

Review

Eradication of Infectious Diseases: Its Concept, Then and Now

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SUMMARY: The concept of disease eradication emerged as recently as the mid-20th century. The successful eradication of smallpox resulted in the concept of the extinction of the causative agent in man as well as in the environment, leading to the cessation of all control measures including vaccination. Subsequently, world resources have been invested in global polio eradication and measles eradication in the Western Hemisphere. The former is apparently now at the “end game”, the latter, after successful campaign in the Americas, aims at program development worldwide. However, both endeavors are being challenged by delays in schedules, unexpected technical problems, lack of global coordination, and ever-increasing political unrest. It is proposed that disease eradication be redefined as the extinction of the pathogen in man, not in nature, making for a more flexible approach in the post-eradication period. Smallpox eradication was a rare event. That concept is unrealistic in today’s world.

1. Background

Man’s fight against infectious diseases can be traced back to 7000-8000 years ago when the development of agriculture resulted in groupings of more than 500 persons, thus providing ample opportunity for frequent transmission of microbes among and between human and animal populations. Current common microbes such as measles virus and tubercle bacillus are examples of those that made humans their natural reservoir.

Man’s fight against these microbes was not particularly successful, as witnessed by epidemics of plague, syphilis, and tuberculosis in Europe during the Middle Ages. Only in the last two centuries, as a result of the discovery of therapeutic substances such as antibiotics and the development of vaccines coupled with surveillance, epidemiology, and modern health systems, has man begun to win the battle against many microbes.

In the context of the conflict between man and microbe, the concept of eradication emerged as recently as the early 20th century. At that time, the concept of eradication varied from simple zero incidence of the disease to extinction of the pathogen in humans and/or the environment. In the early 20th century, the Pan American Health Organization (PAHO) initiated the eradication of yellow fever. The program was not successful because of the existence of an animal reservoir

for the yellow fever virus, which was discovered only when a disease-free area in Brazil was re-infected from a then unknown source of jungle yellow fever. In the mid-20th century, the World Health Organization (WHO) launched a campaign to eradicate malaria and smallpox. While malaria eradication was failing in the 1960’s, smallpox eradication, the campaign for which was reorganized in 1967, succeeded. The last case of endemic smallpox occurred in 1977, marking the end of continuous transmission over the last 6000 years of human history (1).

The successful elimination of smallpox resulted in the concept of eradication as the extinction of the causative pathogen in man as well as in nature. WHO and its member states were encouraged to launch a polio eradication program, which has now entered its final stages. Furthermore, PAHO, with its regional success in polio eradication in the Americas, initiated measles eradication in 1994. However, measles programs on other continents have been unable to imitate the Americas’ campaign because many states engaged in polio eradication. Over time, the political world has been changing. According to Harold James, “the nation state, the decisive driving force of the past two centuries, is dissolving under the pressure of a cross-national integration which has developed with a dynamic and momentum of its own” (2). War, refugees, famine, decline of national authority, border disputes, and international terrorism are all expressions of this phenomenon, and have influenced the course of transmission of many diseases.

Since eradication entails a massive global effort requiring a great deal of funding as well as time and labor, it is important to review the concept of eradication to determine whether it

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should continue to be based on eradication as complete as that of smallpox.

2. Building up the concept of eradication based on the eradication of smallpox

A comparison of the malaria and smallpox programs started by WHO in 1953 and in 1958, respectively, shows that both programs made good progress during the first 10 years, substantially reducing endemic areas. However, the malaria epidemic resurged due to the resistance of mosquitoes to DDT as well as to the heavy burden of national program expenditure. In smallpox, poor surveillance and a sub-standard vaccine slowed progress. Furthermore, the smallpox program had not been well-funded internationally. In the 1960's, WHO had to assess how both programs could be strengthened, in conjunction with advice from the World Health Assembly (WHA)

Following an evaluation by a WHO team, in 1966 it was finally proposed that smallpox eradication be newly intensified, and a substantial increase in the regular budget was granted. The proposal was accepted by the WHA, and the intensified smallpox eradication program started in 1967. Although it was much smaller than that for malaria eradication, the program progressed very well - the last endemic smallpox case (Figure 1) was detected in Somalia in 1977, just 10 years after the start of the intensified program. Meanwhile, in the mid-1970s, WHO renamed the malaria eradication program "malaria control" as the goal of eradication target.

