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THE ERADICATION OF SMALLPOX[1]

by

F. Fenner[2]

HISTORY

Smallpox is one of the oldest recognized diseases of man. Records in China and India go back at least 3000 years, and variolation, i.e. attempted protection by deliberate inoculation with smallpox virus, dates from at least 600 BC. It appeared in Europe about 600 AD, and (apart from early Chinese and Indian descriptions) the first accurate description of the disease was given by Rhazes, physician to the hospital of Baghdad, about 900 AD.

Smallpox was introduced into Central America in 1520 by an infected negro slave who belonged to a rival of Cortes. Three and a half million Indians are said to have died in the ensuing epidemic, and smallpox was probably as important as Spanish arms or the Christian religion in destroying the civilizations of middle America.

It was a common disease in most European countries, and in North America, from the sixteenth to the early twentieth century. As recently as 1930, England and Wales recorded 12 000 cases and the United States 48 000, but since about 1950 endemic smallpox has been eradicated from Europe and North America, although small outbreaks have continued to occur following importations, usually from the Indian subcontinent. Until the mid-sixties the situation in Asia, Africa, and South America can only be described as disastrous, with widespread epidemics every year involving millions of cases and hundreds of thousands of deaths. It is hard for us to realize the severity of smallpox as it occurred in England before vaccination was introduced, and over much of the poverty-stricken world until very recently, but this account by Lord Macauley of the situation in the late seventeenth century gives us some idea. Smallpox, he writes, was then "the most terrible of all the ministers of death. The havoc of the plague had been far more rapid, but the plague had visited our shores only once or twice within living memory; and the smallpox was always present, filling the churchyard with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover. Towards the end of the year 1694, this pestilence was more than usually severe. At length the infection spread to the palace, and reached the young and blooming Queen (Elizabeth I)."

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[1] Talk prepared after returning from the Fourth Meeting of the Informal Group of Experts on Monkeypox in Geneva, February 1976. Given (a) as special school lecture, John Curtin School of Medical Research, 24 March 1976 and (b) in Perth, at Australian Society for Microbiology, July 1976.

[2] Director, Centre for Resource and Environmental Studies, The Australian National University, Canberra.

The WHO Smallpox Eradication Programme

In 1967, WHO initiated a global programme for the eradication of smallpox. The concept of smallpox eradication dates back to Jenner himself, who wrote in 1801 "it now becomes too manifest to admit of controversy that the annihilation of the smallpox, the most dreadful scourge of the human species must be the result of this practice (of vaccination)". Nevertheless more than a century later comparatively few countries, let alone continents, were free of smallpox. And global eradication of disease, a concept not tenable until the mid-twentieth century, has had a disappointing history with yellow fever and malaria, the two diseases first addressed. Nevertheless, in spite of what appeared to be insuperable difficulties as recently as the early 1970s, the last case of smallpox was recorded in South America in 1971, in Indonesia in 1972, in West and Central Africa in 1972, and on the Indian subcontinent in October 1975. The only country in which smallpox remains endemic now is Ethiopia, and there only in four particularly inaccessible provinces (Fig. 1).

What features of smallpox led WHO to launch the campaign for global eradication? Firstly, it was a very serious human disease, with mortalities in different geographic areas ranging from about 1% up to 40% - the latter figure being common in the Indian subcontinent. Further, attempts to keep it out of smallpox-free countries required the maintenance of an elaborate health inspection system and a requirement for regular vaccination for travellers who might pass through endemic areas.

Secondly, it was believed to be a specifically human disease. This was a very important consideration, for the first widely-heralded attempt to eradicate an important disease of man foundered on the fact that there was an enormous animal reservoir. This was yellow fever, discovered at the beginning of this century to be a viral disease transmitted from man to man by the urban mosquito Aedes aegypti. Within a very short period after this, yellow fever was eradicated from the city of Havana, in Cuba, and from Panama, thus permitting the construction of the Panama Canal. In 1916, the International Health Commission of the newly established Rockefeller Foundation undertook what amounted to the global eradication of yellow fever. Initially they were dramatically successful, and yellow fever disappeared from all the well-known centres of infection in North and South America following the application of anti-mosquito measures directed against Aedes aegypti. However, in 1935 the goal of eradication was recognized to be impossible of achievement, when Dr Fred Soper recognized what came to be called jungle yellow fever - a strictly rural disease in which Aedes aegypti was not involved, with jungle nonhuman primates as the vertebrate reservoir hosts.

The third feature of smallpox that led WHO to contemplate its global eradication was the belief that it occurred only as an acute infection, followed by death or complete recovery with lifelong immunity, and without any evidence of recrudescence. The importance of this feature can be appreciated by considering the disease that presents most difficulty in the differential diagnosis of smallpox, namely chickenpox. Chickenpox is caused by a herpetovirus and, after an acute attack subsides, the virus persists for many years in an occult state, probably in cells of the posterior root or cerebral nerve ganglia. Years after recovery from chickenpox the virus can be reactivated and cause the blisters of herpes zoster. The point of epidemiological importance is that susceptible children can catch chickenpox from cases of herpes zoster. Any virus that causes a recurrent disease that is infectious in this way cannot be eradicated.

Finally, with vaccinia virus, different preparations of which have diverse origins but which is closely related to cowpox and smallpox viruses, public health authorities possessed a very effective agent for protective vaccination against smallpox.

