

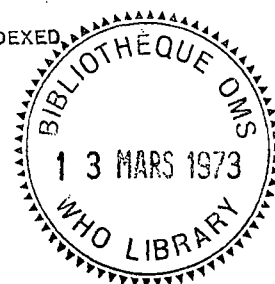


THE ERADICATION OF SMALLPOX - THE CRITICAL YEAR AHEAD

INDEXED

by

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In 1967 the World Health Organization, on the decision of the World Health Assembly, initiated a global programme for smallpox eradication. At that time many, if not most authorities, were openly sceptical of eradication as a realistic objective, let alone in a period of 10 years, the time target proposed in Assembly debate. Such doubts seemed not unreasonable as the history of eradication efforts have been disappointing. As is well-known, the discovery of jungle yellow fever thwarted an otherwise promising effort to eradicate this disease from the Americas and the problems experienced in the malaria eradication programme are a matter of record. Particularly pertinent, of course, is the fact that the global eradication of any disease has no precedent.

However, during the past six years, sufficient progress has been made in the smallpox eradication programme to permit the inauguration in September 1972 of what has been termed the "final phase". The objective, quite simply, is to reduce smallpox incidence to nil throughout the world by mid-1974. How realistic is this objective and where now are the problems which conceivably could thwart this realization? Present problems and uncertainties must be gauged in the perspective of the past. Thus, it is pertinent to review first the history of development of the programme and its strategy as well as certain of the epidemiological observations and techniques being employed.

Historically, 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 vaccine inoculation)". However, more than a century after this was written, comparatively few countries, let alone continents, were free of smallpox. As recently as 1930, for example, England and Wales recorded almost 12 000 cases and the United States that year reported over 48 000 cases (World Health Organization, 1948). Admittedly, the cases were almost entirely variola minor but smallpox nonetheless - and wholly preventable by vaccination. At this same time, in most of Asia, Africa and South America, the situation could only be termed disastrous as widespread epidemics of smallpox continued almost unabated.

Beginning in the late 1930s smallpox began to recede perceptibly. Leake (1943) attributes this change in America to the wider availability of refrigerators, and thus better preservation of vaccine, but more potent vaccines and improved health services certainly played a role. In 1959, when the World Health Assembly first agreed to begin a global eradication programme, both Europe and North America had become free of endemic smallpox. Also smallpox-free were the countries of Central America and several in Asia. This was especially significant as a practical demonstration that smallpox transmission could be interrupted even where health facilities are limited and transport and communication problems are difficult.

Between 1958 and 1966, a number of countries mounted what were termed eradication programmes - in fact, most were simply mass vaccination campaigns. Comparatively few

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countries, however, became free of the disease. Deciding that additional technical and logistical support as well as a better coordination of efforts were required, the World Health Assembly in 1966 decided to provide a special budget of approximately £ 1 000 000 for the programme.

The intensified programme thus began in January 1967. That year 42 countries reported a total of over 131 000 cases (World Health Organization, 1973). Surveys since then suggest that, at most, one case in 20 was actually reported. Thus, it is estimated that at least 2 500 000 cases occurred that year in 30 endemic countries and in 12 others which experienced importations (Fig. 1).

Progress during the past six years has been gratifying. During 1972, 19 countries recorded 65 000 cases. Reporting, however, has been greatly improved to the extent that it was estimated that at least one-half of all cases which occurred were recorded. The actual number of cases which occurred in 1972 is thus estimated to be not more than 150 000 as contrasted to 2.5 million cases in 1967. Of the 19 countries reporting smallpox, 11 experienced cases as a result of importations. As of January 1973, in fact, only five countries were considered to be endemic - Ethiopia, India, Bangladesh, Pakistan and Sudan.

Three factors may be identified which have contributed significantly to this rapid change - (1) universal use of fully potent freeze-dried vaccine in endemic areas and an improved technique for its administration; (2) the introduction of sample survey techniques to appraise vaccination performance and (3) perhaps most important, a change in strategy of the programme from one of mass vaccination to one based on epidemiological considerations.