In the history of disease eradication, the smallpox program is, to date, the first and perhaps last the only one to accomplish its purpose fully. The program was successful for several reasons. Technically, smallpox had no animal reservoir; hence, immunization of the human population was able to arrest transmission. Patients did not shed the virus after recovery. There were no subclinical infections of epidemiological importance, and the clinical features were distinctive, making surveillance effective. Finally, the vaccine was virtually 100% effective. Vaccination complications led non-endemic states to contribute to the global program under the expectation that eradication would render vaccination no longer necessary and



Source: WHO

Fig. 1. Last case of smallpox.

Last case with date of onset of rash, 26 Oct. 1977, in Somalia
The end point of continued transmission in human population.

thereby eliminate its complications. In contrast, malaria did not have these biological advantages; it was transmitted through insect vectors, its clinical features were not distinct from other infectious diseases, and there was no effective vaccine. Managerially, the smallpox program was under the strong leadership of WHO and assisted by the full cooperation of WHO member states in terms of funding as well as operational logistics. Although there were several wars, such as the India/Pakistan war and the Somalia/Ethiopia war, the world was relatively quiet due to the cold war, with nations stabilized as democratic or communist.

When the end of transmission became imminent around 1976, action was taken to identify potential sources of a smallpox resurgence. This included confirmatory studies of animal reservoirs for smallpox including human monkeypox; destruction of laboratory stocks of smallpox virus; studies on residual materials from smallpox patients in cold climate; and the deliberate release of smallpox (3). All the studies and investigations indicated that the threat of the return of smallpox was not significant. This led to the cessation of all control measures including smallpox vaccination.

The program had lasted only 10 years with an additional certification period of 2 years to confirm the interruption of transmission worldwide (1). WHO declared smallpox eradicated in 1980, and smallpox vaccination ceased worldwide. The success of smallpox eradication led the international community to agree on a concept of eradication entailing the extinction of pathogens both in the human population and in the environment.

3. Application of smallpox experience to polio eradication

Following the declaration of the eradication of smallpox in 1980, WHO began to consider the feasibility of polio eradication.

The epidemiological characteristics of poliomyelitis are similar to those of smallpox in the absence of animal reservoir and in the availability of an effective vaccine (oral polio vaccine [OPV]). Polio, causative of severe paralysis, was one of the most feared of vaccine-preventable diseases. In 1985, PAHO, joined in 1988 by WHO, initiated a program for the global eradication of polio. The strategy involved all-out yearly vaccination campaigns directed at those up to 5 years of age, with supplementary vaccination campaigns as needed. Diseases of acute flaccid paralysis (AFP) are the surveillance target, supported by laboratory examination of patient stool samples for detection of polio wild virus. Remarkable progress has been made. Polio transmission was interrupted in the Americas in 1991, in WHO's Western Pacific region in 1997, and in WHO's European region in 1999. However, problems started in 2000 when the global program fell short of its year 2000 target to eradicate polio - in 17 states in Africa and Asia it was still endemic. The situation was comparable to that of the number of smallpox endemic countries 7 years before the end of smallpox transmission worldwide (4).

Since 2000, heroic efforts have been made by all the remaining endemic states to halt transmission as well as by recently endemic-free states to maintain their status. This "end game" has only been partly successful. As of November 2003, there were three major states endemic for polio (Figure 2): Nigeria in West Africa; Pakistan and India in the Indian subcontinent, which reported a total of 500 cases in 2003; and three other states, Niger, Egypt, and Afghanistan, which reported a total of 17 cases that same year (5).

Strikingly, the three major states are the same ones that had recorded the last endemic smallpox cases in West Africa and in Asia during the last phase of the smallpox eradication program. These states have high population densities where intensive mass immunization campaigns were unable to eliminate the groups of susceptibles that maintained chains of smallpox transmission (6). These states are large and in polio eradication long-term efforts to continue vigorous nationwide vaccination campaigns as well as supplemental mop-up campaigns have encountered substantial difficulties.

For smallpox eradication, the epidemic was handled with short-term, crash campaigns using a surveillance-containment strategy, an operation to conduct vaccination focused only on an affected community and on an emergency basis. The operation was conducted under strong leadership by WHO. So far, such an approach has not been available for polio eradication. The program has used repeated mass immunization of children up to 5 years of age and mop-up operations in large areas of continuing transmission. The ineffectiveness of

this strategy has been demonstrated by the resurgence of epidemics in all three states from 2000 to 2003 accompanied by exportations to adjacent states in West Africa, the Middle East, and areas of India previously free from transmission (see section "5. Discussion").

During the same period of 2000 to 2003, there were outbreaks caused by the Sabin vaccine virus (cVDPV), which became pathogenic in the Dominican Republic, Haiti, Madagascar, and the Philippines (7-10). Egypt reported a similar incident in 1991. Despite the fact that incidence has been rare, the number of individual outbreaks small (1-18 cases) and occurring in areas where polio immunization coverage was unsatisfactory, these incidents shook confidence the general belief that simple OPV vaccination could eventually eradicate polio.