Let us now examine in more detail these four propositions as they appear in early 1976, somewhat out of order. We need to devote little time to the first proposition, although there are differences in the virulence of different strains of smallpox virus (Table 1). In spite of modern antibiotics and good nursing, smallpox on the Indian subcontinent in particular remained, until the last case occurred in October last year, a very severe disease with mortality rates of up to 40% in unvaccinated persons.

Mass vaccination

The effectiveness and quality of the vaccine was a very important problem for the WHO programme, which was initially based on mass vaccination. In such a programme, the need to be assured that vaccine is fully potent when it reaches the arm of the recipient is obvious - yet this factor was often neglected. Freeze-dried vaccines which maintain acceptable levels of potency for at least one month at 37°C have proved indispensable to the programme, especially in tropical areas. However, despite the development 20 years ago of practical methods for producing such vaccines, it was found when the programme began in 1967 that not more than 10-15% of the vaccine then in use in the endemic countries was freeze-dried and met requisite standards. Assistance was given to vaccine producers and reference centres were established for routine quality control of vaccine. By 1969, more than 95% of the vaccine in use met accepted standards. Today, two-thirds of the more than 200 million doses required annually in endemic areas is produced in the developing countries. Vaccination programmes were further facilitated by the introduction in 1968 of the bifurcated needle. With this needle and the multiple puncture technique, the efficacy of vaccination improved and a saving of approximately 50% in vaccine consumption was realized.

In addition to improved vaccine and vaccination technique, a simple system was required to monitor the performance of the routine mass vaccination programme. Methods for conducting sample surveys were devised which called for examination of only a small proportion of a population to evaluate the programme. The methods necessarily had to be simple to be employed effectively by field workers. In the assessment, persons included in the sample are examined for the presence or absence of facial pock marks and the presence or absence of a vaccination scar. In children under five years, it is determined whether or not the child was given primary vaccination during the previous 21 days and, if so, whether or not there is evidence of a take. Facial scars, in children, are of special importance as they represent a permanent record of smallpox morbidity in the area. In an area believed free of smallpox for the past three years, for example, such marks in a child one or two years old implies the possibility of unrecognized smallpox foci in the area. The prevalence of vaccination scars provides a reasonably reliable estimate of population immunity, as experience has shown that in endemic countries between 85% and 95% of smallpox cases occur among individuals with no vaccination scar. Thus, in appraisal of immunity, the age of vaccination scars is ignored and a simple operational target for the teams is stated, viz. at least 80% of persons in each specified age-group should have a vaccination scar. Take rates are gauged solely on the success obtained in primary vaccination because of the inconsistencies in interpretation of the revaccination response. If over 95% have a successful primary vaccination response, both the vaccine and the technique are considered satisfactory.

Recurrent infectivity

It was impossible to determine whether smallpox might be subject to recrudescence, with the recurrence of episodes of infectivity, in the presence of widespread primary smallpox. However, the history of smallpox in the countries of Europe, North America and Australia during this century suggested very strongly that recurrence was not a phenomenon of any epidemiological significance. All new outbreaks in these countries could be traced to contact with imported cases of primary smallpox. The same pattern has been apparent as the disease has disappeared from South America, Asia and Africa, and I believe that this risk can be dismissed.

An animal reservoir

The most serious threat to the eradication programme was, and is, the possibility that there is an animal reservoir of smallpox.

WHO set up a small expert group to advise it on this problem. The first meeting of this group was in Moscow and last month its fourth and probably final meeting was held in Geneva, at which the topic for discussion was post-eradication strategy.

Epidemiological theory, best developed in relation to measles, suggests that human smallpox must have originated from some animal host no earlier than the time of the first large villages, at most about 6000 years ago and probably more recently. Since much better data are available for measles than for smallpox, I shall present the argument for this disease.

Measles virus has no animal reservoir, infection is followed by permanent immunity, and recurrent excretion is unknown. The discovery that persistent infection of the brain with measles virus causes subacute sclerosing panencephalitis does not affect the epidemiological situation, for there is no evidence that cases of this disease ever excrete measles virus after their acute attack of measles. Persistence of the virus in a community depends upon a continuous supply of susceptible human beings. With an incubation period of about 12 days and maximum viral excretion early in the disease, at least 30 new susceptibles a year would be needed to maintain the virus if the cases were evenly spaced. Obviously many more than this would be needed to maintain endemicity. Bartlett calculated that in urban areas about 2500 cases per year is the minimum needed to prevent breaks in the continuity of transmission. He checked this estimate against data from British and American cities, and found that such breaks occurred when there were less than 4000-5000 cases per year. The minimum city population size for this number of cases was about 250 000. Island communities provide even better material to study the effects of population numbers. Black analysed data from 19 island communities over a period of about 15 years (Table 2). Measles disappeared for periods in all islands with populations of less than half a million, and the effect of population size on the frequency of fade-out is clear from the figures. Guam and Bermuda, which form exceptions to the pattern, have large transient military or tourist populations and frequent air connexions to large cities, i.e., they are insufficiently isolated to be comparable with other island populations with a similar input of susceptibles.

This pattern indicates that neither measles nor smallpox could have been a disease of early man, who was a relatively long-lived animal that lived in small family groups.

Smallpox virus, or variola virus as it is sometimes called, is highly species-specific, and does not infect most laboratory animals, but some monkeys develop skin lesions and an illness not unlike smallpox. Infection can be passed from one to the next by contact transmission with cage mates, but the number of skin lesions decreased in each successive passage and twice on the third passage and once on the eighth passage, further transmission failed. These experiments supported the belief that a simian reservoir of variola virus was unlikely.