In a programme based on vaccination, the need to be assured that vaccine is fully potent when it reaches the arm of the recipient is obvious - yet this factor is regrettably often neglected. Freeze-dried vaccines which maintain acceptable levels of potency for at least one month at 37°C have proved indispensable in the programme, especially in tropical areas. However, despite the development almost 20 years ago of practical methods for producing such vaccines (Collier, 1955), it was found when the programme began in 1967 that not more than 10 to 15 per cent of the vaccine then in use in the endemic countries was freeze-dried and met requisite standards. Assistance was given to vaccine producers in the endemic areas; reference centres were established for routine quality control of vaccine; and donations were received from many countries. By 1969, more than 95 per cent of the vaccine in use met accepted standards. Today, two-thirds of the more than 200 000 000 doses required annually in endemic areas is produced in the developing countries. Vaccination programmes were further facilitated by the introduction of 1968 of the bifurcated needle. With this needle and the multiple puncture technique, the efficacy of vaccination improved and a saving of approximately 50 per cent 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 vaccination programme. Methods for conducting sample surveys were devised which called for examination of only a small proportion of a population to evaluate vaccination status and, thereby, performance in the vaccination programme. The methods necessarily had to be simple to be employed effectively by field workers. Thus, the more elaborate and precise sample selection techniques required to obtain a valid statistical estimate were abandoned in favour of obtaining what we have termed an "operationally useful" sample. It was everywhere apparent that when the teams knew their work was regularly monitored, performance invariably improved. 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

of one or two years 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 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.

While these improvements in the vaccination programme were of importance, it was apparent from the inception of the programme that mass vaccination, while serving to retard transmission, rarely was successful in interrupting transmission. Particularly emphatic among many examples was the experience in Central Java where in 1969 a carefully designed sample survey revealed that more than 95% of the Province's 23 million persons bore scars of vaccination (Arbani, 1971). Nevertheless, during the same year the surveys were conducted, almost 1700 cases occurred; 85% of all cases were in persons who had never been successfully vaccinated. In brief, infection continued to be transmitted principally among the unimmunized who constituted less than five per cent of the population. While an apparently simple solution would have been to vaccinate the remaining five per cent, the logistical 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 of nothing more nor less than 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 focussed 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 nil levels. Analysis of the data obtained has permitted especially susceptible groups and the common means of transmission of smallpox to be identified, thus permitting redirection of the routine vaccination effort to focus on problem areas.

Necessarily 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. At the beginning of the programme, basic reporting networks in most endemic countries were found to be limited or non-existent. Establishing such networks has been time consuming, requiring not less than one to two years. The key to their development 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 others. Such teams, in addition, investigate all suspect cases, take containment measures and trace the source of smallpox infection to other possibly infected villages. The regular visits of the teams and their demonstrable response if cases are reported considerably facilitate cooperation. For the smallpox programme, the often maligned routine morbidity reporting system has, in fact, been the foundation of the surveillance scheme. While still not functioning optimally in most countries, it has so far functioned well enough to permit the interruption of transmission in 25 of the 30 originally endemic countries.

Where health facilities are plentiful and health workers frequently visit villages, the detection of cases is not a significant problem. Such is the situation in India, and, to a lesser degree, in Pakistan. Most outbreaks in these countries can be detected within four to six weeks after the onset of the first case. If detected within six weeks, it has been found that most outbreaks can be successfully contained before spread occurs beyond the immediate locale.