4. Application to measles eradication of experience gained from the smallpox and polio eradication programs

The epidemiological features of measles resemble those of smallpox and polio though measles has a higher rate of transmission. The Americas made good progress toward eradication with two eradication efforts: the last case of endemic smallpox occurred in 1972, the last endemic polio case in 1991. For measles, regional eradication began in 1994 once polio eradication had been certified. As of 2003, indigenous transmission of measles had been successfully interrupted, a remarkable achievement, under the excellent leadership of PAHO (11). The regional program adopted the strategy of catch-up, check-up, and follow-up. Catch-up campaigns cover the age group up to 15 years with first-time coverage, then there is a check-up operation to vaccinate the age group up to 5 years every 5 years to eliminate the unvaccinated backlog, and a follow-up with routine vaccination of 1-year-old children. However, although at present the region does enjoy



Source: WHO

Fig. 2-1. Polio has gone from Bangladesh since August 2000. Photograph taken in Bangladesh, 1977.

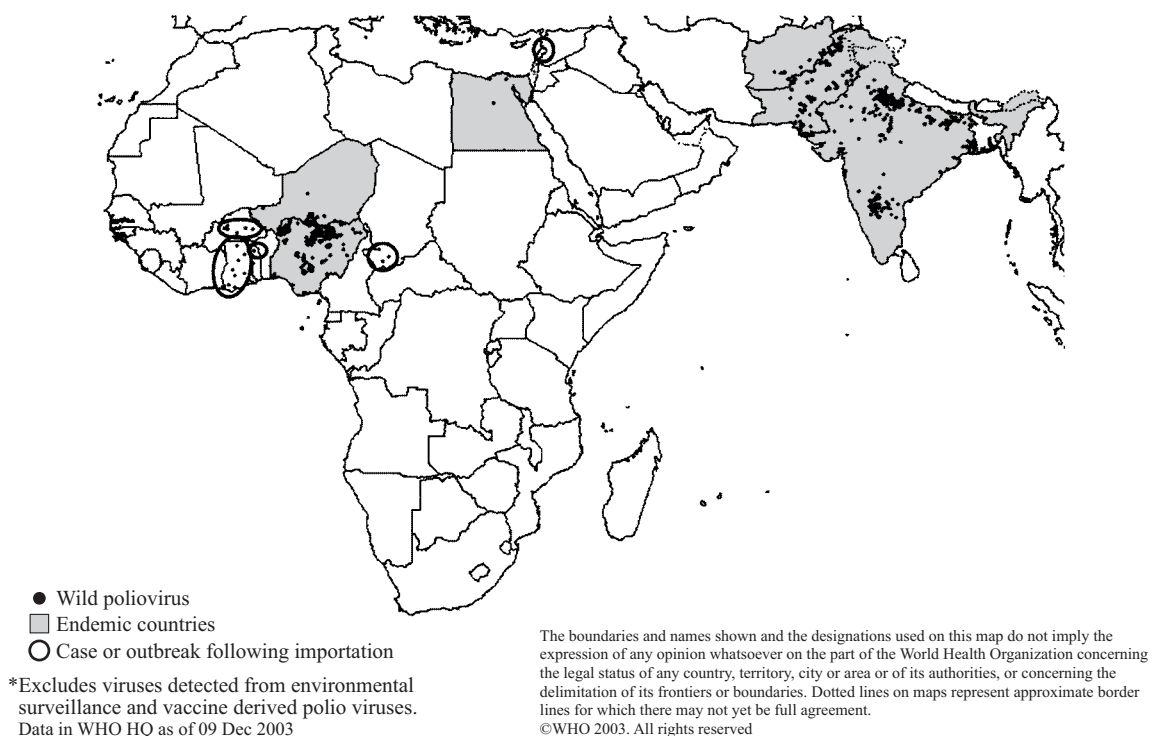


Fig. 2-2. Wild poliovirus*, 10 Dec 2002 to 09 Dec 2003.

freedom from indigenous measles transmission, it will always be susceptible to importations from other continents where measles continue to be endemic. A strategy for global eradication of measles has not yet been decided upon by the world community.