Viruses of the group that variola belongs to, the orthopoxviruses, are relatively common in mammals (Table 3). Two of these viruses have given particular concern as potential reservoirs of human smallpox, viz., monkeypox and the whitepox viruses.

Monkeypox

What has come to be called monkeypox was first recognized in an outbreak of a generalized pox disease in cynomolgus monkeys in Copenhagen in 1958, and between then and 1968 there have been four other outbreaks in Europe and five in the United States of America in animals shipped in from Asia or Africa for use in polio vaccine production. An orthopoxvirus with characteristic properties was recovered from six of the 10 outbreaks. Extensive serological investigations of monkeys from Malaysia and the Philippines in 1970 failed to reveal any poxvirus antibodies in over 2000 sera tested.

In 1970 the first of a series of pox infections occurred in humans in areas of Africa which had been free of smallpox for two years or more. Since August 1970, 20 such cases have occurred. The illness in most was very like smallpox and four patients died. All but two cases were unvaccinated.

The cases were widely scattered from Sierra Leone to southern Zaire (Fig. 2). They occurred in 15 different small villages in dense tropical forest country; one case occurred in a town of 40 000 population. Twelve cases were single case outbreaks; in one, three siblings were infected simultaneously, and in two instances human-to-human infection may have occurred, since disease became manifest in close relatives at intervals of nine and 12 days respectively. The rate of transmission to susceptible household contacts (6%) is far lower than the rate of 35%, which is very generally found with smallpox.

Monkeypox virus differs from variola virus in many properties (Table 4). The recently detected human monkeypox cases were not the first such cases to have occurred, for previous cases would have been obscured by the former high prevalence of smallpox. However, isolates obtained previously from over 500 presumed smallpox outbreaks in these areas revealed typical strains of variola, thus suggesting that outbreaks of monkeypox are, at most, uncommon. This observation plus the fact that 13 patients failed to transmit the virus to more than 100 unvaccinated close contacts suggests that these may be incidental infections of no epidemiological significance.

Epidemiological investigations of human monkeypox cases have failed to reveal the source. It is probably significant that in Africa, in contrast to Malaysia and the Philippines, monkeys are a regular and fancied part of the diet of peoples of the tropical forests, yet it proved difficult to establish evidence of contact with monkeys in several of the African cases. Serological surveys of monkeys, birds and rodents in areas of Central and West Africa have revealed neutralizing antibodies for orthopoxviruses in sera from monkeys and rodents, but cross-reactivity between different orthopoxviruses limits the significance of this finding. However a special immunofluorescence test has revealed monkeypox virus specific antibodies in the sera of two adult Cercopithecus monkeys collected in Ivory Coast. It is still unclear, however, whether monkeys are, like man, only sentinel animals for monkeypox virus, or whether they are the primary natural reservoir.

What is called "monkeypox" remains a puzzle. Isolations have been made from monkey kidneys of Asian and African primates in laboratory colonies between 1958 and 1965, from an outbreak in the Rotterdam Zoo in 1964, and from human patients in West and Central Africa between 1970 and 1975. Antibody surveys revealed no orthopoxvirus antibodies in 2000 Asian monkey sera, but a rather high frequency of such antibodies in several species of primates and some rodents in West Africa. Specific monkeypox antibodies have been looked for only in a few orthopoxvirus-positive monkey sera from West Africa, and three positives have been recorded. Nevertheless, the epidemiological picture suggests that as far as man is concerned, monkeypox is a rare zoonotic disease (20 recognized cases in 200 million people over five years) clinically indistinguishable from smallpox but of limited capacity to spread in man.

"Whitepox" virus

However, there remains another puzzling series of viral isolations. In September 1964, in routine processing of Asian cynomolgus kidney tissues in Holland, orthopoxviruses were isolated on two occasions. Monkeypox viruses had been isolated from similar material before and after these isolates. However, on the chorioallantoic membrane, and in all other laboratory tests, these two isolates resembled variola virus. Among workers in the field, these and other similar isolates have been given the non-committal name of "whitepox" viruses because (in contrast to monkeypox) they produce small dense white pocks on CAM. They would have remained a curiosity except for four isolations made from some 500 samples of kidney tissues of primates and rodents for Zaire between 1971 and 1973. The animals concerned were a chimpanzee and a sala monkey, and two rodents - Mastomys, the common native rat in Zaire, and a squirrel-like rodent.

All these isolates resembled the "wild whitepox" viruses isolated in Holland in all ways; and they resemble variola virus very closely (Table 4), although individual strains can be distinguished from individual strains of variola. Experimentally, a whitepox virus inoculated into Cercopithecus caused a generalized disease with rash.

The only property that could confirm their identity with, or difference from, variola virus is human pathogenicity and transmissibility, and this cannot be tested. They remain, therefore, both a puzzle and a threat, which can be solved, I believe, only by the effluxion of time and continued careful epidemiological surveillance. The suspicion inevitably arises that one or more of these isolates may have been a laboratory contaminant - an ever-present risk in laboratories handling these resistant viruses. This was possible in the Moscow laboratory, but in Holland the monkey kidneys were being processed for polio vaccine production, far from any laboratory handling poxviruses. In the Moscow laboratory three specimens came from animals with neutralizing antibody in their serum, and in the first case, where this could not be tested, reisolation a month after the first attempt was positive. There is thus evidence that they are not laboratory contaminants.

