited 48 different countries. Special visits were made by WHO staff and consultants to an additional 28 countries.

Finally, a WHO Global Commission comprised of persons from 19 countries personally oversaw a two-year program of evaluation to satisfy themselves that global eradication had been achieved.

We now believe that variola virus is now confined to just ~~three experimental~~ two laboratories.

The achievement of smallpox eradication was a dramatic event and inevitably the subject of extensive publicity - although there were some who observed ~~correctly~~ that the program's earlier disastrous setbacks in India received more press attention than did the declaration that eradication had been achieved. Bad news simply makes better press. For those in the field of public health, whose work is often little known and rarely publicized - who do not have the personal satisfaction of grateful patients as do their clinical colleagues - it was a triumph which for once, the world could understand and appreciate.

Inevitably, health planners and politicians sought to identify lessons to be learned from the program. The most obvious and naive has been the assumption that if one disease could be eradicated so rapidly and so inexpensively, other candidates should be identified and, one by one, eradicated in a similar fashion. Measles and poliomyelitis are touted as the two prime candidates. ~~To those who doubt the possibility of eradicating these diseases, there is the retort that in 1967, not more than a handful believed that the eradication of smallpox was possible. It's not easy to answer that one.~~ It is apparent, however, ~~that~~ no disease has the epidemiological characteristics which, taken together, are anywhere near so favorable for eradication as those of smallpox. That man is the only host, that essentially permanent immunity is induced by infection and that there is no carrier state are important characteristics, but these are shared by several diseases. Of importance, however, was the fact that smallpox usually spread slowly, an individual ill with smallpox rarely infected, on average, more than two to three others. ~~In part, this was related to the character of the virus~~

and its characteristics of transmission. There was one additional factor. Unlike most exanthematous diseases, the smallpox patient did not transmit infection until after the rash first appeared. The rash itself developed only after two to four days of prostrating illness which usually caused the patient to take to bed. Thus, when the rash erupted, his contacts were customarily few in number and commonly family members or friends. Once a case was discovered, it was possible, through vaccination, to create a barrier of immunity among contacts and those in the community and thus stop further spread. In the case of measles, however, the patient is most infectious one to several days before he becomes ill. Many are exposed in classrooms, markets and other areas to patients who are not yet ill. Thus, a comparatively simple intensive vaccination program, as was employed for smallpox, has proved far less effective in controlling measles and even when more [illegible] measures have been applied, the results have been disappointing.

Programs of mass vaccination played an important role in the smallpox program in diminishing the number of susceptible persons and thus the spread of disease. Vaccination alone, however, would never have succeeded. For example, in densely populated Central Java, smallpox continued to spread at a time when surveys showed that 95% of the population were immune through previous illness or vaccination. Conversely, smallpox transmission was successfully interrupted over extensive [illegible] areas, when less than 50% were protected. The essential added component was the rapid identification of outbreaks and of chains of virus transmission - and their interruption by patient

isolation and vaccination of contacts. For the rapidly spreading measles, this approach does not work. Poliomyelitis poses a different problem becuase only one in perhaps 1,000 infected persons exhibits symptoms. The discovery of outbreaks and chains of transmission is all but impossible. Extensive vaccination programs will control these diseases, as was the case in smallpox, but eradication is ~~quite another matter~~ a more difficult problem.

The successful eradication of one disease, smallpox, does not imply that the application of the strategy which was used will be effective with another. ~~Each disease has different characteristics and must be dealt with on its own terms.~~ To infer, as a lesson from this program, that now is the time to embark on other disease eradication programs is precisely the wrong lesson to learn.

~~In reflecting on important~~ Among applicable lessons ~~to be derived from this experience,~~ I identify three of fundamental importance. One relates to research, the second to management and health resources, and the third to the role of an international organization.

In May of 1966, when the World Health Assembly made the commitment to undertake the program, no funds were identified for research. The prevalent view was that eradication was simply an administrative problem. A good vaccine was available. The problem was one of vaccinating the 1.2 billion people then residing in endemic areas and - "voila" - no smallpox. When we began the program, I can say that we, in all candor, had no definitive research agenda in mind, only the

conviction that however straightforward the problem seemed to be, an ongoing research program was vital.

Eventually, it was agreed to earmark $40,000 for research. However, it was decided that this would be administered by a more senior official on the grounds that the program's director, then 39 years of age, was too young to be entrusted with the responsiblity for a sum so large. Eventually, this policy, too, was decision was changed!