5. Discussion

Global eradication of a disease requires a major public health effort. Any such programs have serious pros and cons. In the case of smallpox eradication, the Executive Board (EB) of WHO as well as WHA made an extensive review before adopting a resolution in favour of eradication. From 1958 to 1966, when the program was failing to meet its targets, almost every year WHA adopted a resolution to continue the program and to improve vaccine quality and vaccination coverage, and above all to renew efforts to obtain voluntary contributions by member states. In 1966, the EB indicated that the program had to be funded by the WHO regular budget. After heated debate, the 1966 WHA approved an intensified program. At that time, UNICEF and other international organizations were skeptical of the feasibility of the smallpox program. It was regarded as a disease-specific program that might disturb the healthy development of basic health services. These arguments rapidly disappeared as the intensified program was launched in 1967.

Thus, from the time of its inception, smallpox eradication had been seriously debated in terms of feasibility and cost-benefit. In view of the changing world and the experience to date gained about individual eradication programs, it is worthwhile to revisit the basic concept of eradication programs for smallpox, polio, and measles.

5-1. Smallpox

The latest issue regarding incidence of smallpox is that of bioterrorism: so much effort on the part of WHO to study and eliminate the possibility of resurgence of smallpox as previously described may be jeopardised by recent threats of the deliberate release of this virus by terrorists. This has already led a few nations to rebuild their vaccine stockpiles and even to re-initiate limited vaccination. There are currently only two laboratories known to be holding smallpox virus stocks: one in the United States (U.S.), the other in Russia. The destruction of these stocks has currently been postponed, with WHO's agreement to facilitate the research believed to be necessary to cope with the threat of bioterrorism. Recent monkeypox outbreaks have been reported in several states in the U.S. Although this does not represent a direct threat of smallpox virus, such reports indicate that there may still be a few unknowns with regard to the ecology and genetic mutation of poxvirus. Human monkeypox cases resemble smallpox, and the delayed detection of outbreaks of the latter in the U.S. indicates the seriousness of a real smallpox outbreak occurring in countries where surveillance is inadequate (12).

5-2. Polio

The polio program essentially suffers from a lack of global coordination, prolonging unreasonably the duration of such programs beyond affordable sustainability.

Additional handicaps are the result of several biological factors.

In polio, in contrast to smallpox, large numbers of subclinical infections make surveillance-containment ineffective. Assuming all difficulties were overcome with the use of OPV and the last endemic polio case had occurred in

Africa or Asia, additional efforts would still be required to ascertain that cVDPV would not pose future problems. Using inactivated polio vaccine might not be appropriate due to elevated cost and its inability to halt transmission as thoroughly as OPV does. If polio eradication is also aimed at the extinction of wild polio virus in the environment, it will be difficult to search out and destroy all stool specimens, stored in laboratories, that have been or are being collected in endemic and non-endemic areas. Optimistically, even if all the above issues could be resolved, the last case of global wild polio might be seen as late as 2005 or 2006. Considering an additional period of 3-year certification and verification of no risk of cVDPV becoming pathogenic and no risk from the environment including laboratory-stored virus, achieving eradication could be estimated to occur no earlier than 2010. Already in the Americas, since the year of the last reported case, the polio program has continued for 12 years, and in the Western Pacific, 6 years. Simple estimate suggests that the Americas will have to continue "the post-eradication program" for 19 years and the Western Pacific for 13 years, until 2010. Essentially, as discussed in the Dahlem Workshop, Berlin, "eradication together with certification" should be completed within a relatively short period of time, say 10-15 years, as the effort entails a great deal of sacrifice of other health resources (13). In fact, the fatigue owing to prolonged eradication efforts is well known to be one reason for the resurgence of epidemics in Nigeria and the Indian subcontinent in 2000-2003.

It should be noted that due to the small gene sequence of polio, the virus can be easily synthesized in the laboratory, and that because the virus is not as stable as smallpox virus, mutation or recombination with other enteroviruses like coxsackie could occur in nature (14). A large number of recent polio endemic states, despite their limited resources, will move to continue eradication programs over many years to come to sustain freedom of transmission.

Furthermore, even with all this achieved, the world will have to weigh carefully the pros and cons of stopping vaccination.

5-3. Measles

The very rapid transmission of measles demands the nearly impossible task of more or less simultaneously implementing effective programs on every continent. If the concept of eradication includes the criterion that it be worldwide, there are problems to be addressed.

The high rate of measles transmission and the high frequency of importation make it difficult to clearly distinguish between endemic measles and imported measles, although the origins of specific viral strains can be differentiated by genetic analysis. The current measles vaccine is effective only when a child older than 9 months is inoculated. This leaves a large number of susceptibles in the population when vaccination programs aim to develop herd immunity in an area. Also, research may be needed to confirm that measles vaccination of populations with a high prevalence of HIV will not pose problems in terms of complications and satisfactory herd immunity (15). The current PAHO strategy of catch-up, check-up, and follow-up is difficult to sustain over a number of years, especially in poor countries in Africa and Asia. Unlike smallpox vaccination, which is administered by bifurcated needle, oral polio vaccination, measles vaccination is administered with a syringe and needle, an additional burden to national programs. The problem of safe injection is also to be handled (Figure 3).