With the eradication of smallpox from Central and West Africa, it is essential that the utmost care be taken with any material coming from another suspicious case. We can be certain that more cases of smallpox-like disease will occur. If monkeypox virus is isolated from them, it is no cause for concern. If a virus like these wild whitepox viruses is recovered, WHO has a major problem on its hands. Our Committee in Geneva recommended firstly, that in future isolations from suspected cases of smallpox (except from Ethiopia, while it is still endemic there) should be attempted only in special high-security laboratories used for no other purpose and secondly, that the material should be split and separately tested in two laboratories (likely to be the Research Institute for Virus Preparations in Moscow and CDC laboratories in Atlanta, Georgia).

The question of a possible animal reservoir of smallpox remains unresolved, and it probably will only be resolved by continued careful observations for several years after smallpox has disappeared. So far, among all countries of the world where smallpox has been eradicated, human monkeypox is the only zoonotic smallpox-like disease to be found.

From mass vaccination to intensified surveillance

I shall conclude this talk with an examination of the way in which the Smallpox Eradication Programme achieved and confirmed eradication in South America, Asia and most of Africa.

From the inception of the programme, it was apparent that mass vaccination, while serving to retard transmission, was rarely successful in interrupting transmission. For example, in Central Java a carefully designed sample survey in 1969 revealed that more than 95% of the Province's 23 million persons bore scars of vaccination. Nevertheless, during that year almost 1700 cases occurred, 85% of them in persons who had never been successfully vaccinated. In brief, infection continued to be transmitted principally among the unimmunized who constituted less than 5% of the population. While an apparently simple solution would have been to vaccinate the remaining 5%, the logistic problems and costs of so doing would have been prohibitive.

It has long been clear from experience with imported outbreaks of smallpox in Europe that even in much less well vaccinated populations than those in Indonesia, smallpox usually spreads comparatively slowly, infecting those who have had close contact with the patient. Even limited vaccination programmes involving only those at immediate risk have been shown to be effective in stopping outbreaks. As smallpox in endemic areas consists essentially of a series of such outbreaks, a change in the strategy of the programme from one of mass vaccination to one emphasizing containment of outbreaks seemed sensible. Accordingly the strategy of the programme and measurements of progress have focused not on the vaccination of "x" millions of persons, but on the detection and containment of smallpox cases and the reduction of smallpox incidence to zero.

This change in strategy implied the need for the development of reporting systems to permit the early detection of outbreaks and the establishment of trained epidemiological teams to investigate and contain them. The key to the development of such networks has been

the establishment of national and/or regional surveillance teams who regularly visit all health units within their jurisdiction to assure that weekly reports regarding smallpox are sent, and to encourage reporting to the health units by other groups, such as civic and religious leaders, school teachers and so on. The regular visits of the teams and their demonstrable response if cases were reported considerably facilitated cooperation. For the smallpox programme, the often maligned routine morbidity reporting system was the foundation of the surveillance scheme. While not optimal, it functioned well enough to permit the interruption of transmission in 25 of the 30 originally endemic countries by the end of 1973.

Where health workers frequently visited villages, the detection of cases was not a significant problem. Such was the situation in India, and, to a lesser degree, in Pakistan. Most outbreaks in these countries were detected within four to six weeks after the onset of the first case, and were then successfully contained before spread occurred beyond the immediate locale.

Nevertheless, wars and social upheaval constituted enormous problems, notably in India, Bangladesh and Ethiopia.

India and Bangladesh

For example after 18 months of freedom from smallpox, Bangladesh was reinfected in February 1972 by returning refugees from India. Emergency measures were implemented and additional staff provided but over 10 000 cases occurred during 1972. In India, the southern states were smallpox-free, but as 1973 began, major epidemics were occurring in an almost solid band across the whole of northern India. Paradoxically, perhaps, health services in these areas were far better developed than in most endemic areas where transmission had already been interrupted; transport and communications were likewise less of a problem; five to 10 times as many smallpox staff *per capita* are employed; and rarely did one find an area where less than 80% bear scars of vaccination. The failures in these areas could be attributed to the fact that for many years little attention was paid to the development of surveillance activities; the smallpox team was concerned primarily with mass vaccination.

The Smallpox Eradication Programme therefore instituted and intensified surveillance activities, with the gratifying result that the last known case of smallpox in Asia developed rash on 16 October 1975 (Fig. 3). Programmes of search and surveillance for hidden foci of smallpox are now in progress and will continue until the eradication of smallpox can be certified. The search programmes in India, Bangladesh, Nepal and Pakistan are similar and are comprised of several components. First, health workers of all categories participate in a house-by-house, village-by-village search throughout each of the countries at intervals of one to several months depending on the degree of risk of persisting foci. As an inducement to report cases should they be present, a reward ranging from $35 to $125 is offered to the villager who reports a case and a comparable amount to the health worker who receives and investigates the report. The reward has been given wide publicity and sample surveys are routinely conducted to monitor the success of the efforts in publicizing this information. Second, in each health centre and hospital, "rumour registers" have been established so that each report of a suspect case may be entered in a book and the results of the subsequent investigation recorded by local health staff. Third, specimens for laboratory study are obtained from all cases in which there is any question of diagnosis and from patients in chickenpox outbreaks where a death has occurred. National laboratories and WHO reference laboratories in Atlanta and Moscow are collaborating in processing these specimens. Fourth, special search programmes with specially designated staff are being conducted in areas considered by national and WHO health authorities to have a less adequate health infrastructure, in areas where large migrant populations congregate and in areas which for other reasons are considered to be at special risk of harbouring smallpox cases. Many areas, such as Sikkhim, the Chittagong Hill Tracts and remote areas in the eastern wing of India have already been intensively searched in planned programmes extending over several weeks but, as yet, no hidden foci have been discovered.

