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WHO EXPERT COMMITTEE ON SMALLPOX ERADICATION

Second Report

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GENEVA

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WHO EXPERT COMMITTEE ON SMALLPOX ERADICATION

Geneva, 22-29 November 1971

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WHO EXPERT COMMITTEE ON SMALLPOX ERADICATION

Second Report

1. INTRODUCTION

The WHO Expert Committee on Smallpox Eradication met in Geneva from 22 to 29 November 1971. The meeting was opened on behalf of the Director-General by Dr L. Bernard, Assistant Director-General. Dr Bernard recalled that, in accordance with a resolution adopted by the Nineteenth World Health Assembly in 1966, the Organization had embarked on an intensified global programme of smallpox eradication in 1967. At the time it was hoped that this programme could be completed within 10 years. Almost 5 years had elapsed since then and the primary tasks of the Committee were to review the progress of the programme; to assess critically the present smallpox situation and the implementation of global and national programmes; and to consider the strategy and methodology to be employed during the years to come. As it had been 4 years since the WHO Scientific Group on Smallpox Eradication¹ had met, and almost 8 years since the last meeting of the WHO Expert Committee on Smallpox,² it was necessary to review the observations and recommendations of those groups regarding the epidemiology and control of smallpox, including the international quarantine requirements for vaccination, in the light of the latest information.

2. DEFINITION AND CRITERIA OF SMALLPOX ERADICATION

Eradication of smallpox is defined as the elimination of clinical illness caused by variola virus. Since smallpox is transferred direct from man to man in a continuing chain of transmission, and since there is no human carrier state of epidemiological importance and no recognized animal reservoir of the disease, the absence of clinically apparent cases in man may be assumed to signify the absence of naturally occurring smallpox.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 393.

² *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 283.

In order to be able to confirm the interruption of smallpox transmission an effective surveillance is needed so that clinical infections can be detected. Recent experience indicates that, in all countries with a reasonably effective surveillance programme, residual foci can be detected within 12 months of apparent interruption. Thus, in countries with active surveillance programmes, at least 2 years should have elapsed after the last known case—excluding well-defined and contained importations—before it is considered probable that smallpox transmission has been interrupted.

Because of the ease with which smallpox can be transmitted from one country to another, the concept of "eradication" can apply only to a continent. Thus, although smallpox may be considered to have been eradicated from certain continents, it cannot yet be said to have been eradicated from Africa, Asia, or South America.

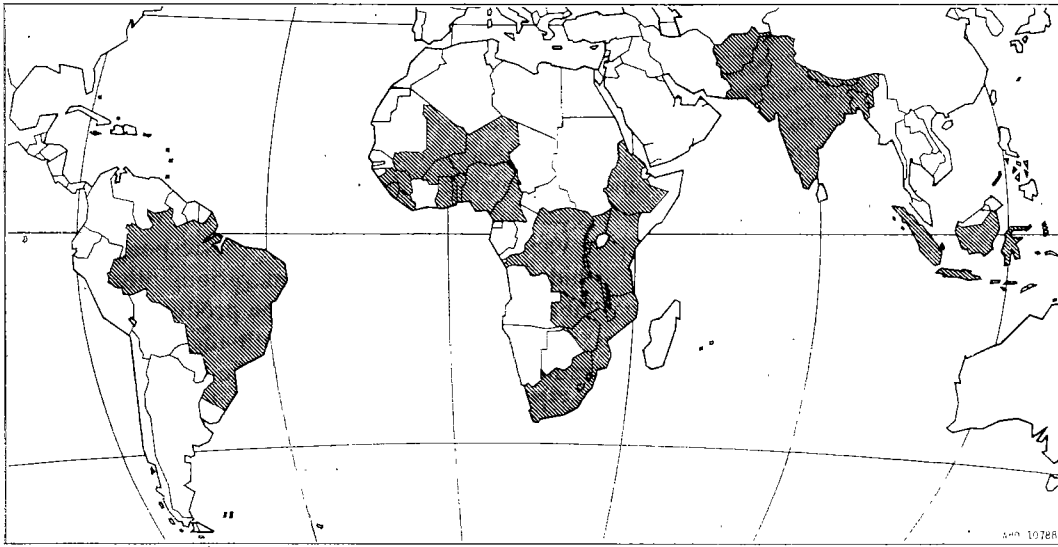
On the basis of epidemiological and technical considerations and the considerable experience acquired so far, the Committee believes that the global eradication of smallpox, as defined above, is possible.

3. DEVELOPMENT AND STRATEGY OF THE PROGRAMME

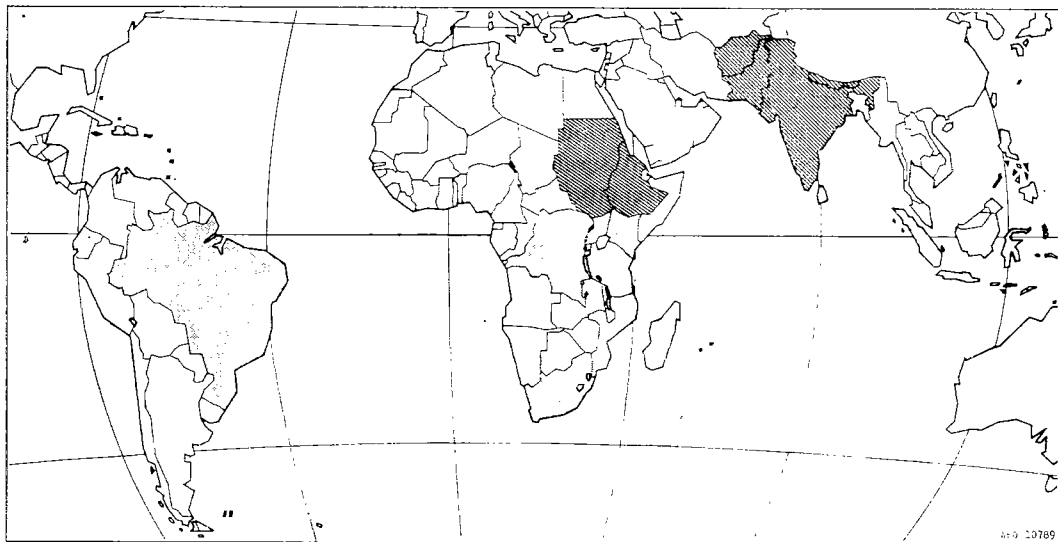
Whereas smallpox was once endemic throughout the world, its geographical limits have been increasingly constricted. In the first half of this century, Europe and North America became smallpox-free through extensive vaccination and energetic containment measures. In the Americas, a regional eradication programme initiated in 1950 succeeded in virtually eliminating the disease from many countries. During the same period, several countries of Asia and North Africa were freed of the disease by intensified vaccination programmes. The continuing threat of the introduction of smallpox into all countries and the evident success of programmes even in countries with comparatively limited health services led the Eleventh World Health Assembly, in 1958, to propose that smallpox eradication be undertaken on a global scale. During the following 8 years, several countries began systematic vaccination programmes directed towards smallpox eradication. Only a few were successful. It became evident that additional technical and material assistance were needed for a programme developed and co-ordinated on a regional as well as a world-wide basis. The Nineteenth World Health Assembly therefore adopted a resolution proposing an intensification of the global smallpox eradication programme and this proposal was put into effect at the beginning of 1967.



In that year, smallpox was considered to be endemic in 30 countries including, in Africa, most countries south of the Sahara; in Asia, Afghanistan, India, Indonesia, Nepal, and Pakistan; and in South America, only Brazil (Fig. 1). Twelve additional countries had reported cases of smallpox which, however, were believed to have been imported. Smallpox trans-

FIG. 1
COUNTRIES WITH ENDEMIC SMALLPOX
SITUATION IN 1967



SITUATION IN 1971



-  Endemic countries
 Countries where transmission is believed to have been interrupted but less than 2 years have elapsed since the last indigenous cases were reported

mission had already been successfully interrupted in many developing countries in Asia and the Americas where health services were limited and communications difficult. This suggested that the objective of global eradication was both technically and operationally feasible.

In developing the programme, it was recognized that adequate supplies of high-quality freeze-dried vaccine were essential to success. Surveys showed that not more than 10–15% of the smallpox vaccine then in use in the endemic countries was freeze-dried vaccine that met recommended WHO standards. The Organization provided vaccine producers with assistance in the form of equipment, fellowship training, and consultants; a detailed manual on vaccine production was prepared; and two WHO Reference Centres for Smallpox Vaccine were designated.¹ The responsibilities of these laboratories included testing vaccines from various other laboratories; training national laboratory workers in vaccine production; and evaluating new techniques of vaccine production. Both the quality and the quantity of vaccines steadily improved. Several of the originally endemic countries—including Brazil, East Pakistan, Guinea, Indonesia, and Kenya—began to produce sufficient vaccine for their own needs. Other laboratories in Asia and South America also began to produce freeze-dried vaccine of acceptable quality for their own use. In addition to indigenously produced vaccine, approximately 150 million doses were required annually to carry out the programme; these were donated by 20 Member States, the largest contributors being Canada, the USA, and the USSR. By 1969, more than 95% of all vaccine in use in the endemic countries was freeze-dried vaccine conforming to the requirements laid down by WHO.

A second consideration in the development of the programme was the technique of vaccination. Previously, most vaccinations had been carried out by the easily performed scratch technique. Under field conditions, this induced successful vaccination less frequently than the more difficult multiple-pressure technique did. Alternative techniques for vaccination were sought. The newly developed jet injectors were introduced for programmes in Africa and South America, where special teams vaccinated large numbers at collecting points in the field. The proportion of successful vaccinations was as satisfactory as that obtained with the multiple-pressure method and less vaccine was required to obtain an adequate response. However, problems were encountered in maintaining and repairing the injectors, and they were found to be unsuitable for house-to-house vaccination programmes in Asia. In 1967, the bifurcated needle—newly developed for multiple-pressure vaccination—was found to be just as effective for multiple-puncture vaccination. It also required much less vaccine. Once

¹ Rijks Instituut voor de Volksgezondheid, Utrecht, Netherlands; Connaught Medical Research Laboratories, University of Toronto, Canada.

the vaccination technique had been simplified, the programme was much easier to carry out.

At the same time as the problems of vaccine and vaccination were being resolved, smallpox eradication programmes were being planned in co-operation with the health authorities in each of the endemic countries and of many countries that were so situated geographically as to be particularly vulnerable to the introduction of smallpox. Some programmes began in 1967 but the majority were undertaken in 1968 and 1969. The last of the endemic countries to start its programme was Ethiopia—in 1971. In all, WHO has assisted programmes in more than 40 countries.

The strategy and operational techniques have been modified to adapt national programmes to existing health structures and patterns of vaccination activities. Every programme consists of two principal components, both of which include assessment: surveillance (disease notification, field investigations, and containment of outbreaks) and systematic vaccination. In the past, eradication programmes consisted almost solely in mass vaccination: the present strategy places greater emphasis on surveillance. There are several reasons for this.

The objective of the programme is a zero incidence of smallpox. If the characteristics of persons who contract the disease are known, the vaccination programme can be modified so as to reach these high-risk groups. Analysis of surveillance data indicates that, in most countries, more than 85% of cases occur among persons who have never been vaccinated, and more than 80% among those less than 15 years old. In many areas, a disproportionate number of cases occurs in lower socio-economic groups in the cities, and these individuals frequently introduce the disease into rural areas. Accordingly, vaccination programmes now place more stress on primary vaccination of children and the vaccination of poorer city dwellers.

In addition to its usefulness in defining high-risk groups, surveillance has an even more important part to play in interrupting the transmission of smallpox. In some areas, despite high vaccination coverage, transmission has persisted at low levels as smallpox continues to spread from one person to another among the very small number of susceptible individuals. However, active measures to identify and contain outbreaks have sometimes caused transmission to be interrupted when less than half the population have been vaccinated. The remarkable efficacy of surveillance and containment measures may be explained by the epidemiological behaviour of smallpox, which has been elucidated through the surveillance programme and in special studies. A smallpox patient does not usually transmit the disease to more than 2 or 3 additional persons, and transmission generally takes place as a result of face-to-face contact in the home, hospital, or school. Outbreaks thus develop rather slowly under most circumstances and are mostly confined to geographically limited areas. Containment measures, consisting primarily in intensive vaccination of contacts and their near

neighbours, are usually effective in stopping transmission. Furthermore, if the source of infection of the first case in a village can be determined, previously unrecognized or unreported foci can be detected and similarly contained. Surveillance has thus been the keystone of the strategy for smallpox eradication. Experience has shown that all outbreaks can be investigated and contained by 1-5 teams based centrally or—in the case of large countries—at the provincial or state level. At the same time, these teams can improve regular notifications from health services.

As a supporting measure, systematic vaccination is being carried out in virtually all countries. By increasing the proportion of immune persons, vaccination is creating a partial barrier to transmission, thus reducing the number of chains of transmission that require the attention of surveillance teams. Vaccination is performed by special teams or individual vaccinators, but efforts are always made to obtain the maximum participation of the existing health services. Where programmes are conducted by teams, an assessment unit evaluates the coverage and rate of successful vaccination in a sample of the population 1-2 weeks later. If 80% or more of all age groups, particularly the 0-4-year group, show a vaccination scar, and if primary vaccination is successful in at least 95%, the performance of the vaccination team is considered to have been satisfactory. In countries where smallpox transmission has been interrupted, it has been found desirable and practicable to extend surveillance to other diseases, and the teams have frequently undertaken the administration of other antigens in addition to smallpox vaccine. In this way, the maintenance of smallpox surveillance and vaccination has been ensured, and it has been possible to undertake other needed programmes of preventive medicine at minimal additional cost. Throughout most of the African countries, teams are now administering BCG vaccine too, and those in the countries of western and central Africa are also vaccinating against measles, yellow fever, and cholera.