In countries where health facilities and personnel are sparse, such as in many countries of Africa, additional measures for the detection of cases are essential. During the past two years, techniques have evolved for what is termed an "active search" for cases. An excellent illustration of the approach employed is provided by Ethiopia. Ethiopia is a vast country, being equivalent in size to the United Kingdom and France combined. The population of 26 million persons is widely scattered, more than half living more than a day's walk from any accessible road. There are, in all, only 600 health centres and health stations or one per 40 000 people. Most are staffed by a single dresser. In all, only 3200 persons of all categories are employed in the medical services. The smallpox programme staff consists of only 100 persons of which four are physicians. On the surface this would appear to be an impossible area in which to implement a surveillance programme - especially with so small a staff. As a first step a reporting system was developed based on the existing health facilities and employing whatever communications existed - and these are limited. In illustration, one report which was received was transmitted from a health unit by a runner who reached a police radio after four days' walk. The system is fostered and encouraged by surveillance teams comprised of Ethiopian sanitarians and health volunteers from the United States of America, Japan and Austria who travel constantly throughout the provinces as one and two-man units. Most travel is done by mule or on foot. In 1971 and 1972, these teams investigated and provided detailed epidemiological reports on over 41 000 cases of smallpox. When there are no known outbreaks with which they must deal, active search is instituted. A specific example may best illustrate how this is done (de Quadros et al., 1973). In June, 1972 one of the three two-man surveillance teams from Shoa Province decided to undertake an active search for cases in Selale Awraja (District), comprising an area almost as large as Greater London and a population of 275 000 persons. While no cases had been reported from this District for over six months, the adjacent province was known to be heavily endemic. A single all-weather road traverses the District from the south-west to the north-west (Fig. 2). The first component of the search included visits to each of the four health stations and the health centre. The second component in the search was the 18 schools which are attended by some 3000 students from all parts of the District, some of whom remain in residence and return to their home villages every four to eight weeks. Parenthetically, it is noted that schoolchildren throughout the world have proved to be one of the most fruitful sources of information as to the occurrence of smallpox cases. The standard approach in the schools is to discuss the characteristics of smallpox using the WHO Smallpox Recognition Card (World Health Organization, 1972) and then to inquire as to whether any are aware of similar cases. A third component in the search was the nine principal markets which are held every week at different locations in the District. Some who attend walk for as many as two to three days. Practically, however, the Ethiopian staff has found that reasonably complete information at a market can be obtained regarding cases within a 12 kilometre radius. Again, the WHO Recognition Card is used. Finally, district and sub-district governors and village leaders were contacted. The investigations were completed during a 14 day period.

Two outbreaks, one of two cases and one of eight cases, were found during the two weeks' active search. Two cases were found in the market town of Gebra Guracha, both with onsets in June. Their source of infection was Ijirri, three hours walk from Gebra Guracha. The outbreak in Ijirri consisted of eight cases in three households. The first case had occurred six weeks previously in a young woman who had been infected in the neighbouring province.

Information regarding this outbreak was provided at a high school nine hours walk from Ijirri at the primary school and in the market at Gebra Guracha, three hours walk away, and at two other market sites, each six hours walk from Ijirri. Not only was it known by various informants that cases had occurred but some were able to provide the names of the heads of households afflicted. Other cases were also reported but, on investigation, these were found to be chickenpox or measles. In all, 3632 persons were vaccinated to contain the outbreak. No subsequent cases were detected in this District during the subsequent six months.

This example illustrates specifically the nature of the active surveillance activities now in progress throughout the endemic world and perhaps conveys best the nature of the present strategy, emphasizing the detection of cases and limited vaccination of the population at greatest risk in order to interrupt chains of transmission. In the meantime, routine vaccination programmes are conducted to improve the overall immunity in the population. With improved levels of immunity, transmission is retarded thus making the work of the surveillance teams easier.

The "final phase" of the global programme was begun with the objective of reaching a nil incidence by the end of the 1974 smallpox season. Superficially, this might appear unduly ambitious. In 1972, more than 65 000 cases were recorded - approximately 23% more than in 1971 and almost twice the number reported in 1970. In addition, significant setbacks were experienced in 1972 when major epidemics occurred in both Bangladesh and Botswana, previously smallpox-free countries.