Ethiopia

The form of smallpox endemic in Ethiopia carries a low mortality - only about 1% - and the practice of variolation used to be widespread and in more remote areas is only now being supplanted by vaccination.

In 1975, Ethiopia reported a total of 3880 cases of smallpox, a decrease of 12% from the total reported during 1974. However, reporting during 1975 was more complete than during preceding years as the smallpox programme staff was increased from less than 100 persons in January to more than 500 persons in October, and additional support was provided by government authorities.

In February 1975, initial efforts were made to assess and to monitor the number of infected villages in which one or more cases had occurred during the preceding six weeks - a system of appraisal previously utilized in Asia. First assessment revealed some 60 known infected villages. However, there were at that time large areas which were believed to be infected with smallpox but where civil disorder or lack of personnel prohibited surveillance being conducted. During the course of the year, the number of staff increased by more than fivefold and civil disorder diminished in many areas. Many additional infected villages were discovered, mostly in almost inaccessible mountainous areas of the central plateau where variolation was prevalent; vaccination was regarded with suspicion if not hostility; and villagers frequently refused to inform the teams about cases or, in some instances, hid patients from such teams. Even when outbreaks were discovered, several weeks were usually required to persuade as many as 60-80% of contacts to accept vaccination. As a result, smallpox outbreaks persisted for weeks to months.

With the additional staff and transport and with added help from local government administrators, it was possible gradually to induce villagers to cooperate with the programme. Most outbreaks are now being detected within the first or second generation of cases. Thorough vaccination of an infected village can now be completed within two to five days with few refusals and thus third generation cases are rare. The number of infected villages has decreased steadily, although not so rapidly as was first hoped, because of the spread of infection due to variolation in the district called Hararghe.

Throughout most of Ethiopia surveillance teams are now able to conduct a planned programme of vaccination and search for hidden foci of smallpox. A few scattered areas where surveillance is not presently possible have been searched and the population vaccinated within the past nine months. Smallpox cases could be occurring in such areas but definitive appraisal will be possible only when they become accessible.

Certification of eradication

Confirmation that smallpox has been eradicated requires that at least two years of active surveillance be conducted following onset of the last known case to be certain that no hidden foci remain. Experience to date shows, in fact, that eight months has been the longest period during which a country was thought to be free of smallpox when actually a hidden focus persisted. The 24-month surveillance period thus provides a margin of safety.

To date, programmes in two major geographic areas have been assessed by specially convened International Commissions - South America (August 1973) and Indonesia (April 1974). In both instances, after a full review of the activities of the programmes in these areas and field visits for on-the-spot verification, the Commissions certified that they were satisfied that smallpox had been eradicated. Other Certification Programmes are envisaged (Fig. 4).

Variola virus after eradication

With the cessation of human to human transmission, the only apparent remaining reservoir of variola virus will be those stocks of virus retained by research and diagnostic laboratories. Although only two or three instances of laboratory acquired infection are known to have occurred, the outbreak in London in 1972 emphasizes that the risk is real.

To minimize this risk, it would seem desirable that variola virus be retained by only a few laboratories whose safety standards and precautions provide assurance that the virus will not inadvertently escape. Efforts are now being made to develop an international registry of laboratories which possess stocks of variola virus.

It is expected that, in all, not more than 15 to 20 laboratories will eventually be registered as retaining variola virus in storage and fewer still which will be conducting experiments with the virus.

Finally, there is the unpleasant reality to be faced that when smallpox is eradicated, and vaccination suspended, variola virus will become a plausible weapon for "bacteriological warfare", or at least for employment as a threat. It is interesting that it is not so listed in a recent report from the Stockholm International Peace Research Institute in the journal "Ambio", but I believe that the situation will change. Even with a highly effective vaccine and well-developed and well-functioning public health measures, a disease that spreads readily in man and causes a mortality of up to 40% is a threatening spectre. So I expect that, as an insurance against human ill-will, most countries will want to retain stocks of freeze-dried vaccine and the capacity to produce more, long after this major triumph of preventive medicine is achieved, and 175 years after Jenner foresaw the possibility.

TABLE 1. SMALLPOX: CASE-MORTALITY RATES

Place	Year	Cases	Deaths	Percentage
Bangladesh	1973-74	4 196	868	20
Punjab	1971	1 674	249	15
West Africa	1967-69	5 628	540	10
West Java	1969	11 966	930	8
Ethiopia	1972-74	21 250	243	1
Brazil	1969	6 795	37	0.5
Botswana	1971-72	1 092	2	0.2

TABLE 2. ENDEMICITY OF MEASLES IN ISLANDS WITH POPULATIONS OF 500 000 OR LESS, ALL OF WHICH HAD AT LEAST FOUR EXPOSURES TO MEASLES DURING 1949-1964[a]

Island	Population	Annual population input[b]	Percentage months with measles (1949-1964)
Hawaii	550 000	16 700	100
Fiji	346 000	13 400	64
Samoa	118 000	4 400	28
Guam	63 000	2 200	80
Tonga	57 000	2 040	12
Bermuda	41 000	1 130	51

[a] Modified from F. L. Black (1966).

