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Case Studies of Major Eradication Efforts: Smallpox
Implications for polio eradication

IOM Forum on Emerging Infections: Consequences of Viral Disease Eradication
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The eradication of smallpox removed, hopefully forever, one of the greatest of all the world's plagues. It was an extraordinary, cooperative effort involving, under WHO leadership, countries throughout the world and perhaps as many as 150,000 field staff at various points during the campaign. It dramatically demonstrated the extraordinary cost-benefit ratios that might be achieved with eradication. The total investment in international assistance was just under $100 million; national investments were estimated to be perhaps $200 million. But, because vaccination and quarantine measures could be stopped, savings of at least $1 billion annually are being realized.

I was asked to review this smallpox eradication experience for such lessons as it might have for other global eradication efforts.

Prospects for eradication of other diseases

So far, there have been seven eradication campaigns intended to eradicate globally an infectious disease. The first four failed; only one -smallpox- succeeded; and two are still in progress. None lasted much more than 18 years. Despite the fact that there has been only one success in eradicating a disease, a number of persons now regularly speculate that a wide variety of diseases and conditions should be susceptible to eradication given sufficient resources, effort and cooperation. To me, this has been precisely the wrong lesson to be derived.

It is instructive to note that throughout the entire course of the eradication campaign, the subject of what next should be eradicated was seldom a topic of discussion by a basically optimistic group that directed the program and knew best its problems. It was clear that there were many factors that uniquely favored smallpox eradication as contrasted to any other disease. With a 30% case-fatality rate, smallpox was in a class by itself as a global health problem. No other disease had features that made diagnosis and surveillance for infection so easy. The presence or absence of the virus could be determined quickly in every area. Every infected person had a characteristic rash. Most transmission was droplet spread by face to face contact making outbreak containment easy. Moreover, it is one of few diseases that both confers permanent immunity and has no human carrier state or animal reservoir. For

none is there a vaccine so heat stable and so inexpensive that can protect with only a single inoculation and can be administered from the time of birth.

Given the fact that all countries were deeply concerned about smallpox and were regularly vaccinating large numbers of their citizens, it was a disease that should have commanded the highest possible political commitment. However, expected voluntary contributions to the program were sparse at best and inadequate funds seriously hampered the program throughout its first 9 years of existence. A number of endemic countries had to be cajoled into undertaking a program at all. The program, on several occasions, hung in the balance because of political and social problems and, despite the best efforts of technical staff, could well have had setbacks sufficiently serious to delay eradication , perhaps indefinitely. Not until some 7 years into the program was there a confident belief by staff that eradication could be achieved and events as late as 12 months prior to the last case threatened a successful conclusion.

I summarized these considerations in a 1982 World Health Forum paper in which I expressed our belief that, at least for the next decade, there was no foreseeable candidate for eradication. Twenty years later, the situation does not look substantially different to me with the possible exception of poliomyelitis, generally considered to be the next most difficult candidate for eradication. An heroic effort is now being made to eradicate that disease. However, given the task yet to be done and the many current uncertainties, it would be presumptuous to forecast a reasonably certain date for polio eradication, its status now being roughly where we were with smallpox some 5 years before transmission was finally stopped. Thus, as the first lesson from the smallpox campaign, I would suggest that before indulging in extended discussions about what might or might not be done post-eradication, it would be productive to ascertain whether, in the cold hard light of accumulating experience and available technology, there are reasonable prospects for the eradication of <u>any</u> other disease within the next 10 to 20 years.

Vaccine played an especially critical role in the smallpox program, however many other contributing factors there were such as political commitment and the health, transportation and communication infrastructure. A heat stable vaccine of assured potency was far more vital than most appreciate. As you know, the vaccine has been known since 1798 but not until the end of the 19th century did it become available in quantity as a result of growth of the virus on the flank of cows. Transporting it, however, was a problem. Thus, smallpox continued to spread, largely unabated in most of the

world except in industrialized countries where sufficiently rapid transport and refrigeration of some sort was possible. In the 1930s, a vaccine air-dried over sulfuric acid was perfected in Indonesia. It retained potency for periods of 6 months or more at 37° C. Although often heavily contaminated, take rates of 80%+ were usual. By the end of the 1930s, Indonesia was smallpox-free. A similar product was introduced into a number of the French colonies with similar dramatic results.