Furthermore, as the incidence of smallpox approaches zero, the surveillance units have been able to extend their activities beyond the improvement of reporting smallpox cases and the investigation and containment of outbreaks, to include an active search for cases. This modification of the programme calls for surveillance units to plan and undertake regular tours, particularly in high-risk areas, during which they contact health units, the civil authorities, and schools to enquire about unreported cases of smallpox. In some areas, this has proved to be the only effective way of detecting remote foci that would otherwise be reported very late or not at all.

4. WORLD MORBIDITY TRENDS

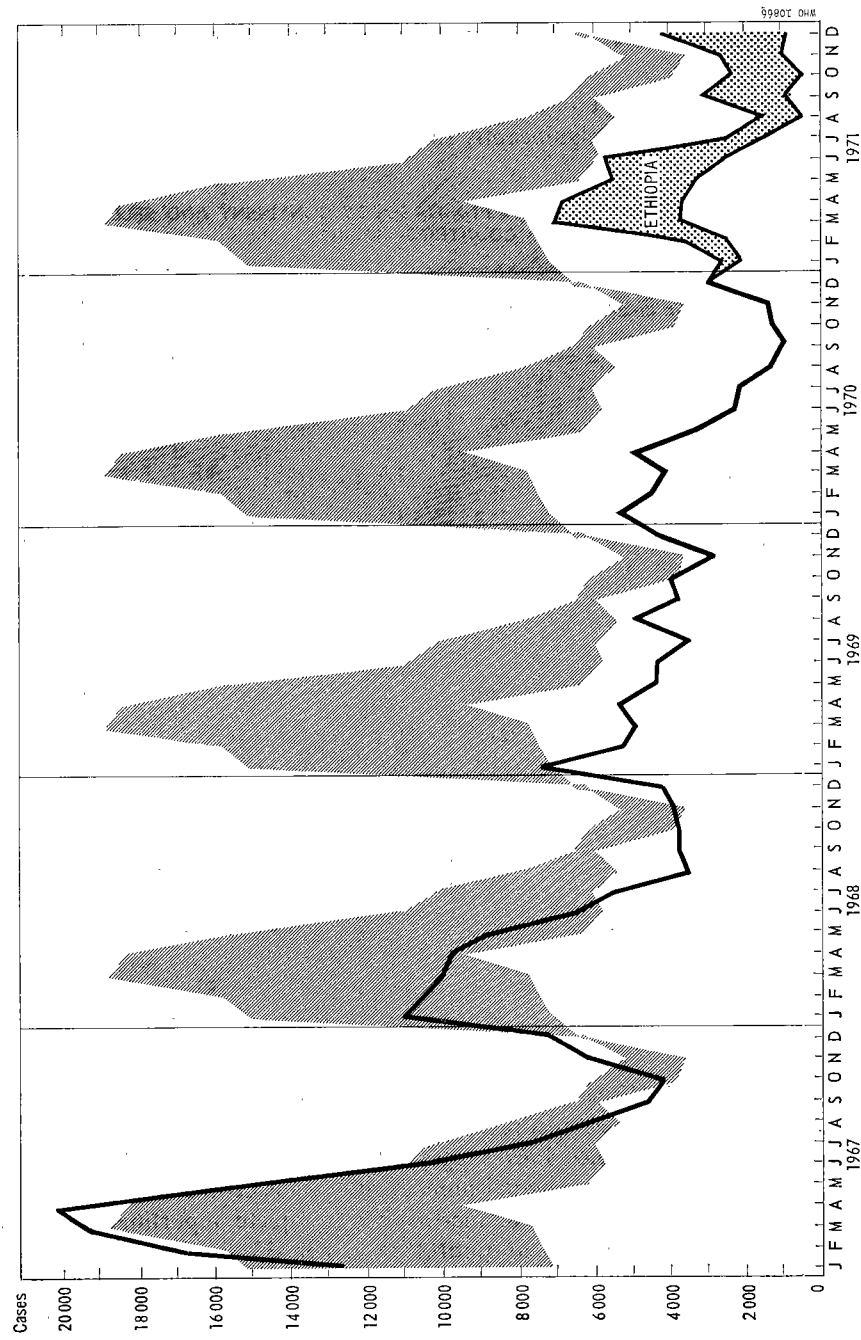
Both the incidence of smallpox and the number of countries reporting cases have decreased significantly since 1967 (Table 1).

TABLE 1. REPORTED SMALLPOX CASES BY CONTINENT AND SELECTED COUNTRIES, 1967-1971

Continent and country	Population (millions)	1967	1968	1969	1970	1971
Africa						
West & west-central Africa	126.5	11 069	5 488	479	64	—
Southern & eastern Africa						
Ethiopia	25.5	466	426	197	722	25 976
Sudan	16.1	9	106	130	1 051	1 141
Zaire	24.9	1 479	3 800	2 072	716	63
Other countries		2 506	1 217	721	606	121
South America						
Brazil	94.0	4 514	4 372	7 407	1 771	19
Other countries		30	3	3	24	—
Asia						
Afghanistan	17.1	334	739	250	1 044	732
India	546.9	84 902	35 179	19 281	12 426	15 690
Indonesia	124.2	13 478	17 350	17 972	10 081	2 100
Nepal	11.3	110	247	162	78	215
Pakistan	132.7	12 461	11 065	5 445	4 665	5 808
Other countries		55	184	98	30	59
Europe		5	2	—	22	—
World total		131 418	80 209	54 223	33 304	51 924
No. of countries reporting smallpox		42	38	30	23	16

In 1967, 131 418 cases were reported—an incidence at the upper limit of the range of cases recorded during the preceding 5 years (Fig. 2). Surveys conducted since 1967 suggest that less than 5% of all cases were then being reported: the actual number of cases is estimated to have been at least 2.5 million. Despite increasingly complete reporting, smallpox incidence declined each year until 1970, when 33 304 cases—the fewest on record—were reported. Yet in 1971 the reported incidence is more than 51 000 cases. Over half of these are accounted for by Ethiopia, which since January 1971 has developed a highly effective eradication

FIG. 2
WORLDWIDE SMALLPOX INCIDENCE, 1967-1971



Note : The grey area represents the range between the highest and lowest incidence reported during the 5-year period 1962-1966.

programme. In the rest of the world, smallpox incidence decreased in 1971 by more than 25% for the fourth consecutive year. With all endemic countries now engaged in eradication programmes, at least one-third of all cases are now believed to be notified. The actual number of cases in 1971 is thus estimated to be about 150 000, in contrast to the 2.5 million cases estimated to have occurred in 1967.

The number of countries reporting smallpox decreased from 42 in 1967 to 16 in 1971. Of the 42 countries reporting smallpox in 1967, 30 were considered to be endemic, whereas the remaining 12 notified only imported cases. At present, continuing endemic transmission is believed to be limited to 7 countries: Afghanistan, Ethiopia, India, Indonesia, Nepal, Pakistan, and Sudan (Fig. 1). Furthermore, 10 other countries have reported indigenous cases within the past 2 years. Since these cases were not known to be imported, the interruption of transmission in these countries must still be regarded as provisional. In addition, cases have been reported by Botswana in 1971 but there is insufficient information to determine their origin. Information from Iran is also insufficient to assess its current status as regards smallpox. During the past 5 years, only one country—Sudan—originally considered to be free of smallpox has again become endemic.

With the decrease in smallpox incidence, importations into Europe have become less frequent: whereas 4 occurred in 1967 and 2 in 1968, there have been only 2 during the past 3 years: 1 each in January and in August 1970. No cases have been imported into North America since 1967.

Considering the present situation and the programmes planned, it seems reasonable to expect that, by the end of 1973, there should be only few residual endemic foci of smallpox. A concerted and co-ordinated effort could result in the interruption of transmission within a short time provided that extensive civil disturbances do not occur.

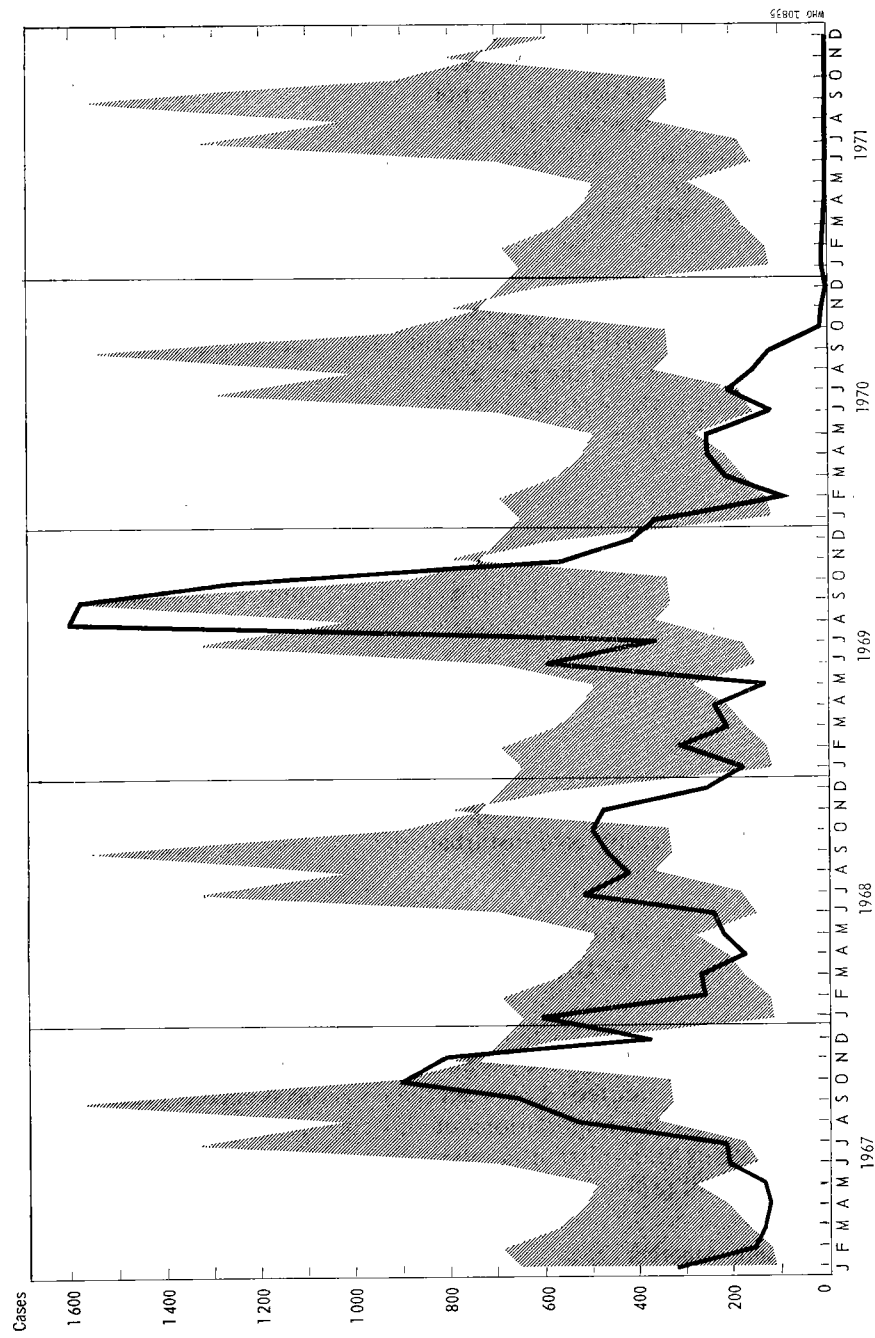
5. SMALLPOX TRENDS IN THE FOUR EPIDEMIOLOGICAL REGIONS

The endemic countries fall within 4 epidemiological regions: Africa, the mainland of Asia, Indonesia, and South America. The probability that smallpox will be transferred between these regions is small. Indeed, during the last 5 years, no importations of this sort have been detected. Thus, when smallpox transmission is interrupted in one of the 4 regions, then that region will probably remain free from smallpox.

5.1 South America

More or less intensive smallpox eradication programmes have been conducted in various countries of South America during the past 20 years.

FIG. 3
SOUTH AMERICA : SMALLPOX INCIDENCE, 1967-1971



Note : The grey area represents the range between the highest and lowest incidence reported during the 5-year period 1962-1966.

By 1967, endemic smallpox was being reported only in Brazil, which began an eradication programme in that year. During the next 4 years, 83.3 million persons (out of a population estimated in 1971 to be 94 million persons) were vaccinated in a well organized and carefully assessed programme. Surveillance activities were begun in July 1969 and the smallpox incidence reported subsequently rose precipitously as the detection and notification of cases improved (Fig. 3). During 1970 a steady decline in incidence occurred until mid-November, when zero incidence was first recorded. Subsequently, a single localized outbreak of 20 cases was detected in suburban Rio de Janeiro and lasted until April 1971 when the last known case of smallpox in South America was reported. Surveillance units in each of the states of Brazil and more than 3 000 reporting posts throughout the country are continuing their surveillance activities.

Several other countries in South America have intensified their vaccination programmes in the past 5 years, although they have devoted less attention to surveillance. Cases were imported into 3 countries during this period and in each instance Brazil was shown to be the source of infection. Since the last case was reported from Brazil, an intensive search for possible residual endemic foci has been undertaken in that and in neighbouring countries. None has been found. Thus transmission has probably been interrupted in South America, but more intensive surveillance will be needed in most South American countries during the next 2 years before this can be affirmed.