The program of research proved decisive. Before the eradication campaign concluded, we had extensively revised our understanding not only of the epidemiology and virology of smallpox but of other poxviruses as well. Even as the last cases were occurring, new questions were arising which today are unexplained - and indeed, we hope, may remain unanswered. Research proceeded at several levels. Initially, an international group of cell biologists, epidemiologists and mammologists was convened to decide what studies should be undertaken to determine whether there was or was not an animal reservoir - a crucial issue. If indeed, there was an animal reservoir, eradication would be impossible. The group met formally every two years and developed a research plan to be followed as a cooperative activity. Between meetings, research findings were communicated between scientists and by a newsletter. The pattern of activity resembled Dr. Lucas' later panels in Tropical Disease Research. The pittance in support provided by WHO was augmented many times over by national laboratories. In the end, convincing evidence was accumulated which indicated there was no animal reservoir. In the process, analytic

studies using restriction endonucleases revealed new understandings about the relationships among the family of poxviruses; a new human disease, monkeypox, was discovered and characterized; the belief that cows were the reservoir of cowpox was shattered; and previously unknown poxviruses were discovered.

A separate panel dealing with vaccine and vaccine production standardized a more effective production technology; modified methods for vaccine testing; developed a stable tissue culture vaccine; and standardized strains for use in production. Field staff participated in a range of collaborative and independent studies with the result that the technique of vaccination was changed. Revaccination was deemphasized in importance when it was discovered that primary vaccination conferred high levels of protection during more than 20 years, rather than the conventionally accepted three years. Most important was the discovery that smallpox spread slowly, that an effective reporting and containment system could rapidly stop transmission.

The findings from various countries and different laboratories were communicated from WHO in Geneva to all program staff in papers and publications every two weeks thus permitting their ~~appropriate translation into field~~ use with the least possible delay. The bifurcated needle, for example, was in universal use little more than a year after we first conceived of its use in a new technique of multiple puncture vaccination.

~~The findings noted are but a few of many.~~ The evident lesson, however, is that however much we thought we knew about this long-studied disease, there was yet another world of basic and practical knowledge which was essential to the ultimate achievement of eradication.

The second lesson pertains to the management and the availability of resources. When the program began, many believed that a principal constraint would be the lack of clinics, health posts and hospitals which could report cases and of health personnel to undertake vaccination and containment activities. ~~In some countries, this was indeed a constraint.~~ However, in the majority, we found that there were surprisingly large numbers of trained, well-motivated health personnel who had few or no supplies with which to work, no supervision and no defined program of activities. Health units were surprisingly numerous in most countries but few had more than the most rudimentary resources. A small number of smallpox eradication program staff with transport to move from place to place could distribute vaccines and needles, train health staff in reporting and containment activities and provide continuing supervision of activities. In many countries, they were the only health staff ~~actively~~ providing training and supervision, ~~in this manner, given this type of support and encouragement,~~ many health personnel responded with interest and enthusiasm and performed both competently and conscientiously. ~~One cannot help but speculate about the existing~~ potential for the delivery of other health services if objectives and procedures were better defined, if continuing effective field supervision of activities were provided and if effective distribution systems were established to provide necessary vaccines and drugs.

Lastly, and perhaps most important, the potential of an international organization - in this case, the World Health Organization must be noted. To the press, the best copy seems to be that which details the impoteney of the United Nations. Again, bad news seems to make for better press than good news. Smallpox eradication, however, epitomizes the best of what the UN can be. Indeed, no bilateral effort or combination of bilateral efforts, however substantial, could have succeeded in this campaign. To persuade nearly 50 countries of disparate political belief and structure to undertake at the same time any sort of program with a common goal is no easy matter. But, within the WHO framework, this could be done. In the World Health Assembly, it was agreed that all vaccine, from whatever source, would be tested by independent international laboratories. And within the WHO framework this was done. At different times, some batches of vaccine from most producers were found to be below established standards - a delicate problem with which to cope, but an international agency was able to document problems and to work out solutions. Through WHO it was possible to mobilize collaborating scientists to work out problems. Scientists from principal research laboratories in the USA, USSR, U.K., Japan, the Netherlands, India and Bangladesh exhanged yet unpublished data and observations, usually by mail, sometimes by telephone and periodically worked in each others laboratories. WHO served to orchestrate this. National sovereignty is always a delicate issue. Yet, all countries openly and willingly cooperated in identifying laboratories which retained variola virus, in persuading most to destroy or transfer their stocks and, finally, to permit independent WHO inspection teams every two years to inspect laboratories still retaining variola virus. Finally, at one time or another, more than 700

international staff from 69 different countries served together in the field. This, of itself, was a memorable experience for many who, in the turmoil and stress of field operations in some of the most inhospitable areas, grew to respect and admire as friends those from diverse cultural and political backgrounds. ~~No bilateral program or consortium of bilateral efforts could possibly have achieved what was able to be done under a WHO umbrella which had sparse fiscal resources but a far-reaching~~ programmatic mandate.

WHO is continuing to demonstrate its potential in the Tropical Disease Program and the Expanded Program on Immunization among others, many of which are less newsworthy, but no less important. Far more could be done given even modestly more generous resources, a commitment to good science - both basic and applied - and more effective management of the extensive health manpower resources even now available. ~~The eradication of smallpox offers a lesson in the perennial birth of WHO and its members. It is not the question of possible eradication of another disease on which we should focus but on a broader range of collaborative initiatives under the WHO umbrella.~~