In 1967, when the global smallpox campaign began, there were a number of countries in Latin America, east Asia and some in Africa where smallpox transmission had been stopped. The successful national programs then were primarily vaccination programs with little emphasis on surveillance and no deliberate intent to completely stop transmission. In substantial part, this was due to the use of the air-dried vaccine or a new freeze-dried product developed in the early 1950s.

A basic point is that vaccine technology had advanced to the point where eradication was a feasible proposition. Had we been dependent on a vaccine no more heat stable nor immunogenic than, for example, polio vaccine, the prospects for eradication would have been significantly diminished

Post-eradication strategies

During the course of the eradication campaign, planning for post eradication strategies and activities received little attention. Procedures were developed for certifying large contiguous geographic areas as being smallpox free but this was the extent of the effort. Not until late 1975, when smallpox was confined only to Ethiopia and the interruption of transmission appeared to be only a matter of months away, were significant efforts made to define post-eradication needs. In major part, this reflected our belief that the margin for error in the program was small and that all available resources had to be directed toward the goal of interrupting smallpox transmission. Otherwise, there would be no post-eradication era. In fact, transmission continued for one year beyond the date anticipated when smallpox invaded Somalia, spread throughout the country, and threatened the whole of the Middle East.

In December 1979, the Global Commission for the Certification of Smallpox Eradication, as part of its final report, made 19 recommendations for actions to be taken post-eradication (Annex I). The recommendations were subsequently approved by the 1980 World Health Assembly. A special committee, the Orthopoxvirus Committee was constituted that met every four years or so over the next 20 years. A number of the recommendations are relevant to the subject of this symposium.

Vaccine and vaccination (Recommendations 1-6)

Most countries discontinued routine vaccination by 1982 and all of them by 1984. Use of certificates for travelers attesting to the fact of recent smallpox vaccination had also stopped by then. A few countries continued to vaccinate their military but that practice ceased about 1990. Seed lot vials of smallpox vaccine were produced at the Rijks Institute (Netherlands) and distributed to all vaccine production centers for storage to assure that vaccinia virus would be available at several sites should it ever be needed. Vaccine was stored in rented cold storage lockers at two locations in Switzerland and regularly retitred to assure that it retained potency, which it did. The costs of vaccine storage and of periodic retitering were not inconsiderable and WHO budgets were under great stress, what with the U.S. failure to pay its assessments. Thus, In 1990, nearly 13 years after the last known case, the Committee recommended that the WHO stockpile be reduced from 200 million doses to 500,000 doses and that the balance of the vaccine be sent back to the respective donor countries. As of 1999, individual countries reported retaining some 80 million doses of vaccine, not all of which has been properly stored or retitred.

Suspect cases of smallpox (Recommendations 7,8)

As anticipated, rumors of possible cases continued to be reported to WHO and to be investigated. It was considered important that all rumors be thoroughly investigated so as to provide assurance to the international community that there were no further naturally occurring cases. The number of rumors decreased from 30 or so annually in the first two years to 10 per year by 1985 with a scattering of cases thereafter. About half were found to be chickenpox or measles; one-third were erroneous news reports; and the rest, a miscellaneous collection of skin diseases.

Laboratory retention of specimens (Recommendations 9-15)

A major concern was the question of possible reintroduction of smallpox virus from a laboratory given the fact that the virus did not survive for long periods under ambient conditions and there was no animal reservoir. Limiting the number of laboratories that retained smallpox virus was considered an important step in mitigating the risk of this occurring. In 1975, a survey was undertaken to determine which laboratories might have retained smallpox isolates. All countries and 823 laboratories included in the WHO list of Virus Laboratories were contacted. Special contacts were made with those laboratories that had published papers over the preceding 25 years that indicated that they had grown smallpox virus. In all, 75 laboratories reported having

smallpox virus isolates in 1975, nearly two-thirds of which were in Europe and the Americas. For several reasons, the number of laboratories that processed smallpox virus specimens was not large.