[b] 1956 births less infant mortality.

TABLE 3. ORTHOPOXVIRUSES IN MAMMALS

Genus	Orthopoxvirus
Virus	Host
Variola (smallpox)	Man
Cowpox	Bovines
Buffalopox	Buffalo
Camelpox	Camel
Turkmenia rodent-pox	Wild rodents
Ectromelia	Mice
Monkeypox	Monkeys
"Whitepox"	Monkeys, rodents
Vaccinia	A derivative of cowpox

TABLE 4. COMPARISON OF SOME ORTHOPOXVIRUSES

	Variola	Whitepox (primate)	Whitepox (rodent)	Monkeypox	Vaccinia
Isolated from	Man	Monkey K.	Rodent K.	Man Monkeys	Man
Pocks	Small white	Small white	Small white	Small pink	Large white
Ceiling temperature	37.5-38.5°	38.5°	38.5°	39°	41°
Growth in					
1. Rabbit skin	-	-	-	+	+
2. RK13 cells	-	-	-	+	+
3. Pek cells	+	+	+	-	+
Pathogenicity					
1. Mice	Low	Low	Low	High	High
2. Chick embryo	Low	Low	Low	High	High
Haemagglutination	Low	Low	Low	High	High
Special antigen	Var.	Var.	-	Mo	Var. + Vac
Polypeptides	Var.	Var.	Var.	Mo	Vac; variable
Host range					
1. Man	+	Unknown	Unknown	+	+
2. Monkey	+	+	Unknown	+	+
3. Mice	-	Unknown	Unknown	+	+
4. Other	-	Unknown	Mastomys anteater cow		