As the 1972-1973 smallpox season began, however, there were for the first time, surveillance activities throughout the endemic areas. More cases were being discovered but more chains of transmission were being interrupted. The quality of the surveillance efforts was not yet at the level desired in some of the endemic areas but the gap was rapidly narrowing. This is important as experience has shown that when surveillance activities, even of a moderate quality, are extended throughout an endemic area, transmission is usually interrupted within two years.

In sharper focus, what is the status of the programme as of January 1973. In 1967, endemic smallpox was present in Brazil, in most countries south of the Sahara in Africa, and in six countries of Asia. In South America, the last case was detected in April 1971, near Rio de Janeiro. As of December 1972, Brazil, the only endemic country in the Americas during the past seven years, had 26 surveillance units and over 5000 reporting posts. None have reported cases since April 1971. A special active search was conducted between March and October 1972, during the usual peak of the smallpox season. In all, 448 municipios (countries), almost 10% of the country's total number were searched much as is being done in Ethiopia. A total of 875 000 persons were contacted. No cases were found. In brief, it seems reasonably certain that after 450 years smallpox has been eliminated from the Western Hemisphere.

In Africa as of January 1973, smallpox appeared to be confined to only two countries - Sudan and Ethiopia. Outside of these two countries and Botswana, no endemic foci have been detected since August 1971. Botswana experienced major outbreaks in 1972 following an earlier importation from South Africa. Beginning in April that year, this was aggressively dealt with - the last cases being detected six months later, in October 1972. Four surveillance teams are engaged in an active search for cases. Sudan detected only 40 cases in the last quarter of 1972, all confined to remote foci in two southern provinces. The interruption of transmission is expected early in 1973. The programme in Ethiopia, begun as recently as January 1971, has made excellent headway (Fig. 3). By March 1973, smallpox was expected to be confined to four of the country's 14 provinces. By the end of 1973, a nil incidence in Ethiopia and on the continent of Africa itself is not an unreasonable expectation.

In Asia, three of the six countries which were endemic in 1967 appeared to have stopped transmission as of January 1973: Indonesia where cases last occurred in January 1972; Afghanistan where all cases since February 1972 have been among nomads infected in Pakistan; and Nepal where all cases since June 1972 have been traced to importations from India. Problem areas in Pakistan, as of January 1973, were virtually confined to 10 districts in Sind Province containing only 15% of the country's population where an intensive surveillance programme has been implemented.

In terms of achieving eradication within the time targets noted, the most difficult problem appears to be that of interrupting transmission in certain areas of India and Bangladesh. Bangladesh after 18 months of freedom from smallpox 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. Fortunately, as of January 1973, the epidemics were still largely confined to the western and south-western districts but no significant reduction in incidence had yet been achieved. In India, on the positive side, the southern states have virtually interrupted transmission and about half of the country's population lives in states which are smallpox-free. Almost all states have a good surveillance programme. However, as 1973 began, major epidemics were occurring in almost a solid band across the whole of northern India. Paradoxically, perhaps, health services in these areas are far better developed than in most endemic areas where transmission has already been interrupted; transport and communications are likewise less of a problem; five to 10 times as many smallpox staff per capita are employed; and rarely does one find an area where less than 80% bear scars of vaccination. The failures in these areas can be attributed to the fact that for many years little attention was paid to the development of surveillance activities. Comparatively recently, government officials finally began to take steps to remedy the situation and additional assistance was given by the World Health Organization. As of January 1973, however, much remains to be done.

Thus the problems of northern India and Bangladesh are of greatest concern and appear to pose the principal threat to the realization of global eradication. A second, although presently doubtful concern, is the question of the significance of certain variola-related pox viruses recently isolated.