1) The disease was sufficiently characteristic clinically that laboratory confirmation was seldom required;
2) For diagnosis, growth on chick CAM was necessary and, in many areas, suitable uncontaminated eggs were extremely difficult to obtain;
3) Laboratory researchers preferred to work with orthopoxviruses other than variola for which there were suitable animal models for infection.
4) The need for many countries to develop their own laboratories was diminished because WHO Collaborating Laboratories provided laboratory services.

Following a request by the World Health Assembly that the laboratories destroy their isolates or transfer them to one of the two WHO Collaborating Laboratories, 57 of the 75 reported that by July 1977, they had done so. No effort was made by WHO to confirm these reports nor was this contemplated. It was recognized that laboratories customarily retain microbial isolates for later reference and that such specimens were not always well-referenced. A search of all deep freezers in the relevant laboratories throughout the world was far beyond the resources of WHO. The objective of mitigation of risk of release of smallpox virus was as much as could be reasonably expected.

A laboratory associated outbreak in Birmingham, England in 1978 stimulated a number of countries to destroy or transfer isolates to WHO laboratories. By 1980, only 6 laboratories reported holding the virus. This hard core strenuously resisted parting with specimens but, by 1983, the number of laboratories was able to be reduced to the two. WHO designated laboratories. These were regularly inspected by WHO consultants.

In 1994, the WHO Orthopoxvirus Committee, in a report to the Director General, recommended that the 1995 World Health Assembly pass a resolution calling for the destruction of all remaining stocks of smallpox virus in June 1995. By that time, representative strains of variola virus had been prepared as a cloned fragment library and sequenced. A 5 year study of monkeypox fully characterized the human form of the disease and demonstrated it to be a zoonotic virus only occasionally infecting man and unable to sustain human to human transmission. No research was known to have been

conducted using smallpox virus for at least 12 years. In fact, it was known to have been grown only at CDC to produce material for sequencing and to validate diagnostic tests. The WHO laboratory in Moscow ceased research in 1982 and, in a later written report, Dr. Sandakhchiev, Director of the Novosibirsk Laboratory to which the Moscow strains had been sent, asserted that they had undertaken no laboratory studies using variola virus until July 1996. The only stated reason for retaining the virus was a hypothetical one-- that perhaps some day, some one would wish to undertake some type of research that would require the intact variola virus. Weighing the risks associated with retaining it against a hypothetical scientific need, the Committee, supported by five major scientific societies that had been explicitly consulted, recommended its destruction.

Beginning in 1995, some U.S. and Russian scientists argued that the virus should be retained for research purposes, perhaps to develop an anti-viral drug, perhaps to develop an improved vaccine. All acknowledged that to do so would be costly, time-consuming and, even if a product were produced, it could not be known whether it would be effective in man. Nevertheless, U.S. and Russian officials persuaded World Health Assembly delegates to defer destruction of the virus until 2002. Meanwhile, fearing that smallpox might be used as a biological weapon, the U.S. has contracted for 40 million doses to be produced for use in an emergency.

(SLIDE 9) What lessons does the smallpox eradication experience provide?

1. Eradication of a disease is extremely difficult even when political commitments should be easy because of the severity of the disease, even when the epidemiological characteristics are as close to ideal as one might wish and even when a highly effective, heat stable vaccine requiring but a single dose is available.

2. The direct implications of a failed eradication program can be significant. For most diseases, the cost of eradication is far greater than for control and unless eradication is achieved within a finite time and control measures can be stopped or significantly decreased, the added costs of eradication will not be recouped. Moreover, experience has shown that failed eradication programs in most areas, although resulting in better control while special measures are in place, gradually revert to a pre-eradication status as special funds and interest fade.