FIG. 1. SMALLPOX INCIDENCE, JUNE 1974-1975

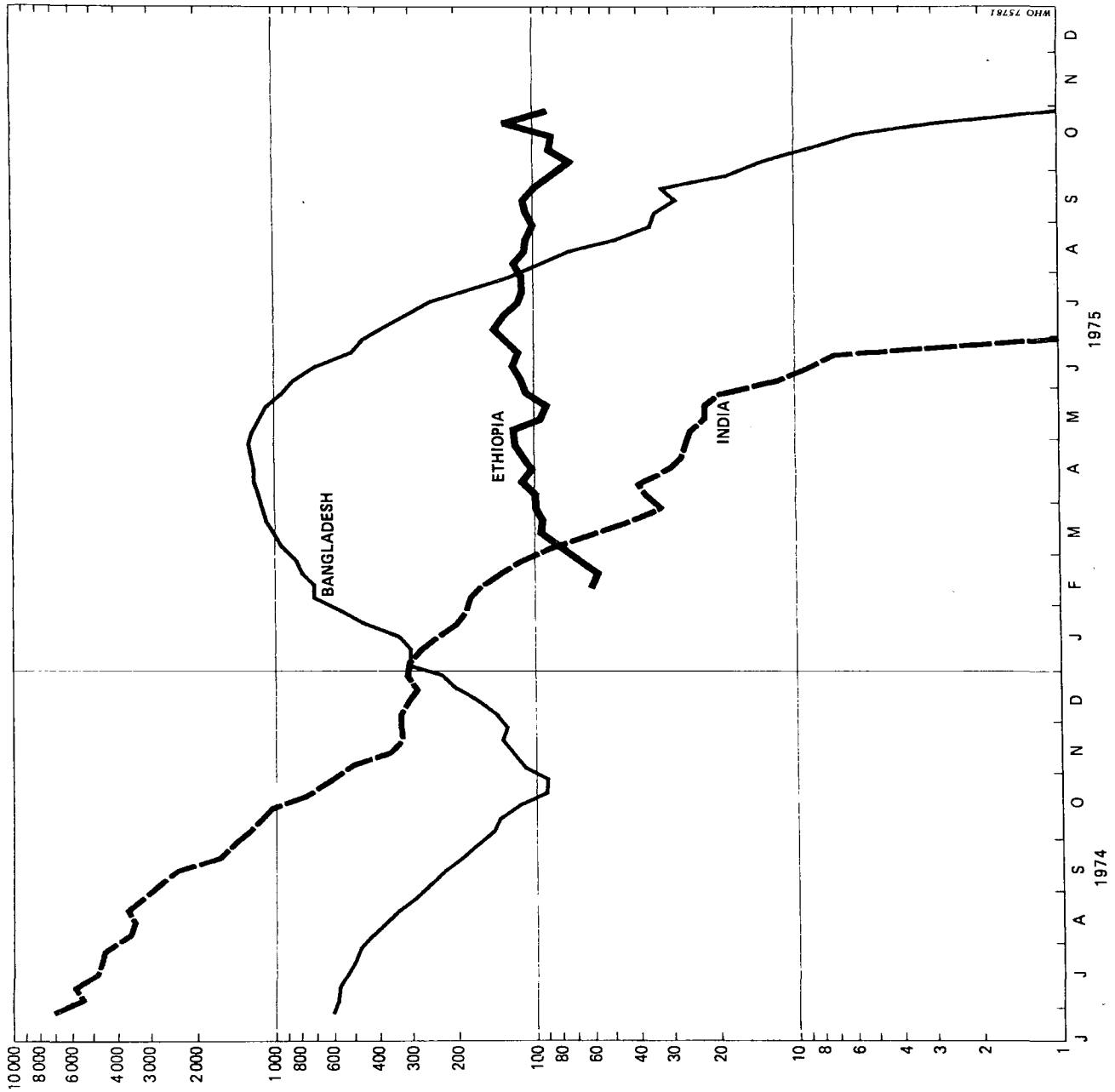


FIG. 2. AFRICA: LOCATION OF HUMAN MONKEYPOX CASES, 1970-1975

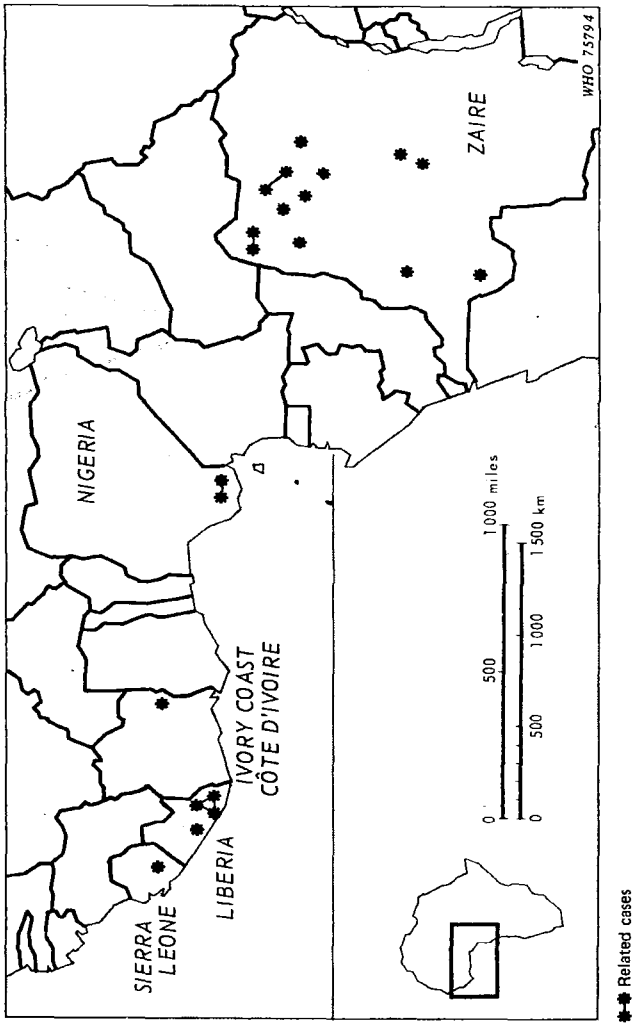
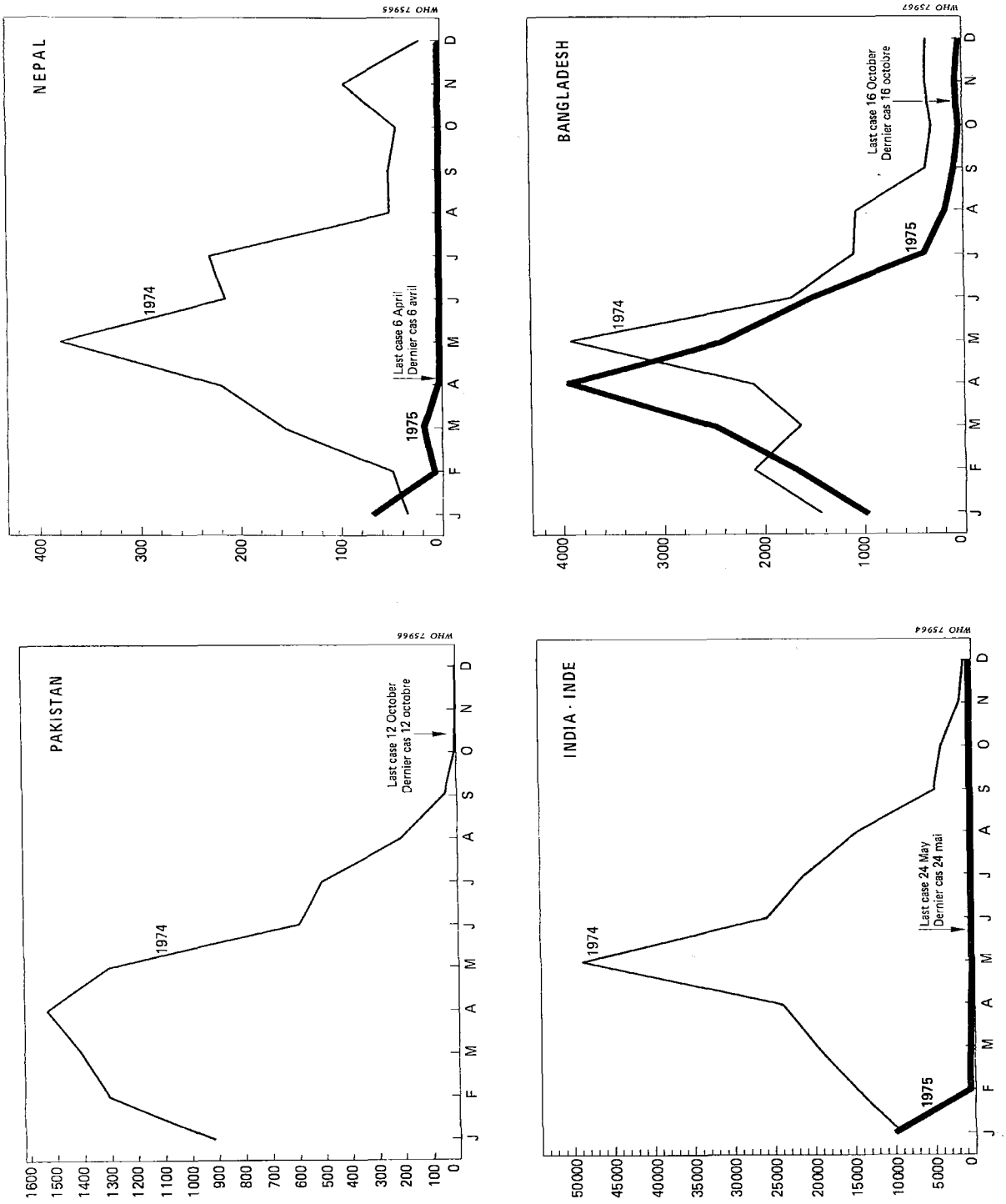