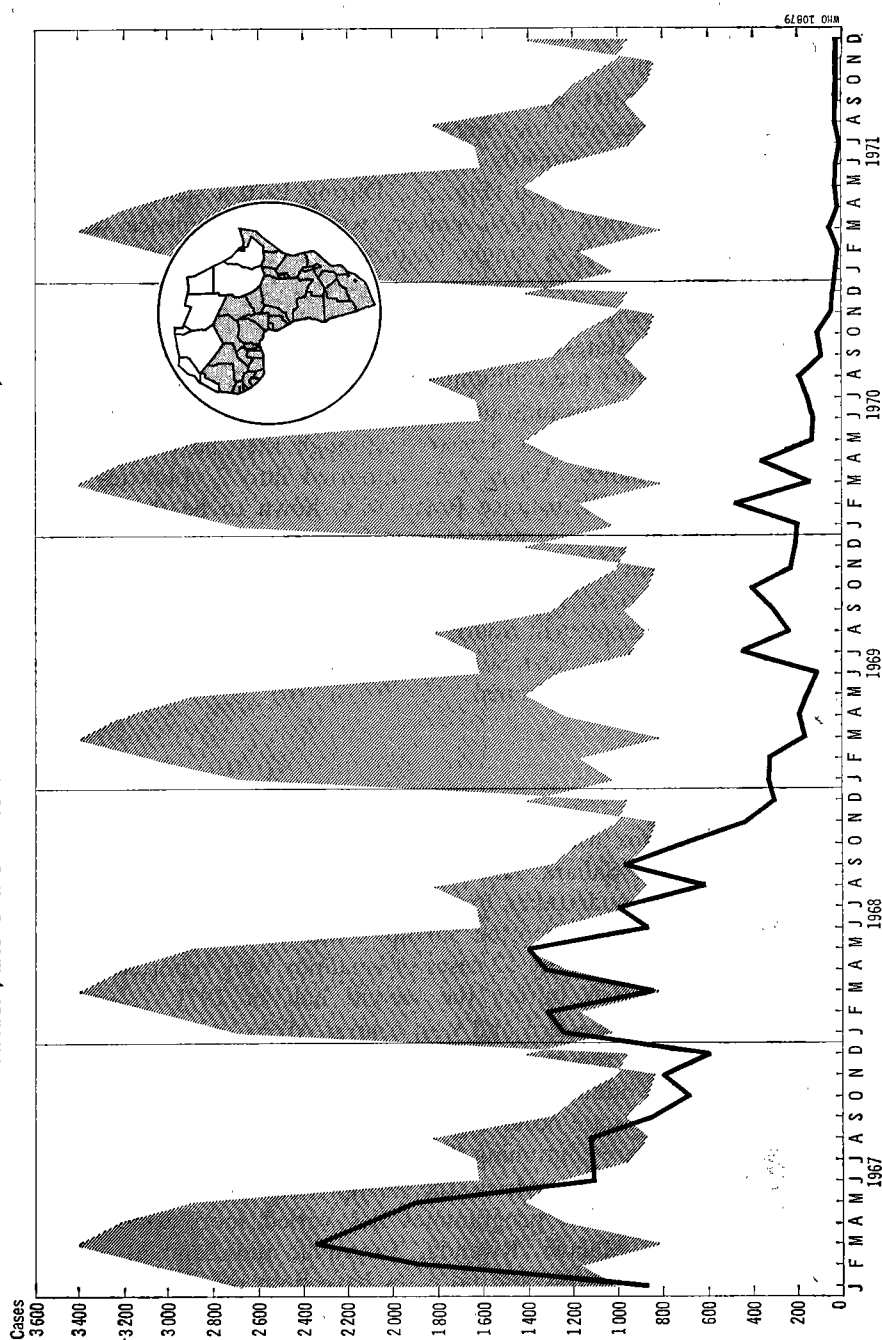
5.2 Africa

In 1967, smallpox was widely endemic throughout most countries of Africa south of the Sahara. During the past 5 years, eradication programmes have been undertaken by most of the African countries. Except in Sudan and Ethiopia, reported smallpox incidence has decreased virtually to zero (Fig. 4). Only 52 cases of smallpox were reported from all other African countries during the second half of 1971.

In 20 countries of western and west central Africa, with a total population of 126 million, reported smallpox incidence had declined to zero by October 1969. One additional outbreak was detected in Nigeria in March 1970, the last known case occurring in May 1970. Surveillance and vaccination programmes are continuing throughout this subregion.

In eastern and southern Africa, the smallpox situation and progress in the individual eradication programmes has varied more widely. In 5 countries (Burundi, Malawi, Rwanda, Tanzania, and Zambia), effective programmes are in progress and no cases have been reported since 1969. Two others (Kenya and Uganda), have notified cases imported in 1971 from Ethiopia and Sudan, but continuing endemic transmission has not

FIG. 4
AFRICA, EXCLUDING ETHIOPIA AND SUDAN : SMALLPOX INCIDENCE, 1967-1971



Note: The grey area represents the range between the highest and lowest incidence reported during the 5-year period 1962-1966.

been recorded in either of them for more than 2 years. Zaire, in the concluding phases of a systematic vaccination programme, had cases in June 1971 and 2 further cases in August, but an excellent surveillance system is believed to have resulted in the interruption of transmission. There is less information regarding smallpox in the southern part of Africa. Angola, Lesotho, Mozambique, Southern Rhodesia, and Swaziland have reported no cases for a year or more, but little is known regarding the quality of the surveillance and the nature of the programmes in these countries. No reports have been provided by South Africa since January 1971. Finally, the occurrence in Botswana in 1971 of 23 proved cases whose sources could not be traced strongly suggests that endemic foci still persist, if not in Botswana, then perhaps in neighbouring areas of South Africa. Even if smallpox incidence in the countries of southern Africa may be approaching zero, it is doubtful whether transmission can be interrupted without substantially improved surveillance and international co-ordination of activities.

The two countries of main concern to Africa—and the only two in which significant smallpox transmission is known to be occurring—are Ethiopia and Sudan. In Ethiopia, a programme commenced in January 1971 with a strategy chiefly consisting in surveillance, vaccination in conjunction with containment activities, and systematic vaccination in the largest towns and along the main roads. During 1971, over 25 000 cases have been detected, compared with only 722 in 1970; over 3 million persons were vaccinated during the year. Because vaccination was carried out on only a limited scale before 1971, there is a large susceptible population. Not surprisingly, the disease is widespread throughout most provinces, and no definite trend in incidence is yet discernible. In Sudan, more than 1 000 cases were reported both in 1970 and in 1971—the highest incidence recorded in 15 years. Present information suggests that Sudan succeeded in interrupting transmission in the early 1960s. The disease appears to have been reintroduced in 1968 and, in the absence of effective surveillance, spread throughout the country during the next 2 years. Since 1968, a partially effective eradication programme has been in progress in the northern and central provinces, but few activities have been undertaken in the 3 southern provinces, from which more than half of all cases are now being reported.

In summary, the problem areas in Africa are primarily southern Africa, Ethiopia, and Sudan. If the programme in Ethiopia can be sustained or augmented, and a modest increase and reorientation of activities can be effected in Sudan and southern Africa, smallpox could probably be eliminated from the whole of Africa within the next 2 or 3 years. In the meantime, continued programmes of surveillance and vaccination in the other African countries will be important in preventing the reintroduction and re-establishment of the disease.

5.3 Mainland of Asia

Since 1967, the only known endemic countries on the mainland of Asia have been Afghanistan, India, Nepal, and Pakistan. The trends in incidence in these countries are shown in Fig. 5. China is reported to have become smallpox-free after intensive vaccination campaigns in the 1950s. Burma and Iran have recorded only infrequent importations of smallpox from the above-mentioned endemic countries.

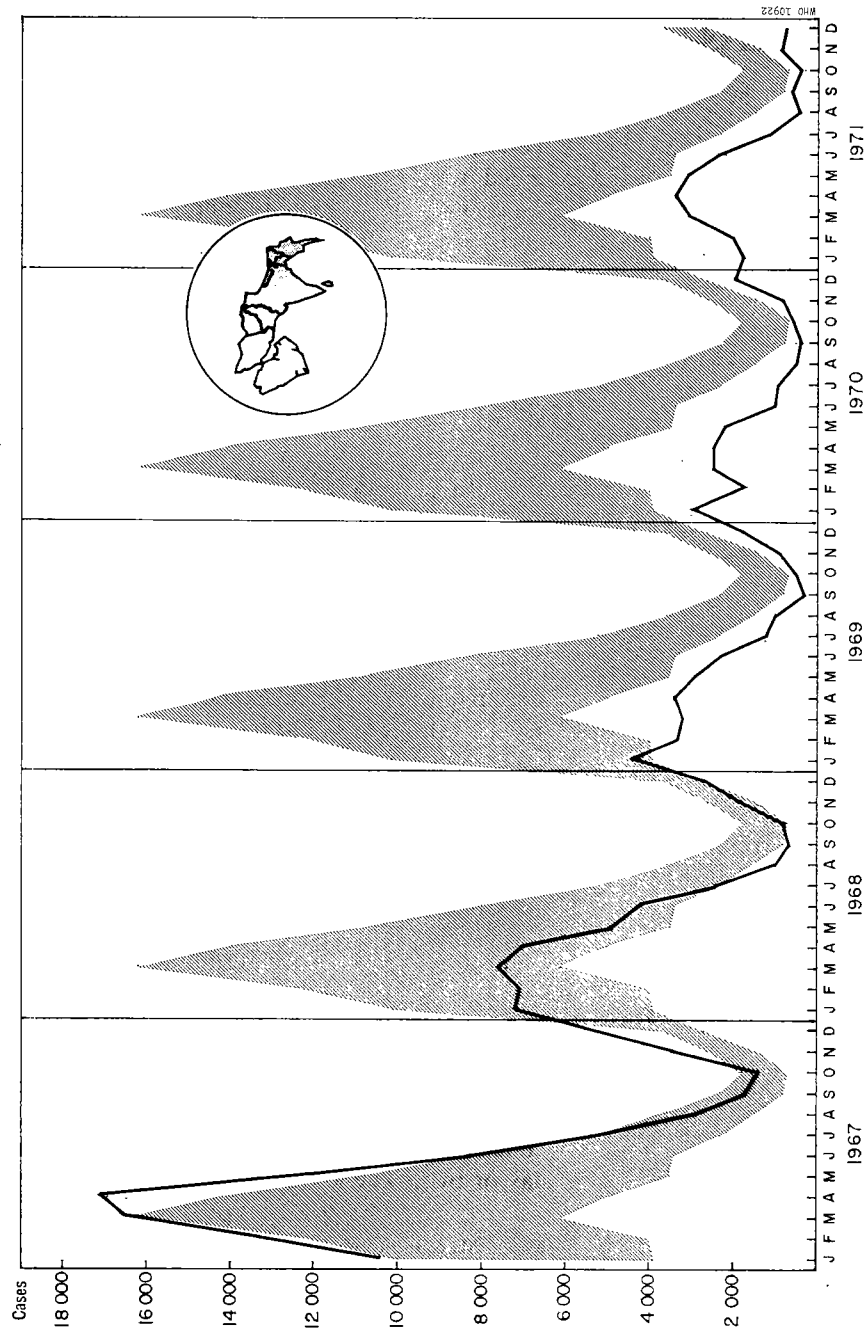
In the third year of a well executed programme, Afghanistan has been experiencing a considerable decrease in incidence: many of the recent cases were infected by variolated persons from remote areas, who had not yet been vaccinated in the systematic vaccination programme. This programme was due to be completed at the end of 1971 but surveillance is being intensified. If the measures now being taken to curb itinerant variolators are successful, incidence may be expected to fall to zero in Afghanistan during 1972.

India is expected to report more than 15 000 cases for 1971, chiefly from the western and northern states. This increase of about 20% over the record low incidence of 1970 is attributed to improved reporting. After 9 years of intensive vaccination, immunity throughout India is comparatively high. Surveillance activities have improved substantially during 1971 but are not yet satisfactory in all states. Progress will depend mainly on how rapidly surveillance and the still unsatisfactory reporting system can be improved. Experience in several Indian states has shown that, once an effective surveillance programme has been developed, transmission can be effectively interrupted within 12-24 months.

Smallpox in Pakistan now appears to be confined to the western provinces. In East Pakistan, smallpox incidence declined to zero in August 1970, within 8 months of the development of a surveillance programme. No cases have been found since by surveillance teams despite an active search. Two of the 4 provinces of West Pakistan began an active surveillance programme in 1971 and transmission there appears to be on the verge of being interrupted. A third province (North-West Frontier), is in its eighth month of an eradication programme and appears to be making satisfactory progress. In Sind—the fourth province—only limited activities have been undertaken so far. Since immunity in West Pakistan, as in India, is already moderately high, transmission could probably be interrupted within 12-24 months of the development of satisfactory surveillance programmes in all provinces.

In Nepal, the vaccination programme and surveillance activities have been gradually extended during the past 3 years. Most outbreaks in 1971 occurred near the Indian border and nearly all these are suspected of having originated in India. The problems of smallpox eradication in Nepal are

FIG. 5
ASIA, EXCLUDING INDONESIA : SMALLPOX INCIDENCE, 1967-1971



Note: The grey area represents the range between the highest and lowest incidence reported during the 5-year period 1962-1966.

inseparably linked with those in India. Additional outbreaks can be expected as long as smallpox is present in the bordering states of India.

5.4 Indonesia

The programme in Indonesia was started in July 1968 in Java and Bali and was subsequently extended to include the outer islands. Routine vaccination was improved and surveillance strongly emphasized. Transmission appears to be confined to limited foci in Java and in the southern part of the island of Sulawesi and may be interrupted soon. Trends in reported cases during the intensive eradication programme are indicated in Fig. 6.

6. CLINICAL SMALLPOX

6.1 Classification of the principal types of variola

Rao's classification of smallpox¹ according to the nature and evolution of the lesions is an improvement on older systems based primarily on the density of the lesions. In addition to presenting a more coherent picture of the disease, it is more useful for prognosis and has proved its value in field investigations. The classification includes 4 recognizable clinical types:² (1) ordinary—the most frequent; (2) modified—mild and occurring in previously vaccinated persons; (3) flat; and (4) haemorrhagic. Variola sine eruptione is a febrile illness occurring after the usual incubation period has elapsed. It is seen in well vaccinated individuals and can be confirmed only by antibody studies or, rarely, by virus isolation.