Fig. 3. Nationwide measles immunization campaigns.

The global eradication of measles would require uniform worldwide collaboration by all nations in terms of geography and timing. Unless specific measures are developed to meet these requirements, measles will not be eradicated worldwide in the foreseeable future.

5-4. Changing world

Lastly, circumstances unfavourable to global eradication are part of the circumstances of the changing world. There is increasing global inequality: the rich become richer, poor get poorer. Nations with a per capita GNP of \$30,000 constitute less approximately 10% of the global population. The situation appears to be most unfavourable for a globally coordinated program of disease eradication. Certification of freedom of wild polio virus faces substantial difficulties in many war-affected areas of Africa and Asia.

6. Reconsideration of the concept of eradication

History and current circumstances warrant a reconsideration of the concept of eradication. It appears unproductive to maintain the current concept of eradication, based on smallpox, aiming at complete extinction of a target pathogen both in the human population and in nature followed, consequently, by the cessation of all control measures. Perhaps eradication should be redefined as the worldwide eradication of a pathogen only in the human population. Thus, eradication of a pathogen in the environment would not be a condition, avoiding the considerable work which would need to continue over many years even after interruption of transmission had been achieved, as discussed in the preceding sections.

Then, what would be the strategy during the post-eradication era? How would the global program of polio eradication be recast and maintained, using this definition? The principal strategy would be to integrate polio immunization into routine vaccination programs while strengthening surveillance at the same time. A vaccine stockpile would be established, and at any sign of transmission, administration of emergency containment vaccination would be instituted by WHO in

collaboration with member states. Effective control or elimination in a wide area of measles and even of rubella could be managed by a similar strategy. Appropriately cautious, WHO has not yet declared a campaign for the global eradication of measles.

In all cases of viral pathogens, research is of high priority to augment the effectiveness of programs in terms of vaccines, epidemiological surveillance, and maintenance of pathogen-free status in humans. In the near future, it would be appropriate for WHO to ask selected leaders in different disciplines from the international community to review and formulate a new concept of eradication and, if they agreed, to declare that the concept of global eradication of a vaccine-preventable disease requires reconsideration; namely: (i) to achieve zero incidence of a target disease in the human population; (ii) to develop and maintain surveillance and response capability, thus reinforcing the health service system; and (iii) to continue research to maintain what the program has achieved. Ideally, WHO has the courage to explore such a possibility. Cessation of immunization programs should not be a condition for the success of these new “eradication” campaigns. As described in the preceding section, the possibility of reappearance of a once-eradicated pathogen cannot be ignored; if reoccurrence occurs, reintroduction of immunization as well as vaccine production, although an enormous task, must be surmountable.

WHO and its member states have thus far made tremendous efforts for eradication. These efforts have not been in vain, though their goal is not yet achieved. The contribution to the health of the world has been significant. Smallpox eradication saved millions of lives yearly and resulted in an annual saving of one billion dollars in health expenditures worldwide (1). Substantial progress has been made toward polio eradication, including the reduction of the number of endemic states from 150 in 1988 to 3 in 2003, together with a reduction in medical costs for the management of paralytic polio patients. Similarly, regional measles eradication has resulted in the disappearance in 2003 of measles deaths caused by

indigenous transmission in the entire Western Hemisphere (16).

To meet the criteria of this new definition of eradication, the eradication of both polio and measles, if it is to take place, still requires substantial efforts in terms of finance, organization, personnel, international coordination, sustainability, and logistics.

7. Conclusion

Eradication campaigns undertaken thus far have provided a great deal of benefit, but the delay in polio eradication and the uncertain feasibility of worldwide measles eradication demands the reexamination of the definition of eradication. The emerging threat of bioterrorism contributes a sense of urgency to this matter. It is proposed that eradication be redefined as the extinction of a pathogen in the human population worldwide, though not necessarily in the environment, and not necessarily followed by the cessation of all control measures such as vaccination. Appropriate post-eradication strategies would be founded on careful assessment and research. This proposal is further justified by the widening global inequality and socio-political unrest present in the world today. Clearly, a new concept of disease eradication would require endorsement by the international community. Eradication is a clear-cut goal of disease control, but pursuing that goal requires careful weighting of costs and benefits. Undue investment of resources would be counter-productive while the world is suffering a major threat from many infectious diseases.

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