3. There were no difficult problems encountered in stopping smallpox vaccination. The only likely source for smallpox virus to be introduced was from victims exhumed from the tundra or as a result of escape of the virus from the laboratory. In either case, it was felt that the outbreaks would be small and readily able to be contained. Use of smallpox as a biological weapon was considered to be unlikely, both morally and practically. Only comparatively recently was it revealed that the Soviet Union, during the 1980s, had undertaken a massive research and development program to produce smallpox virus as a biological weapon.

4. Persuading most laboratories to destroy or transfer smallpox virus to WHO collaborating laboratories posed few problems. A few objected strongly and cooperation was achieved only with difficulty. The World Health Assembly has now resolved that all stocks of the virus should be destroyed but no later than December 2002 and all parties have agreed to this.

5. It was evident during the smallpox program that a failed eradication effort could have serious repercussions for other global initiatives. Financial support for smallpox eradication was problematical throughout its course, in large part, because a WHO sponsored global malaria eradication program was clearly failing at that time after the investment of more than two billion dollars. The credibility of expert public health advice was then at a low ebb and most countries wanted nothing to do with another eradication fiasco.

6. Sustaining interest and support was extremely difficult, especially after a nil incidence was achieved. Each country was understandably anxious to transfer money and manpower to deal with other critical health problems as soon as possible. They were not enthusiastic about sustaining two years or more of intensive surveillance to confirm that eradication had been achieved. This needs to be borne in mind for eradication campaigns that would need to be phased in over a long period.

In brief, eradication is not a program to be undertaken lightly. To do so before it is clear that the needed technology is in hand and before the practicability of eradication has been demonstrated in the field is to invite a costly failure and, more important, a loss of professional public health and medical credibility.

Case Studies: Lessons from Smallpox Eradication

The eight eradication campaigns

Disease	Method	Duration	Years
Hookworm	Sanitation:Rx	1909-22	13
Yellow fever	Vector control	1915-32	17
Yaws	Penicillin	1948-66	18
Malaria	DDT	1955-73	18
Smallpox	Vaccine	1967-80	13
Guinea worm	Water: Rx	1986-	14+
Poliomyelitis	Vaccine	1988-	12+

Case Studies: Lessons from Smallpox Eradication

Key factors favoring smallpox eradication

- An important disease problem to all countries
- Presence of virus readily determined
- Outbreak containment-- straightforward and effective

  Most transmission -- face to face contact after rash
- Permanent immunity upon recovery
- No chronic carriers or sub-clinical infection
- Vaccine

  One dose
  Inexpensive ($.01 per dose)
  Stable for one week at 37° C.
  Bifurcated needle
  Effective from time of birth

Case Studies: Lessons from Smallpox Eradication

Post-eradication Strategies

December 1979

19 recommendations --

Global Commission for the Certification of Smallpox Eradication

Approved by the 1980 World Health Assembly

- Vaccine and vaccination (1-6)
- Suspect cases of smallpox (7,8)
- Laboratory retention of specimens (9-15)

Case Studies: Lessons from Smallpox Eradication

Laboratories retaining smallpox virus

Region	No. of Labs	No. retaining virus 1975	1977	1983
Americas	506	18	13	1
Europe	185	29	19	1
Africa	15	5	4	0
Southeast Asia	57	13	13	0
Eastern Med.	25	3	3	0
West. Pacific	35	7	5	0
	823	75	57	2

Case Studies: Lessons from Smallpox Eradication

Applicable lessons from smallpox eradication - I

- Eradication of a disease is extremely difficult even under highly advantageous circumstances and the costs are substantially greater than those needed for control.

- Health authorities were very receptive to stopping smallpox vaccination and this proceeded with few problems.

Case Studies: Lessons from Smallpox Eradication

Applicable lessons from smallpox eradication - II

- Laboratories and scientists were generally cooperative in destroying or arranging to transfer variola virus stocks to designated WHO laboratories. Although virus destruction was supported by most countries, last minute U.S. and Russian objections delayed this by 7 years -- until 2002.

- A failed eradication effort can have serious adverse repercussions on other programs.

- Sustaining interest and support for a special program for long periods, especially when transmission has been stopped, is extremely difficult and needs to be recognized in the phased planning of global programs.