FIG. 3. ASIA: SMALLPOX CASES AND DATE OF ONSET OF RASH OF LAST KNOWN CASE



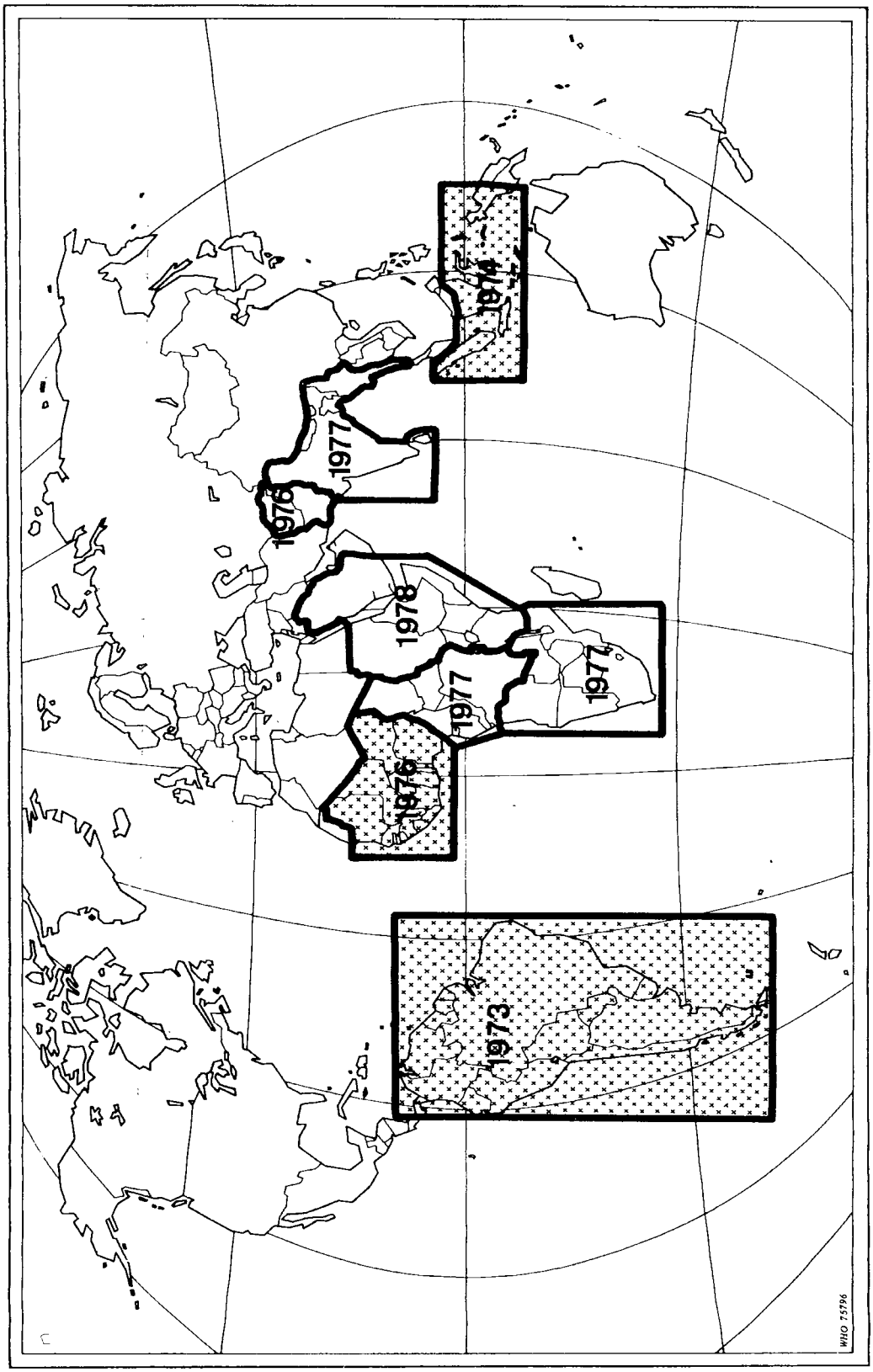


FIG. 4. CERTIFICATION OF ERADICATION OF SMALLPOX