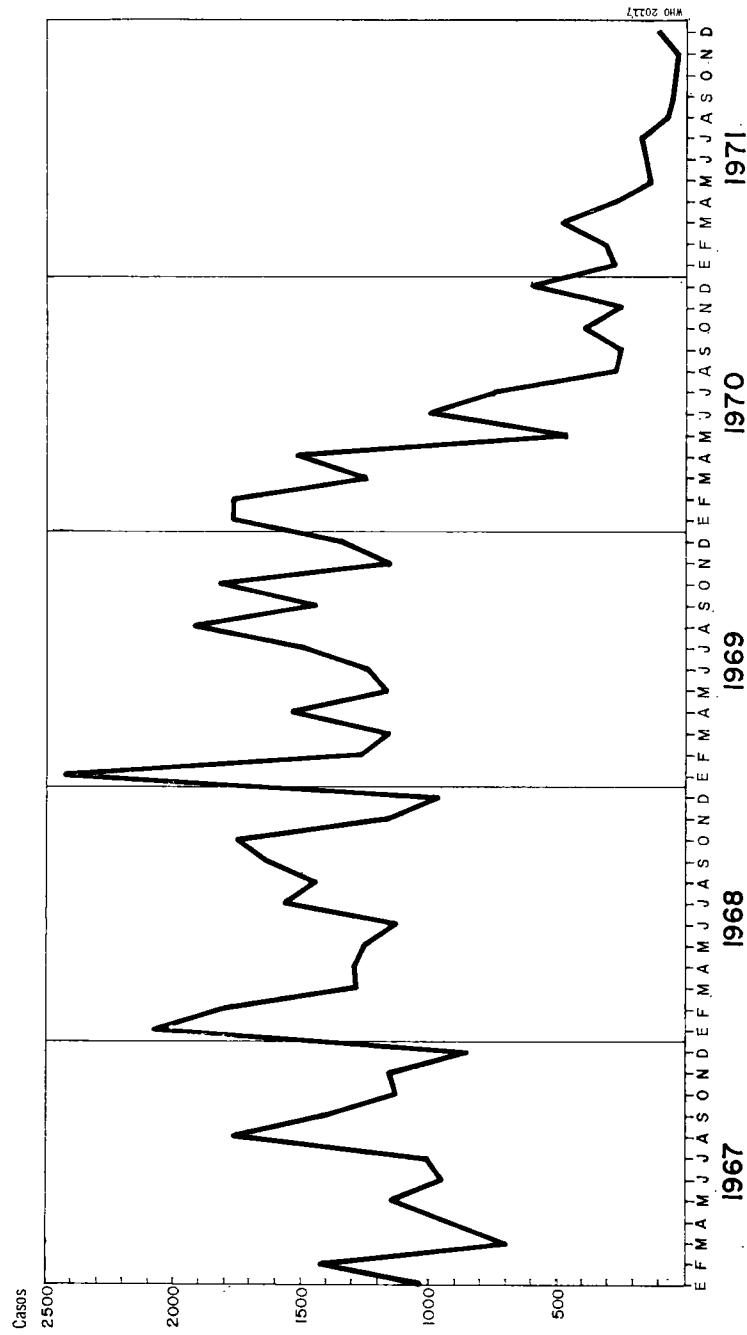
(1) Ordinary

The majority of cases, in both the vaccinated and unvaccinated, are of this type, which corresponds to the classical description of smallpox. The febrile, pre-eruptive illness is of varying severity and lasts 2–4 days. As the eruption develops, the patient's temperature usually drops and he feels better. Fever may return with the development of the pustular stage, depending on the severity of the rash. The lesions appear as papules on the third or fourth day of illness; fluid begins to collect in them, usually within 24–48 hours. The vesicles may be umbilicated and their contents may become pustular in a day or two. The lesions are sharply raised, and

¹ Rao, A. R., cited in Ramsay, A. M. & Edmond, R. T. D. (1967) *Infectious diseases*, London, Heinemann.

² The descriptions of the 4 types given here have been slightly modified from those given by a WHO Scientific Group on Smallpox Eradication, *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 393, p. 12.

FIG. 6
INDONESIA : SMALLPOX INCIDENCE, 1967-1971



tend to be tense and firm to the touch. Drying up of the pustules and scabbing begin from the eighth to the tenth day after the eruption. The eruption shows a centrifugal distribution, and lesions in any one area are at the same stage of development. In general, the severity of the clinical picture parallels the extent of the rash.

(2) *Modified*

In this clinical type, which occurs in vaccinated persons, the modification relates to the character of the eruption and the rapidity of its development. The pre-eruptive illness is usually less severe than in the ordinary type, and secondary fever may not occur during the evolution of the eruption. The skin lesions are often few, though they may sometimes be numerous. They tend to evolve more quickly, are more superficial, and may not show the uniformity characteristic of the typical smallpox eruption. Cases of the modified type are never fatal.

(3) *Flat*

With this type, which is frequently fatal, there is a severe pre-eruptive illness with fever persisting throughout the eruptive phase. The lesions are slow to mature and the vesicles tend to be flat, so that they project little from the surrounding skin. They are soft and velvety to the touch. In the patients who survive, the lesions resolve without pustulation. Cases with haemorrhages into the base of the lesions may not be readily distinguishable from late haemorrhagic cases.

(4) *Haemorrhagic*

Haemorrhagic smallpox is almost invariably fatal. The pre-eruptive illness, which may be prolonged, is marked by fever, intense headache and backache, restlessness, a dusky flush or sometimes pallor of the face, extreme prostration, and toxicity. There is little or no remission of fever throughout the illness. In the fulminating form, haemorrhagic manifestations appear on the second or third day as subconjunctival bleeding, bleeding from the mouth or gums, petechiae in the skin, epistaxis, haematuria, and, in women, bleeding from the vagina. Death often occurs suddenly between the fifth and seventh days of illness, when only a few insignificant maculopapular cutaneous lesions are present. In patients who survive for 8–10 days, the haemorrhages appear in the early eruptive period, and the rash is flat and does not progress beyond the vesicular stage.

6.2 Frequency of clinical types

In outbreaks of variola major, whether in well vaccinated or poorly vaccinated populations, approximately 85% of cases are of the ordinary

type, whereas the flat and modified types may each account for 5-7% and the haemorrhagic type, less than 1%. In outbreaks caused by variola minor and so-called intermediate strains, the severe flat and haemorrhagic forms are extremely rare. Most patients have a less extensive rash than in the ordinary type of variola major, and case fatality rates are lower.

Identification of an outbreak based on the clinical appearance of patients is comparatively straightforward, as the ordinary type of smallpox is readily recognized and accounts for 85% of cases. In addition, more than half the cases of the flat and modified forms are easily diagnosed. Cases of haemorrhagic and other rapidly fatal forms of smallpox, as well as highly modified cases, may be missed even by the alert physician. Thus, an outbreak is rarely identified at the outset by diagnosis of these comparatively uncommon forms. When an outbreak has been identified, any acute haemorrhagic illness should be regarded with suspicion and all precautions taken, as such patients may be highly infectious. Those with the more highly modified forms of smallpox, including variola sine eruptione, disseminate comparatively little virus for a limited time, and are thus less important epidemiologically. Epidemiological investigations show that the patient becomes infectious for others as much as a day before the rash is apparent and is at his most infectious during the following week. Lesions in the mouth and upper respiratory tract, from which the infecting virus is mainly excreted, usually appear at the beginning of the eruptive phase. The virus is present in the skin lesions and crusts, but this source appears to be less important in the transmission of infection. The patient remains potentially infectious until all crusts have separated.

6.3 Differential diagnosis

In endemic countries, much of the surveillance work is usually entrusted to sanitarians, health inspectors, and others who have not been trained as physicians. Instruction in differential diagnosis must accordingly be simplified to the maximum extent. Thus, emphasis is placed on recognition of the ordinary type of smallpox which, as mentioned above, accounts for by far the largest proportion of cases in an outbreak. In non-endemic areas, it is becoming increasingly likely that physicians and other health workers will not have seen clinical smallpox. If the more easily diagnosed ordinary type of case can be recognized, an outbreak may be detected and less typical cases identified by epidemiological investigation. Posters and teaching slides that have been prepared by WHO emphasize recognition of the ordinary case.

Textbooks consider numerous factors in the differential diagnosis of smallpox, but generally place the emphasis on the haemorrhagic or atypical types. In practice, comparatively few diseases simulate ordinary smallpox closely enough to cause misdiagnosis. The experience of the past 5 years

indicates that chickenpox causes the greatest confusion in diagnosis. Less frequently, yaws, secondary syphilis, herpes simplex, impetigo, generalized vaccinia, and scabies are confused with smallpox.

During the first few days, the rash of ordinary smallpox and that of chickenpox may seem similar. The distribution of lesions—more on the limbs than on the trunk in smallpox and the reverse in chickenpox—may provide a clue. However, when the smallpox rash is sparse or the chickenpox rash very extensive, the distribution of lesions may be of little help. The fact that in smallpox there is fever for 2–4 days before the onset of the rash, whereas in chickenpox it occurs simultaneously with the rash, may also be a useful indicator, but there are many exceptions to this pattern. If there is doubt about the diagnosis during this early period, the illness should be regarded as possible smallpox, and containment measures should be taken while the evolution of the lesions is observed. Over a period of 2 or 3 days, the lesions should show either the uniform development of the smallpox rash or the non-uniformity observed in chickenpox, in which scabs form while new vesicles are appearing. It is of considerable assistance to the diagnosis to note the day in the evolution of the rash when scabs are first observed: In smallpox, scabs do not begin to form before the 8th or 9th day of the rash; are present on virtually all lesions at the 14th day; and persist, at least on the extremities, for not less than 3 weeks. In chickenpox, on the other hand, scabs are usually seen within the first 4 or 5 days after the rash develops. Differential diagnosis is facilitated considerably by examining the person from whom the patient contracted the illness or those who contracted the infection from him. As atypical cases are uncommon, it is probable that, even if the infection is atypical in the patient, the contacts will develop typical, easily diagnosed, ordinary smallpox. However, this approach to diagnosis is not always successful, as the seasonal increases in the incidence of both smallpox and chickenpox overlap. Finally, death from smallpox is not uncommon, whereas chickenpox is seldom fatal. Therefore any death ascribed to chickenpox should always be investigated.

In the other diseases mentioned above, the rash develops quite differently from that of smallpox except during the first few days. Thus continued observation of the patient should lead to a correct diagnosis.

In non-endemic areas, specimens from suspected cases should always be obtained for laboratory examination (see section 12, p. 53).

6.4 Variola major, variola minor, and disease caused by intermediate strains

For over a century, a sharp distinction has been drawn between smallpox outbreaks with a high mortality (variola major) and those with a low mortality (variola minor). It was recognized that the two could not be differentiated by clinical examination of the individual patient. However,

cases of variola minor, when considered as a group, were associated with less marked constitutional symptoms; a slightly shorter eruptive period; and a less extensive and more superficial rash that is less likely to leave scars. Differences have also been observed in certain laboratory characteristics between viruses isolated from Asia—where mortality is high—and those from Brazil, where the disease is milder. One of these differences is the maximum temperature at which the virus will grow on the chorioallantoic membrane of chick embryos.

In 1963, virus strains with characteristics intermediate between those of variola major and variola minor were isolated during outbreaks in Tanzania, where the case-fatality rates also appeared to be intermediate between those observed in Asia and in South America.¹

During the past 5 years, more comprehensive data have been obtained regarding case-fatality rates in different areas, and more specimens have been examined in the laboratory. Table 2 shows case-fatality rates in 3 areas in Asia, 2 in Africa, and 1 in South America. In each area, a reasonably complete enumeration of both cases and deaths was obtained through field investigations. From these data, it appears that there is a range of case-fatality rates. Laboratory studies carried out so far reveal that all strains collected in South America and during outbreaks in Europe in which case-fatality rates were of a comparable level do not grow on the chorioallantoic membrane of embryonated eggs incubated at a temperature of less than 38.3°C. Strains obtained from Pakistan and during European outbreaks with comparably high case-fatality rates grow well at 38.3°C. However, the growth of many strains from Indonesia, Kenya, Tanzania, West Africa, and Zaire is partly inhibited at this temperature.

Additional studies, both in the field and in the laboratory, are clearly needed. There may be a range of strains with pathogenicities varying between the extremes of variola major and variola minor.

6.5 Subclinical infection

Although subclinical smallpox infections have previously been considered as rare, recent studies² have shown that they may occur frequently among previously vaccinated household contacts, as well as among very young infants, presumably protected by maternal antibody. However, subclinical infection in persons with no previous contact with either variola or vaccinia virus must be an exceptional event. This is suggested by the fact that during some outbreaks all susceptible persons in households and

¹ Bedson, H. S., Dumbell, K. R. & Thomas, W. R. G. (1963) *Lancet*, **2**, 1085.

² Heiner, G. G., Fatima, N., Daniel, R. W., Cole, J. I., Anthony, R. L. & McCrumb, F. R. (1971) *Amer. J. Epidemiol.*, **94**, 252.