Mindful of the unhappy late discovery of animal reservoirs of yellow fever and malaria, the Organization, since 1967, has encouraged and supported studies to determine whether or not variola virus could have an animal host other than man. It seems that if there were an alternate host, non-human primates would be the most likely candidates. Strongly militating against this possibility was the demonstrable fact that smallpox had disappeared from the Philippines, Malaysia, Central America and several other areas where large colonies of primates are closely associated with man.

It was felt that more should be done to define the behaviour of variola in primates when artificially inoculated and to determine the natural ecology of the closely related monkeypox virus, outbreaks of which had been documented only in captive monkeys. Any type of special search for naturally occurring outbreaks of pox infections in monkeys seemed of doubtful value as only a few such outbreaks had been described in the literature, the last in 1936 (Arita & Henderson, 1968). None had been documented virologically and subsequent observations suggest that some, if not most, were caused by other viruses.

Surveys in 1967 and 1970 of 51 biological institutions (Arita et al., 1972) revealed that 10 outbreaks of monkeypox had been observed in captive monkeys since first isolation of this virus in 1959 (Magnus et al., 1959). No human cases had occurred in conjunction with these outbreaks. The virus strains recovered were identical and although similar to variola

virus, clearly distinguishable from it. Considering that over 130 000 monkeys are imported annually into the United States of America and perhaps as many into Europe, the number of outbreaks seemed surprisingly small.

In an effort to identify geographic areas where monkeypox virus might be circulating and subsequently studied, 2200 sera from 14 species of African and Asian monkeys were examined (Arita et al, 1972). None contained significant levels of pox-virus antibody. This was an unexpected finding as it has been shown that antibody of high titre persists for at least six years after infection. Special studies were undertaken in Malaysia, the area from which many of the monkeys involved in the monkeypox outbreaks had come. Over 500 sera were processed. None contained antibody. In the meantime, none of the laboratories with which the Organization had been in contact observed further outbreaks of monkeypox. This line of investigation seemed to have reached a dead end.

In the meantime, transmission experiments with variola virus were conducted in *Macaca irus* monkeys, a known susceptible species (Noble & Rich, 1969). When infected with variola virus, these monkeys develop skin lesions and an illness not unlike smallpox. It was found that infection could be passed from one to the next by contact transmission with cage mates. Interestingly, however, the number of skin lesions observed in each successive passage decreased and twice on the third passage and once on the eighth passage, further transmission failed. These experiments added further support to the belief that a simian reservoir of variola virus was unlikely.

In 1970, just as consideration was being given as to what, if any, other avenues might profitably be explored, 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 (Ladnyj et al, 1972). Since August 1970, 13 such cases have occurred (Table 1). The illness in 10 was wholly typical of smallpox; three patients each had fewer than 10 lesions from which the scabs had separated by the fifth day. All but one was unvaccinated. The cases were widely scattered from Sierra Leone to southern Zaire (Fig. 4). All were single cases except in Liberia, where a group of four cases developed almost simultaneously among children living in adjacent huts and in Zaire, where a mother and child became ill within a few days of each other. Most occurred in remote villages in or near the tropical rain forest. Intensive investigations were conducted over a wide geographic radius surrounding each of these cases. No source of infection was discovered for any and none of over 100 unvaccinated close contacts subsequently contracted the disease. Seven isolates were recovered by the WHO Regional Reference Laboratories and all appeared indistinguishable from monkeypox virus isolated from outbreaks in captive monkeys (Marennikova et al, 1972). Residents of these areas, however, reported having observed no illnesses among monkeys or other mammals. In some instances, the patients had had close contact with monkeys before becoming ill but one case which occurred in eastern Nigeria lived in an area almost bereft of mammals. A serological and virological survey of several hundred mammals of all types was conducted in Liberia in the vicinity of a case. No viruses were isolated.

It would seem probable that the recently detected human monkeypox cases were not the first such cases to have occurred, previous cases undoubtedly having been obscured by the formerly 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 the 13 patients failed to transmit the virus to their more than 100 unvaccinated close contacts suggests that these may be incidental, infections of no epidemiological significance.