TABLE 2. CASE-FATALITY RATES IN SELECTED AREAS

Country	Year	Age (years)	Cases	Deaths	Case-fatality rate (%)
Afghanistan	1970	<1	49	12	24.5
		1-4	361	67	18.6
		5-14	385	45	11.7
		15+	109	20	18.4
		All ages	916 ^a	156 ^a	17.0
Brazil	1969	<1	247	12	4.9
		1-4	1 578	10	0.6
		5-14	3 177	5	0.2
		15+	1 750	10	0.6
		All ages	6 795 ^b	37	0.5
Ethiopia	1971	<1	262	38	14.5
		1-4	2 178	70	3.2
		5-14	4 809	45	0.9
		15+	2 806	55	2.0
		All ages	10 357 ^c	211 ^c	2.0
Indonesia (Djakarta)	1970	<1	37	12	32.5
		1-4	159	26	16.4
		5-14	127	14	11.0
		15+	18	0	0
		All ages	371 ^d	57 ^d	15.4
Pakistan (Punjab)	1971	<1	105	28	26.7
		1-4	665	110	16.5
		5-14	677	77	11.4
		15+	227	34	15.0
		All ages	1 674	249	14.9
Sierra Leone	1968-69	<1	35	7	20.0
		1-4	163	14	8.6
		5-14	270	10	3.7
		15+	627	84	13.4
		All ages	1 180 ^e	131 ^e	11.1

^a Includes 12 cases and 12 deaths (age unknown)

^b Includes 43 cases (age unknown).

^c Includes 302 cases and 3 deaths (age unknown).

^d Includes 30 cases and 5 deaths (age unknown).

^e Includes 85 cases and 16 deaths (age unknown).

small villages either ultimately experience clinical smallpox or develop primary reactions when vaccinated.

These observations appear to be of more academic than practical interest since the contribution of subclinical infection in enhancing immunity is epidemiologically unimportant. Furthermore, persons with subclinical infection are of no epidemiological significance since studies in many outbreaks indicate that they do not transmit disease.

6.6 Inoculation smallpox (variola)

Inoculation smallpox (variola) is induced by introducing into the skin variola virus contained in vesicular, pustular, or scab material. It confers immunity against the natural disease in much the same way as a vaccinia infection does. The incubation period is usually shorter than that following variola infection by the usual route. A local lesion begins to develop at the site of inoculation before constitutional symptoms occur at about the seventh or eighth day. In some individuals, a generalized rash breaks out at the same time and this resembles the typical smallpox rash in all respects. The person with a generalized rash appears to be as capable of transmitting infection as the naturally infected person, but the frequency of transmission from the individual with a single, localized lesion is unknown. Although the risk of death from variolation is less than that from naturally acquired smallpox, the practice has serious implications in that the infected individual may transmit the disease to others and so begin an epidemic.

Variolation is an ancient practice. Before Jenner's discovery of vaccination, it was the only available means by which the high mortality from smallpox could be reduced. It was formerly practised in many parts of the world, but is now to be found only in remote, rural areas. During the past 5 years, instances of variolation have been encountered frequently in several African countries and in Afghanistan, Nepal, and Pakistan. In most areas, variolation was undertaken only after the appearance of the first case of naturally acquired smallpox in a household or village. As soon as the outbreak of smallpox was over, the practice was stopped. In Afghanistan, however, the problem has been more serious as itinerant variolators have been moving from village to village, irrespective of the occurrence of smallpox, leaving multiple outbreaks in their wake. The practice of variolation is rapidly dying out as a result of various measures, but it is still causing concern as the virus used by the variolators is known to retain its infectivity for as long as 3-12 months.

7. EPIDEMIOLOGY OF SMALLPOX

7.1 Reservoir of infection

Smallpox has long been considered as a disease occurring only in man. If a reservoir were present in nature, it would seem most likely that this might be found in monkeys or apes. However, naturally occurring outbreaks of poxvirus infections in free-living simians have not been documented. Experimentally, variola virus infection can be transmitted to Old World monkeys and transferred from one animal to another by close contact and by the respiratory route, but in cynomolgus monkeys the infection dies out after a few generations.¹

Von Magnus et al.² described a pox disease in captive cynomolgus monkeys and isolated from affected animals a virus belonging to the vaccinia-variola subgroup of poxviruses which they named monkeypox virus. Outbreaks of monkeypox have been reported only in collections of captive animals and virus identified as monkeypox virus has been isolated in 7 of the 10 reported outbreaks.³ Monkeypox has never been reported in wild monkeys or apes. In one of the 7 outbreaks during which isolations of virus were made, 3 strains were isolated from routine cultures of cynomolgus kidney cells. There was no recognized disease in the colony of monkeys concerned although, at about the same time, an outbreak of monkeypox occurred among animals at a nearby zoo. Two of these isolates were later shown not to be classical monkeypox virus.

Between August and December 1970, 6 cases of suspected smallpox occurred among unvaccinated persons inhabiting isolated villages located in tropical rain forest areas of 3 African countries.⁴ Virus was isolated from a 9-month-old baby who lived in an area of Zaire that apparently had been free from smallpox for 2 years; from 2 of 4 cases in Liberia; and from 1 in Sierra Leone. In both the last 2 countries, no smallpox had been observed for 18 months. A further isolate was obtained in April 1971 from a patient in Nigeria, also from a smallpox-free area. Five of the 7 patients had a clinical illness similar to the ordinary type of smallpox; in 2, however, the duration of the eruption was only 5 days. None died, and no cases occurred subsequently among contacts, despite the presence of substantial numbers of unvaccinated susceptible persons. All 5 isolates

¹ Noble, J. & Rich, J. A. (1969) *Bull. Wld Hlth Org.*, **40**, 279-286.

² Von Magnus, P., Andersen, E. K., Petersen, K. B. & Birch-Andersen, A. (1959) *Acta path. microbiol. scand.*, **46**, 156-176.

³ Arita, I. & Henderson, D. A., (1968) *Bull. Wld Hlth Org.*, **39**, 277-283; Arita, I., Gispén, R., Kalter, S. S., Lim Teong Wah, Marennikova, S. S., Netter, R. & Tagaya, I. (1972) *Bull. Wld Hlth Org.* (in press).

⁴ Foster, S. O. et al. (1972) *Bull. Wld Hlth Org.* (in press); Ladnyi, I., Ziegler, P. & Kima, E. (1972) *Bull. Wld Hlth Org.* (in press).

were identified as monkeypox virus. Many species of monkey and ape are present in these areas and, although the specific mode of contact between such animals and the patients could not be established, there was circumstantial evidence that contact was probable in all but the Nigerian case. These are the only recorded cases of monkeypox infection in man.

Many efforts have been made to identify a reservoir of monkeypox virus in nature. Since cynomolgus monkeys (*Macaca irus*) have figured in several of the reported outbreaks in monkey colonies, a survey was made of over 500 sera from cynomolgus monkeys captured in Malaysia. No significant concentrations of poxvirus antibodies were found in this survey or in an analysis of more than 2 000 sera from monkeys captured in Africa and in other parts of Asia.¹ However, recently, a serological investigation of forest mammals in Africa, including simians and rodents, has demonstrated that some non-simian species possess high concentrations of neutralizing antibody. Further studies are in progress to identify the viruses.

Following the diagnosis of human monkeypox infection in Zaire, several monkeys and apes were captured in the same area and examined for the virus. Significant concentrations of neutralizing antibody were found in sera from a *Cercopithecus* monkey and from a chimpanzee, and a poxvirus was isolated from the kidneys of the chimpanzee—the first evidence of the infection of wild primates with a poxvirus.² Two of the 3 above-mentioned strains that were isolated from kidney cell cultures from apparently healthy monkeys, as well as the chimpanzee strain, were more closely related to variola virus than to monkeypox virus. These 3 viruses were almost indistinguishable from variola virus, but differed from it in that they produced necrosis in the skin of some types of rabbit during the first passage, and in the extent of their pathogenicity for white mice.

The 7 recorded cases of human monkeypox infection are probably not the only ones that have ever occurred: previous cases were no doubt obscured by the large number of smallpox infections that were prevalent in much of Africa until recently. Since the virtual elimination of smallpox in many African countries, the more efficient and sensitive surveillance systems now in progress may be expected to detect even a very small incidence of vesicular disease and subsequently to identify infections caused by other viruses.

Although it is not possible on the basis of present information to deny categorically the possibility of an animal reservoir of variola virus, a consideration of the epidemiological facts shows this to be unlikely. In several

¹ Arita, I., Gispén, R., Kalter, S. S., Lim Teong Wah, Marennikova, S. S., Netter, R. & Tagaya, I., (1972) *Bull. Wld Hlth. Org.* (in press).

² Marennikova, S. S., Sheluchina, E. M., Maltseva, N. N., Chimishkjan, K. L. & Macevich, G. R., (1972) *Bull. Wld Hlth Org.* (in press).

parts of the world—e.g., Malaysia, Central America, and the Philippines—the presence of large populations of simians and other mammals, often in close proximity to man, has not prevented the eradication of smallpox.

7.2 Transmission patterns

The household is the basic epidemiological unit in smallpox as in most other infectious diseases; transmission is most frequent in the close association of the family group. Enclosed areas, such as hospitals and schools, where smallpox patients and susceptible persons may be in close contact are also important centres of transmission. Markets and open air festivals are rarely implicated. The probability of transmission depends on the infectiousness of the patient, the susceptibility of the contact, and the physical, social, and environmental factors that may influence exposure.

Although, as stated earlier, all cases of smallpox are potentially infectious from the development of the enanthem until the last scab separates from the skin most infections among family contacts take place within the first week and only few after the second week. Various studies suggest that transmission results predominantly from virus shed from the respiratory tract. Virus may also be recovered from the skin, clothing, and bedding of the patients, and transmission may sometimes take place after infectious material has been disseminated from these sources.

The infectiousness of the patient is primarily related to the extent and severity of the enanthem in the mouth and throat, and this in turn depends on the severity of the case. In general, transmission is greatest from severe or fatal cases, less from those of intermediate severity, and even less from mild or modified cases. The infection is three times as likely to be transmitted by the index case if he has not been vaccinated previously than if he has. However, even severely ill patients usually infect not more than 2 or 3 other persons, thus accounting for the slow development of smallpox outbreaks in comparison, for example, with those of measles or influenza.

The most important factor determining whether or not an exposed contact will become infected is his degree of immunity. Recovery from smallpox almost always protects the individual from subsequent disease, and vaccination greatly reduces susceptibility. There is no evidence that nutrition, the general health status, or intercurrent infection influence the likelihood of smallpox infection or clinical disease.

In the home, the frequency of transmission is related to the degree of crowding and intimacy of contact. Transmission is more likely to occur when case and contact share the same bed. The association of high attack rates with a lower socio-economic status reflects both household crowding and a lower level of vaccination immunity.

The age and sex of the index case, and of his contacts, also influence the likelihood of transmission. The secondary attack rate is higher from index cases 5–14 years of age than from those younger or older. It is also higher from boys than from girls in this age group. Among unvaccinated contacts, the secondary attack rate is highest in those under 5 years of age.

The interplay of case, contact, and environment may result in an unpredictable pattern of transmission in households. Not all susceptible persons may be infected and those infected may not be infected at the same time. Cases have been observed in as many as 4 or 5 generations in a household. Thus, the vaccination of family contacts is strongly indicated, even if the primary case has been discovered some weeks after the onset of illness.

Transmission between households in the community usually occurs as a result of visits by susceptible neighbours and relatives to the household of the infected person. Consequently, many outbreaks are initially confined to adjacent houses or to a small segment of a town. As when transmission occurs within the household, unvaccinated children 5–14 years old are the principal disseminators of infection. Wider and more rapid spread throughout the community and to other communities frequently occurs as a result of transmission within hospitals or schools.

The infection is spread from one community to another usually by an individual who has become infected in a household or hospital and who travels while incubating the disease. Less often, after becoming ill, patients return to their villages, either for want of care or from a desire to die at home. Transmission occurs most frequently between adjacent villages where the frequency of contact is greatest. This accounts for the observation that, in a state or country as a whole, smallpox outbreaks are usually found in a limited number of geographically related areas.

Cities, and particularly their slums, constitute a continuing reservoir and source of widespread transmission. Moreover, vaccination coverage tends to be less complete in villages than in towns, and villagers frequently migrate to urban areas and settle with relatives or friends in crowded slums. In such areas, smallpox is spread readily; vaccination programmes are rarely conducted effectively; reporting and health services are usually inadequate; and outbreaks are not detected promptly. Since labourers, their families, and others—e.g., persons bringing produce to market—are constantly moving in and out of slum areas, fresh sources of susceptible persons are continually being provided. Those leaving the city carry smallpox back to their home villages. Effective control of smallpox in urban areas has regularly been found to reduce sharply the incidence in rural areas.

Movements of other groups, such as nomads, seasonal migrants, and pilgrims, also afford opportunities for contacts between infectious cases and susceptible individuals and may serve to transmit the infection from

one place to another. However, movements of such groups are less important in maintaining endemicity than are those of individuals.

7.3 Airborne and fomite transmission

The transmission of smallpox can almost invariably be related to close personal contact between a patient and a susceptible person, presumably because virus particles in droplets or droplet nuclei are conveyed through the air only over short distances. Airborne spread over longer distances has been documented in only two outbreaks, both of which occurred within the confines of hospitals in Europe.¹ In each instance, there was severe confluent disease and cough in the index case, so the patient was presumably expelling large quantities of virus into an atmosphere of low humidity, which favours the survival of the variola virus.

In the early literature, transmission by fomites was frequently assumed when direct contact could not readily be identified. However, from more recent epidemiological observations, fomites clearly play only a minor role in transmission. An example of such transmission is the occasional infection of laundry workers who have handled bedding and clothing contaminated by smallpox patients. This mode of spread obviously accounts for only a small proportion of the cases occurring in outbreaks. Other instances in which transmission by fomites has occurred are difficult to identify.

That contaminated bedding and clothing may remain a risk for fairly long periods has been illustrated in studies in Madras. These studies showed that virus could be recovered for as long as 60–70 days from infected bedding that had been bundled and kept in a cool, dark room or box. However, if the bedding was exposed to indirect sunlight, virus was recovered for only a few days and, in the case of exposure to direct sunlight, for 3–4 hours. A room formerly occupied by a smallpox patient may remain infectious for several days. Instances have been cited in which nurses and cleaners have become infected while working in such surroundings. Thus, infection might be acquired from a room as long as several weeks after a patient has vacated it. However, the epidemiological evidence indicates that delayed infection of this type is infrequent.

Transmission through the ingestion of contaminated food has not been reported, nor has infection of bloodsucking arthropods, or mechanical transmission by them, been demonstrated. Flies attracted to the open lesions of smallpox patients may become contaminated, but there is no evidence that this is important in the transmission of the disease. Finally, scabs may be eaten by animals such as dogs, cats, and birds, or may contaminate their fur or feathers, but transmission resulting from such contamination has not been demonstrated.

¹ Wehrle, P. F. et al. (1970) *Bull. Wld Hlth Org.*, **43**, 669.

8. IMMUNOLOGY

The protection that vaccination confers against smallpox depends on the close antigenic relationship between vaccinia and variola viruses. Response to challenge, whether by vaccinia virus (as in revaccination) or by variola virus (as in exposure to infection) depends on the balance between immunity and the dose of challenge virus. Resistance to reinfection after a primary infection, whether by variola or by vaccinia virus, slowly lessens with time; there is wide individual variation in the rate of this loss. Whether or not an infection occurs in the person with waning immunity depends on the dose of the challenge virus. Partial immunity may withstand a small challenge such as a vaccine of low potency or exposure to a smallpox patient excreting very little virus; greater immunity may withstand even an intense exposure to infection.

8.1 Antibody response¹

After a person has been infected by vaccinia or variola virus, antibodies appear in his serum. Antibody concentrations may be measured by tests on serum for neutralizing, complement-fixing, precipitating or haemagglutinin-inhibiting activity. Neutralizing antibodies are detectable for many years; precipitating and complement-fixing antibodies have a much shorter life—generally less than a year—and thus may be useful indicators of recent infection. Haemagglutinin-inhibiting antibody diminishes less predictably and may be detectable longer than complement-fixing antibody.

8.1.1 *Antibody response after smallpox*

Neutralizing antibody usually appears by the sixth day of illness except in very severe forms of the disease, reaches a high concentration during convalescence, and persists for many years.

Complement-fixing antibody appears on about the eighth day of illness and usually reaches a higher titre than is found after vaccination. Normally, this antibody does not persist at significant concentrations for more than a year.

Precipitating antibodies are detectable in the sera of convalescent smallpox patients by the precipitation-in-gel technique for at least 4–6 weeks.

¹ This section is based on the papers by McCarthy, K., Downie, A. W. & Bradley, W. H. (1958) *J. Hyg. (Lond.)*, **56**, 466 and Downie, A. W. & McCarthy, K. (1958) *J. Hyg. (Lond.)*, **56**, 479; it represents only a minor modification of the section on antibody response in the report of a WHO Scientific Group on Smallpox Eradication, *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 393, p. 21.

Haemagglutinin-inhibiting antibodies usually appear on about the fifth or sixth day of illness. Like complement-fixing antibodies, they reach a maximum in 2–4 weeks ; thereafter they diminish, but may still be detectable in low concentrations for more than a year.

8.1.2 *Antibody responses after primary vaccination*

Neutralizing antibody is not usually detectable until after the tenth day. The concentrations attained are low in comparison with those following smallpox or revaccination, but neutralizing antibodies persist for many years. Complement-fixing antibodies can be detected towards the end of the second week in a proportion of cases, depending on the sensitivity of the test used. Precipitating antibodies are not demonstrable in most laboratories. Haemagglutinin-inhibiting antibodies usually appear from about the tenth day, reach a maximum after 3–4 weeks, and fall to low levels within a year.

8.1.3 *Antibody responses after revaccination*

A major reaction following revaccination results in a marked increase in neutralizing antibody, detectable towards the end of the first week. The concentrations attained are about 10 times greater, on the average, than after primary vaccination. About half of the revaccinated persons with an equivocal dermal reaction show a significant increase in antibody.

Complement-fixing antibody also may appear more quickly after successful revaccination than after primary vaccination, but despite a good neutralizing-antibody response there may be no detectable complement-fixing antibody. Similarly, the response of haemagglutinin-inhibiting antibody is variable and may be absent even though there is a marked increase in neutralizing antibody.

8.2 **Duration of immunity**

Immunity against smallpox wanes with time at a rate varying with the individual. The duration of resistance to smallpox, however, cannot be accurately predicted. Whereas it is believed that levels of neutralizing antibody correlate with protection, no specific data are available that define these levels. Resistance to revaccination was previously regarded as a reliable measure of immunity. However, the potent vaccines available today provide a stronger challenge than exposure to smallpox ; thus a large proportion of individuals who have been successfully vaccinated only 1–2 years previously will develop a major reaction following revaccination.

Information regarding the duration and degree of immunity has been derived from epidemiological observations. Even here, there are special problems in interpretation : although vaccination histories are generally

considered to be unreliable, the presence of a vaccination scar is taken in most countries as evidence of a previous successful primary vaccination. In India and Pakistan, however, vaccination by rotary lancet has been practised until recently, and vaccination by this technique may produce a scar simulating that of successful primary vaccination, even when inactive vaccine is used. The relative degree of protection afforded by revaccination is even more difficult to assess, as a scar of revaccination is not usually observed except when the rotary lancet is used. Moreover, a higher vaccine potency is required for revaccination than for primary vaccination; the vaccines employed more than 4 or 5 years ago were often of low titre and unsatisfactory for revaccination.

8.2.1 *Duration of immunity after smallpox*

Epidemiological observations indicate that, after an attack of smallpox, immunity to the disease is virtually life-long. Second attacks occur very rarely, usually after an interval of several decades.

8.2.2 *Duration of immunity after primary vaccination*

Smallpox rarely occurs during the 4 or 5 years following successful vaccination in infancy. This implies that immunity is virtually complete during this period. In areas where variola major is prevalent, a small but gradually increasing number of cases is seen among older persons as protection slowly diminishes. Even after 15–20 years, the individual may retain some protection against the disease and substantial protection against a fatal outcome. With variola minor, the duration of protection appears to be longer and the degree of protection greater; cases among successfully vaccinated persons are unusual, even many years after vaccination. Similarly, the incidence of major reactions following revaccination increases with time, but even after 10–20 years the vaccine required to produce a high percentage of successful vaccinations must be at least 5–10 times more potent than that required to obtain the same proportion of successful primary vaccinations.¹ Vaccine that meets the minimum requirements established by WHO² (see Smallpox vaccine, p. 36) will elicit a satisfactory proportion of responses following revaccination.

8.2.3 *Duration of immunity after revaccination*

Not enough is known about the occurrence of smallpox in successfully revaccinated persons to permit a firm estimate of the duration of immunity. After revaccination, the greater concentration of antibody and

¹ Espmark, J. A. (1965) *Acta path. microbiol. scand.*, **63**, 97.

² *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 323.

its longer persistence suggest that immunity to infection is considerably greater and more durable than after primary vaccination.

8.3 Significance of antibody concentrations

There is little reliable information about the concentration of antibody that may be expected to prevent clinical smallpox. As in other virus diseases, high concentrations of neutralizing antibody are likely to be protective. However, it is not possible to indicate the minimum protective level of antibody.

Revaccination within a few years of primary vaccination is often successful even when circulating neutralizing antibody is present in measurable concentrations. However, revaccination with a fully potent vaccine is an extremely severe challenge that may overcome even a well established immunity.

9. SMALLPOX VACCINE

The experience that has been accumulated in programmes throughout the world has amply confirmed that good-quality freeze-dried vaccine is essential. Such vaccine must have a titre of at least 10^8 pock-forming units (pfu) per ml *after* incubation at 37°C for 4 weeks. Detailed requirements were laid down by a WHO Expert Group on Requirements for Biological Substances¹ in 1965.

9.1 Vaccine characteristics

The greater part of the vaccine used both routinely and in WHO-sponsored smallpox eradication programmes is prepared from virus propagated in the skins of animals. Microbial contamination of such vaccines during growth is inevitable, and thus as many as 500 non-pathogenic organisms per ml are permissible. However, information from the WHO International Reference Centre for Smallpox Vaccine reveals that most vaccines tested in recent years actually contain less than 50–100 organisms per ml.

Chick embryos and tissue cell cultures have also been employed in the propagation of vaccinia virus with the object of producing a vaccine containing less extraneous matter. However, the difficulty of achieving stability after drying has retarded progress in changing from vaccinifers to cell cultures as a source of virus. Recently, a vaccine grown in primary cultures of rabbit kidney cells has shown both adequate stability and

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 323.

freedom from adventitious viruses and other micro-organisms. Take rates and serological conversion rates were satisfactory in a field trial involving 1 000 persons. Production of smallpox vaccine by this method would be suitable for highly developed countries, but the level of technology required is such that the method would not be feasible in the developing countries.

With a satisfactory vaccination technique, vaccines of adequate potency should give more than 95% major reactions following primary vaccination and at least 90% after revaccination of subjects vaccinated 10 or more years previously. If performance in the field is less satisfactory than this, the method of storing the vaccine, the vaccination technique, and the skill of the vaccinator should be examined. If all are adequate, the lot of vaccine should be withdrawn and retested in the laboratory for potency.

The testing of vaccine solely by primary vaccination of a group of children is still practised occasionally. This is mentioned here only to be condemned. A skilful vaccinator can achieve an acceptable rate of major reactions in primary vaccination with low-potency vaccines. Successful vaccination of children provides no information about the efficacy of the material when used for the vaccination of newborn infants or for revaccination, for both of which purposes vaccine of full potency is required; nor does it show whether the vaccine is stable—a most important consideration, particularly in tropical countries. The only acceptable method of determining the potency of a vaccine is by an assay in a properly staffed and equipped laboratory.

Finally, it is to be emphasized that dried vaccine, once reconstituted, is no more stable than liquid vaccine. It should therefore be protected from direct sunlight and used only on the day on which it is reconstituted. In field operations, any vaccine remaining at the end of the day must be discarded.

9.2 Vaccine strains

The multiplicity of vaccinia virus strains that were in use only a few years ago has been greatly reduced. Most, if not all, of the highly pathogenic strains have been abandoned by vaccine producers. Vaccines used in the WHO eradication programme are prepared mainly from derivatives of either the Elstree (Lister Institute) strain, the EM 63 strain (Moscow Research Institute of Virus Preparations), or the New York Board of Health strain.

9.2.1 *Attenuated strains*

From time to time it has been suggested that strains of reduced pathogenicity might be used for prevaccination in order to diminish the slight risk of disabling or fatal complications following the administration of traditional strains. Only one attenuated strain—CV1-78—has been tested

extensively so far. Whereas initial reports on the strain were encouraging, more recent trials have raised serious questions regarding the degree of protection that it might afford. In one trial, a group of children was vaccinated with the strain, and a control group with a standard strain. There were fewer successful vaccinations and serological conversions in the group vaccinated with CV1-78 than in the control group. When the former group was revaccinated 5 to 9 months later with the standard strain, one-third continued to have no neutralizing antibody despite major dermal reactions. All the children in the control group developed neutralizing antibody. It might be profitable to undertake additional studies with other attenuated strains. However, although it will be possible to measure the febrile and local reactions that such strains produce, it will be much more difficult to quantify the incidence of serious complications resulting from their use, as this would require careful observations in millions of persons having undergone primary vaccination.

9.3 Inactivated vaccine

Immunization with non-infectious smallpox vaccine has also been proposed as a method of inducing sufficient immunity in a subject for him to react to challenge with live virus as though it were a revaccination, thus perhaps reducing the incidence of complications.

Large-scale clinical studies have been made with antigens grown in cell cultures and inactivated with formalin, but the experiments reported so far have lacked adequate controls and so cannot be interpreted.

Experiments have also been made, largely in animals, with other vaccines inactivated by ultraviolet irradiation, the photodynamic action of dyes, heat, β -propiolactone, and other agents. In the light of the differences in immunogenicity between vaccinia virus spontaneously freed from cells in culture (cell-free virus) and cell-associated vaccinia virus, the interpretation of much of this work is doubtful. Suspensions made from material grown in the skins of animals contain almost exclusively cell-associated virus. Antibody to inactivated cell-associated virus does not neutralize infective cell-free virus, nor does antibody penetrate cells. Since cell-free virus presumably occurs in the viraemic stages of poxvirus infections, antibody to non-infectious vaccine prepared from cell-associated virus will be ineffective in preventing spread via the blood stream.¹

Cell-free vaccinia virus can be obtained with certainty only from the supernatant medium of infected cell cultures. As a rule little more than 1% of the total infective virus in a culture infected with vaccinia virus is in the cell-free form. The preparation of inactivated cell-free vaccine is there-

¹ Appleyard, G., Hapel, A. J. & Boutler, E. A. (1971) *J. gen. Virol.*, **13**, 9; Turner, G. S. & Squires, E. J. (1971) *J. gen. Virol.*, **13**, 19.

fore likely to be extremely expensive. Much more study is required before inactivated smallpox vaccines can be considered for use.

9.4 Experimental vaccines

A vaccine in silicone emulsion, still in the process of development, shows promise. This is freeze-dried vaccinia virus suspended in silicone fluid. The vaccine can be packaged in a multiple-dose container and applied by multiple puncture without reconstitution. The silicone is said to prevent moisture from reaching the vaccine, thus increasing the stability of the preparation. The vaccine should retain its potency for 30 days when incubated at 37°C. Well controlled field trials have yet to be conducted. If this vaccine becomes generally available its use will reduce wastage of vaccine in health centres where comparatively few vaccinations are given each day.