One further puzzling finding has been the isolation of three strains of poxvirus from monkey kidney which differ significantly from monkey pox and, in fact, are difficult to distinguish from variola (Marennikova et al, 1972). These have been called "white poxviruses"

(Gispen & Brand-Snathof, 1972). Two strains were isolated from monkey kidney tissue cell culture and one from the kidney of an apparently healthy chimpanzee captured in the area where a human monkeypox case had occurred. The relationship of these viruses to smallpox and monkeypox is, as yet, uncertain. A number of laboratories are now collaborating in a variety of different lines of research to appraise these strains.

In brief, this is the status of the smallpox programme as of January 1973. In the main, the results are encouraging. The problems in India and Bangladesh are difficult but should be able to be overcome with a concerted effort directed specifically toward the development of surveillance activities. At the same time, the possibility must continue to be explored, however remote it may seem - and it does seem remote - that a reservoir of variola virus other than man might exist. Many are collaborating actively in this effort.

It would seem, however, not unreasonable to anticipate that sometime in 1974, a milestone in medical history could be reached - the occurrence of the last case of smallpox. The events of 1973, the most critical year for the programme, will determine this.

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FIGURE 1

SMALLPOX ENDEMIC COUNTRIES, 1967 AND 1973 (JANUARY)

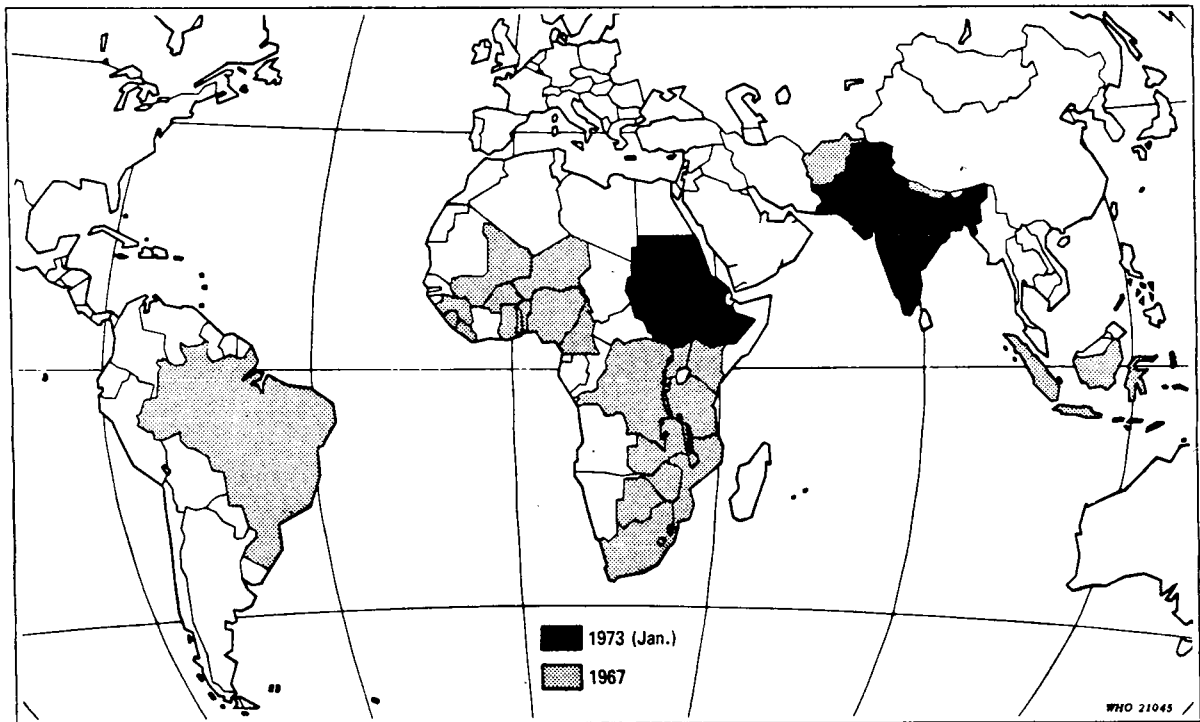


FIGURE 2

EPIDEMIE DE VARIOLE DANS LE DISTRICT (AWRAJA) DE SELALE, ETHIOPIE

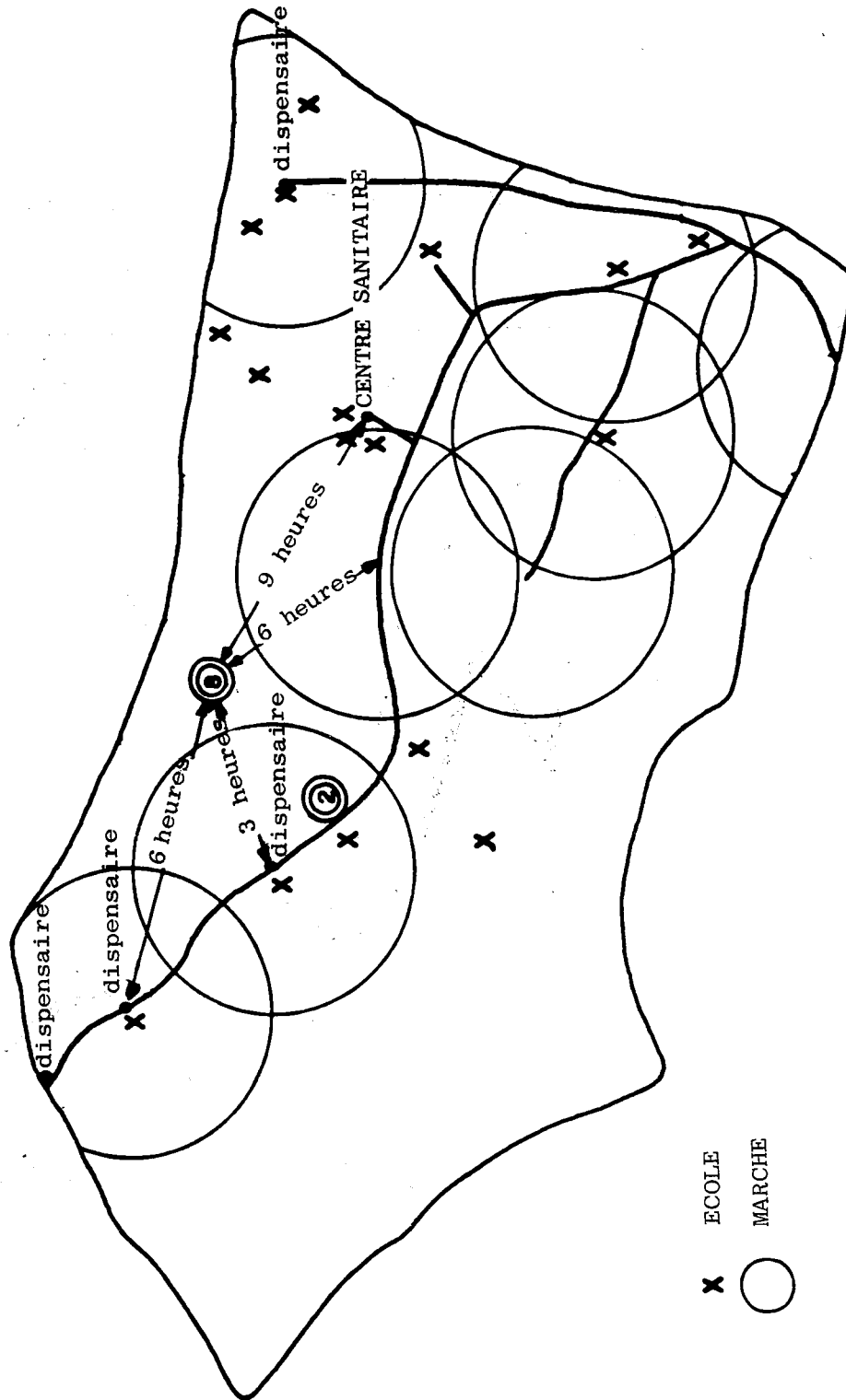


FIGURE 3

CAS DE VARIOLE NOTIFIES EN ETHIOPIE, 1971-1972

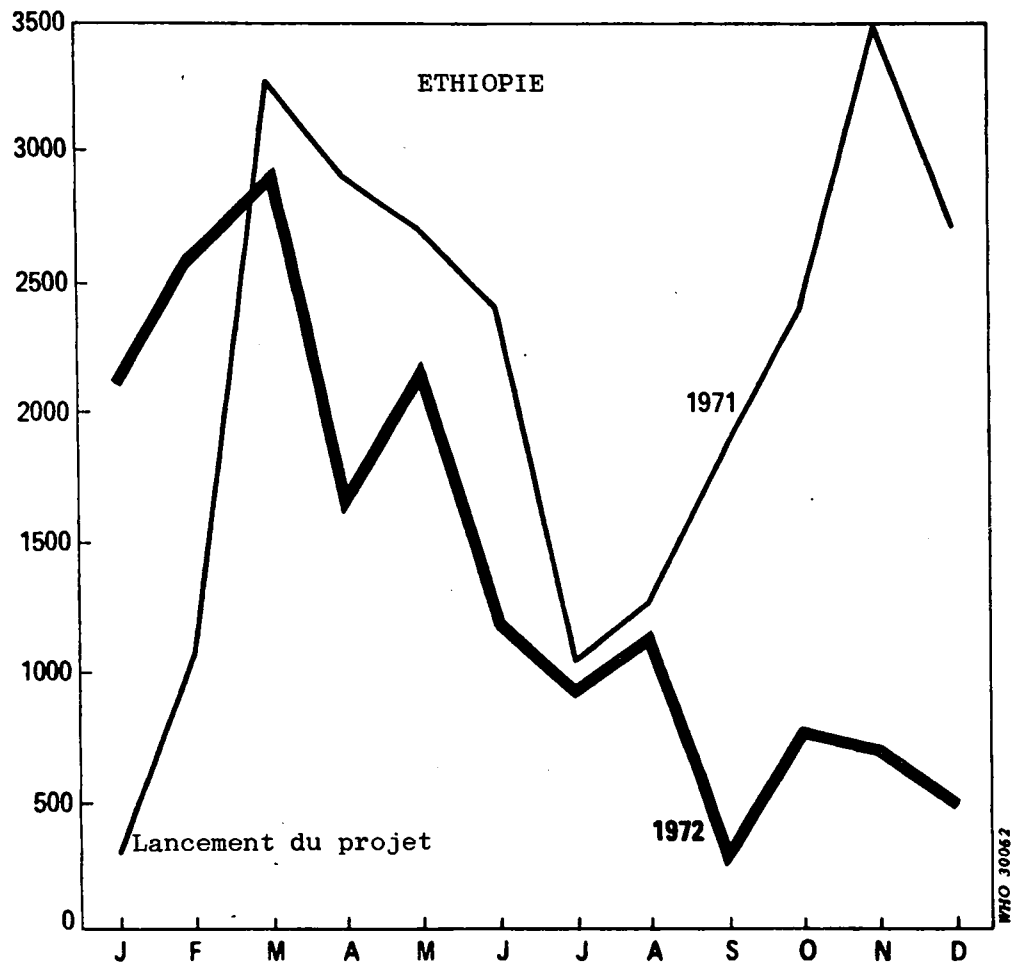


FIGURE 4

SITUATION DES CAS DE MONKEYPOX, 1970-1972