Brief reports have appeared in the press regarding an oral smallpox vaccine. No statistically valid systematic trials of such a preparation have yet been made. Considering the route of administration, extensive field trials would be needed to assess not only the efficacy of the vaccine but more especially the rate of complications that its use would entail.

Existing vaccines are generally so effective that any new vaccine developed, if it is to be considered seriously, must have been subjected to carefully controlled and thorough tests of safety and effectiveness. Since large amounts of vaccine are still needed for the global eradication campaign, there should be clearly demonstrable advantages to be gained before changing established vaccines or methods of application.

10. VACCINATION AGAINST SMALLPOX¹

Vaccination consists in introducing into the basal layers of the epidermis sufficient vaccinal virus to infect susceptible cells and produce a local lesion. The vaccinia infection usually brings about localized skin involvement, with mild systemic symptoms. An insertion of vaccine at a single site is sufficient for protection. When the lesion of primary vaccination heals, a scar remains.

10.1 Techniques of vaccination

The preferred site for vaccination is the outer aspect of the upper arm over the insertion of the deltoid muscle. This area is usually easily accessible and the lesion that develops is less likely to become macerated by

¹ Based in part on the corresponding section of the report of a WHO Scientific Group on Smallpox Eradication, *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 393, p. 29.

body moisture. Unless the selected site is obviously dirty, no treatment of the skin is needed: disinfectants inactivate vaccinia virus more effectively than they kill skin bacteria. Moreover, cleansing is liable to create slight abrasions that may become infected with vaccinia virus to form "satellite pocks". If the area is obviously dirty, it should be gently wiped with a cloth or cotton wool moistened with water, and allowed to dry.

Vaccine may be introduced by a variety of techniques, but only a few of these are satisfactory. The multiple-puncture and multiple-pressure methods and vaccination by jet injection give the highest percentage of successful vaccinations.

The *multiple-puncture* technique, in which the bifurcated needle is used, is technically the easiest and is now almost universally applied in the endemic areas. A dry, sterile, bifurcated needle is dipped into the vaccine and, on withdrawal, a droplet of vaccine, sufficient for vaccination, may be seen between the two prongs of the needle. The needle is held perpendicular to the skin, the wrist of the vaccinator resting against the arm of the person to be vaccinated. Fifteen perpendicular (up and down) strokes of the needle are made rapidly in an area about 5 mm in diameter. The strokes must be sufficiently vigorous to induce a trace of blood at the vaccination site within 15–30 seconds of vaccination. Even if a drop or two of blood sometimes appears, this does not reduce the proportion of successful vaccinations.

In the *multiple-pressure* technique, a small drop of vaccine is placed on the skin. A sharp needle is held tangentially to the skin and pressure is applied several times with the side of the needle, not the point. Thirty strokes are completed in 5–6 seconds, using an up-and-down motion perpendicular to the skin. Sufficient pressure should be employed to induce a trace of blood at the vaccination site 15–30 seconds after vaccination.

By means of the *jet injector*, 0.1 ml of a specially prepared vaccine is injected into the superficial layers of the skin through a very small orifice and under high pressure. Correct deposition is indicated by the presence of an intradermal bleb after vaccination. Jet injectors differ in their characteristics and only a few are suitable for the administration of smallpox vaccine.

The *scratch* method gives satisfactory results in persons being vaccinated for the first time but a smaller proportion of cutaneous responses in those being revaccinated. In endemic areas, the use of this method has been abandoned in favour of the multiple-puncture method. A small drop of vaccine is placed on the skin and a single linear scratch not more than 6 mm long is made through the vaccine. The scratch should be vigorous enough to cause a trace of blood to appear at the site within 30 seconds. The vaccine is rubbed into the scratch with the side of the needle.

10.2 Classification and interpretation of vaccination results

Following successful primary vaccination, a vesicle develops after 3–5 days; subsequently, the lesion becomes pustular, achieving its greatest size after 8 or 9 days. A scab is then formed, which separates at 14–21 days, leaving a typical vaccination scar.

In successful revaccination, multiplication of vaccinia virus occurs. Revaccination is shown to have been successful if, on examination after about one week (6–8 days), there is a pustular lesion, or an area of definite induration or congestion surrounding a central lesion, which may be a scab or an ulcer. This is termed a "major reaction"; all other responses are termed "equivocal reactions".

If an equivocal reaction is observed, it may be interpreted in various ways. In several studies in which potent vaccine and a satisfactory technique were employed, approximately half of those with equivocal reactions were found to exhibit a satisfactory antibody response. However, an equivocal reaction may be exhibited also by persons with high levels of immunity, or those who have been vaccinated with an insufficiently potent vaccine or by an unsatisfactory technique. In most groups of revaccinated persons, a considerable number will show, at 1 week, a type of reaction about the classification of which experienced observers may differ. Some may classify such a response as a major reaction whereas others will consider it to be an equivocal reaction. As it is so difficult to classify such reactions, the frequency of responses to revaccination is not a useful index in the evaluation of mass vaccination programmes. In such programmes, it is assumed that, if freeze-dried vaccine meeting WHO requirements is employed and if more than 95% of primary vaccinations are successful, the vaccination technique is satisfactory and an adequate response is being obtained in revaccinated persons.

10.3 Complications of vaccination

As with other immunizations, a small but definite risk of serious complications is associated with smallpox vaccination.

Vaccinia virus can be transferred from the vaccination site by the fingers to mucous membranes or to abraded skin surfaces and so give rise to *auto-inoculation* lesions. Except in the rare instances where ocular infection is followed by permanent scarring of the cornea, this complication has no serious consequences. A transient viraemia may occur, resulting in *generalized vaccinia*, in which vaccinia lesions begin to appear 5–10 days after vaccination. This complication is not progressive and is never fatal. Hypersensitivity reactions in the form of urticarial, morbilliform, and erythema multiforme eruptions are sometimes seen. These may sometimes be confused with generalized vaccinia. Of greater concern is the danger that the virus will be transferred to the eczematous skin of either a vac-

cinated person or the contact of a vaccinated person, causing *eczema vaccinatum*. Although many such cases resolve satisfactorily, some—particularly in persons infected by contact—tend to result in extensive lesions and may occasionally prove fatal. *Progressive vaccinia* (*vaccinia necrosum*) is a very rare and serious complication occurring in persons with immunological defects, either of a congenital nature or resulting from neoplastic disease of the reticulo-endothelial system (leukaemia, multiple myeloma, etc.), therapy with immunosuppressive or corticosteroid drugs, or radiation therapy. *Postvaccinal encephalitis* is a rare but serious complication, most cases occurring in the second week after primary vaccination. It is extremely infrequent after revaccination. Although most persons affected with postvaccinal encephalitis recover completely, some die and a few of those who recover have residual neurological sequelae.

Information regarding the relative frequency of complications is regrettably incomplete. Several published reports have given the number of complications in different countries, but data are often not provided or are not available regarding the numbers of vaccinations performed or else these have been recorded but not analysed separately according to the numbers of primary vaccinations and revaccinations. The results are difficult to interpret since complications are much more frequent after primary vaccination than after revaccination. The analysis of data pertaining to postvaccinal encephalitis poses a special problem, as the criteria for diagnosis, particularly in infants less than 1 year old, differ substantially from one country to another. Finally, serious complications, such as postvaccinal encephalitis and progressive vaccinia, are so infrequent that very large populations must be studied in order to assess the relative risks involved.

In an extensive study in the USA, complications of all types were far less frequent in revaccinated persons than in those being vaccinated for the first time (Table 3).¹ For example, 16 cases of postvaccinal encephalitis were observed among 5.6 million persons who underwent primary vaccination but no cases among 8.6 million revaccinated persons. The frequency of postvaccinal encephalitis was somewhat higher among those less than 1 year old than in other age groups. All the cases in infants less than 1 year old occurred between the ages of 6 and 12 months. (It should be noted that vaccination in the USA is seldom performed at an earlier age.) Presumably preventable complications were the 11 cases of vaccinia necrosum in persons with an immunological deficiency, and the 126 cases of eczema vaccinatum. Less serious complications, such as generalized vaccinia and accidental inoculations, were observed more frequently. None was fatal. In all, 9 deaths, 1 of which occurred in a contact, were

¹ Lane, J. M., Ruben, F. L., Neff, J. M. & Millar, J. D. (1969) *New Engl. J. Med.*, **281**, 1201.

TABLE 3. MAJOR COMPLICATIONS ASSOCIATED WITH SMALLPOX VACCINATION IN THE USA, ACCORDING TO DIAGNOSIS AND VACCINATION STATUS (1968) ^a

Age (years)	No. of vaccinations	No. of cases (deaths in parentheses)		
		Postvaccinal encephalitis	Vaccinia necrosum	Eczema vaccinatum
Primary vaccinations				
<1	614 000	4 (3)	0	5
1-4	2 733 000	6	1	31
5-9	1 553 000	5 (1)	1 (1)	11
10-14	295 000	0	0	1
15-19	111 000	0	1 (1)	2
20+	288 000	1	2	7
Total (all ages)	5 594 000	16 (4)	5 (2)	58 ^b
Revaccinations				
<1	0	0	0	0
1-4	478 000	0	0	1
5-9	1 643 000	0	1 (1)	4
10-14	1 440 000	0	0	1
15-19	1 217 000	0	1	2
20+	3 796 000	0	4 (1)	0
Total (all ages)	8 574 000	0	6 (2)	8
Contacts				
<1		0	0	4
1-4		0	0	38 (1)
5-9		0	0	8
10-14		0	0	0
15-19		0	0	1
20+		0	0	9
Total (all ages)		0	0	60 (1)
GRAND TOTAL	14 168 000	16 (4)	11 (4)	126 (1) ^b

^a From Lane, J. M., Ruben, F. L., Neff, J. M. & Millar, J. D. (1969) *New Engl. J. Med.*, **281**, 1201.^b Includes 1 case of unknown age.

attributed to vaccination. Six deaths occurred among 5.6 million persons who underwent primary vaccination—a rate of approximately 1 death per million primary vaccinees. The 2 deaths in 8.6 million revaccinated persons constitute a rate of 1 death in more than 4 million.

On the basis of the available data, complications appear to be somewhat more frequent in Europe and substantially less common in tropical countries. However, for reasons already stated, a direct comparison of the data from the various studies is not possible.

Complications following the vaccination of pregnant women were not recorded in the study discussed above. Other studies have indicated no apparent increase in the risk of abortion, miscarriage, or malformation of the fetus following vaccination. However, some 20 fatal cases of fetal vaccinia are recorded in the medical literature, virtually all of which occurred following primary vaccination of the mother during pregnancy. In endemic countries, the vaccination of newborn infants has been widely practised without apparent untoward results.

10.4 Contraindications to vaccination

Specific contraindications are clearly recognized but their clinical importance varies inversely with the probability that any given individual will be infected by smallpox virus. Clinical decisions will therefore differ according to the epidemiological circumstances.

10.4.1 Contraindications in endemic regions

In endemic regions, the risk of acquiring smallpox far exceeds the danger of vaccination complications. Thus in endemic regions there are no recognized contraindications to vaccination. Whereas the eczematous individual is at increased risk from vaccination, the risks from smallpox as well as from accidental contact inoculation with vaccinia are greater. Thus eczema should not be considered as a contraindication to vaccination in endemic areas. Pregnancy also is not a contraindication: smallpox is more frequently fatal in pregnant than in non-pregnant women and, as mentioned earlier, the risk of complications following vaccination is small.

10.4.2 Contraindications in non-endemic regions

Among the principal complications of vaccination, postvaccinal encephalitis, generalized vaccinia, and autoinoculation are not associated with identifiable host factors and thus must be accepted as small but definite risks associated with the procedure. Other complications are substantially more frequent among persons with particular characteristics. Thus, in countries where the risk of acquiring smallpox is negligible, the hazards of vaccination may be reduced if persons with certain conditions are not vaccinated. The following are the most usual contraindications to smallpox vaccination in non-endemic regions:

(a) *Eczema.* The risk of eczema vaccinatum after vaccination of eczematous subjects is unknown, but probably does not exceed 1%. If this complication does arise, the case-fatality rate is around 1% (Table 3) and the period of disability may be considerable. The risk of severe involvement is greatest in persons with generalized eczema and in eczematous contacts

of recently vaccinated persons. Individuals with eczema or who have had extensive eczema in the past should avoid vaccination and close contact with recently vaccinated persons. No member of the family should be vaccinated unless the person with eczema can be excluded from the household until the vaccination site in the person vaccinated has healed. This precaution applies to families but not to other groups, such as school-children and industrial workers, among whom transmission is less likely to occur.

(b) *Deficient immune response syndromes ; leukaemia, lymphoma, Hodgkins disease, and related neoplastic diseases.* Conditions of these types are associated with a greatly increased susceptibility to the often fatal progressive vaccinia.

(c) *Conditions necessitating the use of immunosuppressive drugs, glucocorticosteroids, or radiation therapy.* The use of these drugs or procedures enhances susceptibility to many infectious agents, including vaccinia virus, and progressive vaccinia may follow vaccination.

(d) *Infancy.* In non-endemic regions, vaccination is usually postponed to the second year of life as a higher incidence of complications has been observed among infants vaccinated between the sixth and twelfth months than among those vaccinated during the second year. Thus, the usual practice in Europe and North America is to vaccinate during the second year. Comparative data are not available on the frequency of complications among those vaccinated at 6-12 months of age and those vaccinated at birth or within the first few months of life, when maternal antibody is present. This situation is perhaps comparable to the administration of vaccinia immune globulin at the time of vaccination.¹ Therefore, the first few months of life may be one of the safest periods for vaccination.

(e) *Pregnancy.* Although fetal vaccinia is rare and other possible complications are not clearly documented, the usual practice regarding pregnant women is to avoid administering live virus vaccines and other procedures that might induce fever. Thus elective vaccination is normally postponed until after the end of the pregnancy.

(f) *A history of postvaccinal encephalitis or other vaccinal complications.* Although there is no documentary evidence to that effect, it is generally believed that persons who have previously had complications attributed to vaccination should not be vaccinated again.

(g) *Other.* Although skin diseases, infections, childhood exanthems (including chickenpox), and a variety of other conditions have been regarded by some as contraindications, none of these conditions appears

¹ Nanning, W. (1962), *Bull. Wld Hlth Org.*, **27**, 317.

to increase either the susceptibility to vaccinia virus or the likelihood of complications.

10.5 Vaccination for those travelling abroad

10.5.1 *Endemic countries*

All travellers to endemic countries should be successfully vaccinated both to protect themselves and to prevent the transfer of smallpox from the endemic country to their own or other countries. Experience has shown that smallpox may spread from one part of an endemic country to another and may not be detected in the new location for periods of 4–8 weeks, or even more. Thus, if any part of a country harbours endemic smallpox, the whole of that country should be regarded as possibly infected. Travellers for whom vaccination would normally be contraindicated should, if possible, refrain from travelling to infected countries. If it is essential for them to travel, they should be given vaccinia immune globulin at the time of vaccination. In November 1971, endemic smallpox was known to be present in only 7 countries—i.e., Afghanistan, Ethiopia, India, Indonesia, Nepal, Pakistan, and Sudan. Thus, this recommendation applies to very few countries and may be expected to apply to even fewer in less than 2 years' time.

10.5.2 *Non-endemic countries*

Many visitors to countries in Africa, Asia, and South America have been required to present valid smallpox vaccination certificates, whether or not they have come from an endemic country. Difficulties have arisen in the case of those persons for whom vaccination is normally contraindicated but who have not visited an endemic country. It seems both logical and desirable to exempt from this requirement persons with a valid contraindication to vaccination who have not visited an endemic country during the preceding 16 days. To minimize confusion, a standard form should be developed to meet this situation. The form would provide space for the name of the traveller and a statement that vaccination is contraindicated on medical grounds. It would be signed by the physician concerned and bear an official stamp similar to that used on vaccination certificates. This form might be incorporated into the internationally recommended vaccination booklet or could be attached to it.

A special problem is presented by countries in which smallpox is not considered to be endemic but where outbreaks have occurred as a result of an importation. Contrary to the experience in previous decades, such outbreaks in recent years have usually been small, have affected a limited geographical area, and have been rapidly contained. Accordingly, unless

such outbreaks increase to a substantial size and/or continue over an extended period, the risk to the traveller and the risk of further transmission to other countries should be negligible. Under such circumstances, the country should continue to be regarded as non-endemic, and the very few persons for whom vaccination is validly contraindicated should continue to be exempted from it.

10.5.3 *International certificate of vaccination*

The present International Certificate of Vaccination against smallpox is not valid until 8 days after successful primary vaccination has been performed. This delay permits the response to be examined before certifying the vaccination as having been successful. After revaccination, the certificate becomes valid on the date when revaccination is performed. Some have argued that, as with primary vaccination, the revaccination response should be examined after 7 or 8 days and that, if a major reaction is not observed, the revaccination should be repeated. It should be emphasized that the response to revaccination is far more difficult to read than that to primary vaccination; the reading is subject to error and a proportion of immune persons will not show a major reaction. Furthermore, in recent years importations into non-endemic African and South American countries have mostly occurred over open borders where certificates were not examined. Only 2 importations into Europe have occurred during the past 3 years, one of which *might* have been prevented had a reading at 7 days been stipulated. Thus, little benefit and considerable inconvenience would have accrued from a change in procedure affecting millions of travellers by air and sea.

10.6 **Vaccination policies**

Smallpox vaccination remains the most reliable measure for protecting persons likely to be exposed to the disease. In the community, it serves to retard transmission should the disease be introduced. With the volume and speed of modern air travel, all countries are at some risk of importing smallpox. Nevertheless, as with other vaccinations, there is a small but finite risk of serious complications from vaccination against smallpox. In determining the vaccination policy, therefore, the risk of endemic or imported smallpox must be carefully weighed against the risk of complications. Furthermore, due attention must be paid to the population groups most likely to acquire and transmit the disease, as well as to the quality of surveillance, the duration of immunity afforded by vaccination, and the administrative and logistic problems encountered in applying the vaccine.

(a) *Endemic countries.* In endemic countries, the necessity of vaccinating extensively is well accepted, as the risk of serious illness or death from

smallpox is great compared with the low risk associated with vaccination. Special efforts should be made to vaccinate those groups at high risk of acquiring the disease or of transmitting it widely. Since, in most countries, 80–90% of all cases occur among unvaccinated children less than 15 years of age, the importance of primary vaccination of children must be emphasized. Vaccination of children at birth or as early in life as possible protects the highly vulnerable infant group in which the smallpox case-fatality rate is highest. In infectious disease hospitals, the staff, visitors, and all patients (including those with suspected smallpox) should be routinely vaccinated, since the spread of the disease within hospitals constitutes a major problem. The safety and effectiveness of the procedure have been demonstrated in routine practice in the Infectious Diseases Hospital, Madras, and other hospitals in Asia and North America. Schools and slums should also receive special attention.

Whereas primary vaccination is of the highest importance, revaccination at periodic intervals serves to reinforce immunity. The intervals between revaccinations are based primarily on administrative convenience. The available evidence suggests that, with present vaccines, successful primary vaccination followed by a successful revaccination 5 years later should provide durable immunity that may protect most persons throughout their lifetimes. However, greater protection is assured by revaccinating at 5–10-year intervals.

(b) *Non-endemic countries at high risk.* The attention of non-endemic countries must be directed mainly towards surveillance—i.e., improved reporting, the prompt investigation of all suspected cases, and the containment of introduced outbreaks. However well the population may be vaccinated and however rigidly the requirements for vaccination among travellers may be enforced, smallpox may be imported and subsequently spread. The essential requirement for keeping a country free from smallpox is an alert surveillance system.

Since all the non-endemic countries at high risk must rely on incompletely developed networks of health services for detection, vaccination should be maintained at a high level in order to deter transmission. As in the endemic countries, vaccination at or soon after birth is recommended, and revaccination should be ensured at least for all children at school entry and, again, perhaps, at 10 years of age.

For countries bordering the endemic countries, a particular danger exists and thus a high level of immunity is especially necessary. In border provinces and districts as well as in the slums of the main urban centres, continuing programmes of active surveillance (case-finding) and vaccination should be conducted.

(c) *Non-endemic countries not at high risk.* For countries in Australasia, Central and North America, Europe, and Oceania, the risk that

smallpox will be introduced is much lower than in other regions, and is decreasing steadily. The extent of the vaccination programme must be decided after an assessment of the risk of an introduction, the probability of its early detection, and the resources that could be rapidly mobilized to contain any outbreak.

In the USA and the United Kingdom, both of which discontinued routine vaccination in 1971, the network of health services is extensive and surveillance well developed. Should an introduction occur, it would be rapidly detected and contained. Thus, the risk associated with terminating routine vaccination is minimal. However, for health service and hospital personnel, as well as travellers to endemic areas, vaccination at appropriate intervals is required.

For non-endemic countries with less developed health services, such a policy might have disastrous consequences, since an introduction could lead to extensive spread before it was detected, particularly in highly susceptible populations. In these countries, the emphasis should be placed on vaccination as early as possible in childhood and revaccination at school entry. As elsewhere, health service personnel and travellers to endemic areas should be well vaccinated.

10.7 Simultaneous administration of several vaccines

The concurrent administration of several immunizing agents is sound public health practice, provided that there is no interference with the immunological response, that reactions are not intensified, and that vaccination complications are not increased. Smallpox vaccine has been given simultaneously with diphtheria, pertussis, tetanus, cholera, typhoid, and inactivated poliomyelitis vaccines, although not at the same vaccination site. All these vaccines maintained their full efficacy and there was no intensification of reactions. Smallpox and BCG vaccines have been inoculated at different sites in the same newborn infants, and the response to each vaccine has been comparable to that obtained when the vaccine was given alone.¹ In Africa, concurrent administration of smallpox and 17-D yellow fever vaccines did not result in any increase in adverse reactions.² When the vaccines were given concurrently but as separate injections, the results were comparable to those following their administration on different occasions. However, when they were given in a single combined injection, the proportion of vaccinated persons in whom yellow fever antibodies

¹ Moodie, A. S. & Cheng, G. K. K. (1962) *Tubercle (Edinb.)*, **43**, 155; Lin, H. T. (1965) *Bull. Wld Hlth Org.*, **33**, 321.

² Dick, G. W. A. & Horgan, E. S. (1952) *Amer. J. Hyg.*, **50**, 376; Meers, P. D. (1959) *Trans. roy. Soc. trop. Med. Hyg.*, **53**, 196; Meyer, H. M., Hostetler Jr., D. D., Bernheim, B. C., Rogers, N. G., Lambin, P., Chassary, A., Labusquière, R. & Smadel, J. E. (1964) *Bull. Wld Hlth Org.*, **30**, 783.

developed was reduced. When smallpox vaccine was administered at the same time as measles vaccine, either mixed or at separate sites, febrile reactions were somewhat more marked, but the serological responses were unaltered.¹ Smallpox vaccination is compatible also with the simultaneous administration of oral poliomyelitis vaccine.² Thus, smallpox vaccine has been given concurrently with all the usual immunizing agents, and no difficulties have resulted.

Assuming that the technical problems of vaccine administration can be solved, there is no reason why non-endemic countries should not adopt programmes for the delivery of other antigens simultaneously with smallpox vaccine. Indeed, this seems to be a logical extension of successful smallpox eradication programmes in many countries.

11. SURVEILLANCE

Surveillance is the most important aspect of an eradication programme. In several countries, the transmission of smallpox was interrupted less than a year after surveillance activities were instituted but long before a systematic vaccination programme was completed. Conversely, in other countries, when surveillance has been omitted, transmission has persisted despite intensive and systematic programmes of mass vaccination.

The object of surveillance is to detect all cases of smallpox that may occur and, through appropriate field investigation and the application of containment measures, to interrupt further transmission. The basis for case-finding is a network of notification posts that report weekly whether or not cases have been observed. Each health unit should serve as a notification post and all health personnel should be alert to the discovery of possible cases in the course of their duties. A network such as this takes time to develop and requires repeated reminders and frequent visits by a surveillance officer or team to remind all concerned of the need to report regularly. The prompt arrival of a surveillance unit in response to the report of a case will do much to stimulate reporting from these notification posts. The reporting network can be extended, particularly in countries where health facilities are few, by enlisting the support of village leaders, school authorities, and the police, as well as malaria project personnel and other health staff. However, it has not been found generally feasible to

¹ Budd, M. A., Scholtens, R. G., McGehee Jr., R. F. & Gardner, P. (1967) *Amer. J. publ. Hlth*, **57**, 80; Sherman, P. M., Hendrickse, R. G., Montefiore, D., Peradze, T. & Coker, G. (1967) *Brit. med. J.*, **2**, 672; Kalabus, F., Sansarricq, H., Lambin, P., Proulx, J. & Hilleman, M. R. (1967) *Amer. J. Epidem.*, **86**, 95; Weibel, R. E., Stokes, J. Jr., Buynak, E. B., Leagus, M. B. & Hilleman, M. R. (1969) *Pediatrics*, **43**, 567.

² Winter, P. A. D., Mason, J. H., Kuhr, E., Schaafsma, A. W. & Robinson, M. (1963) *S. Afr. med. J.*, **37**, 513.

ensure regular weekly reporting from these other sources regarding the presence or absence of cases.

In many countries, national surveillance reports charting the progress of the programme, recording and interpreting the smallpox morbidity data, and providing technical and specialized information have been invaluable in stimulating more effective performance at all levels.

When a suspected case is reported, immediate field investigation and containment are required. These should be undertaken by a specially trained surveillance officer or team from the national level; in very populous countries, an officer or team from the state or provincial level should be available to work in co-operation with the local staff.

The surveillance unit must confirm the diagnosis, trace the source of infection, and ensure that all possible containment measures are taken. These tasks require special skills: district and other local staff cannot be expected to execute them reliably since special training is required. The local staff are usually already overburdened with responsibilities and are not infrequently transferred from one place to another or from one function to another. If called upon only occasionally to deal with a smallpox outbreak, they are very likely to experience difficulties in differential diagnosis and in the techniques required for the proper investigation and containment of an outbreak. When the source of infection is in another health jurisdiction, failures in cross notification are frequent, with the result that transmission inevitably persists. In most countries, a well trained surveillance unit can cope effectively with smallpox surveillance in a population of 3-20 million, depending on the extent of co-operation from the existing health services.

Once a reporting network has been established and all cases can be detected by field investigation, valuable information can be obtained about the location and extent of endemic areas and the characteristics (age, sex, vaccination status) of the individuals in whom smallpox occurs. The systematic programme of vaccination can then be modified to place greater emphasis on reaching those areas or groups at the highest risk from smallpox. Similarly, special surveillance activities can be undertaken in high-risk areas.

When the occurrence of cases has become so rare that the surveillance units are not engaged full-time in investigating and containing outbreaks, an active search for cases should be undertaken, giving priority to areas considered to be the likeliest to harbour unrecognized foci. Unsuspected foci have most frequently been detected in areas where cases were last known to have occurred; where the notification network is deficient; in city slums; and in places where immigrants and seasonal workers congregate. Experience has shown that schoolchildren are frequently the most knowledgeable about cases in the area. By visiting schools, information may be obtained regarding possible smallpox cases over a wide area. The

use of the WHO Smallpox Recognition Card has proved invaluable for this activity. In this way, surveillance units working according to a schedule and itinerary prepared in advance can systematically visit schools, civic leaders, and health units over a considerable area in a comparatively short period. If suspected cases are reported, an immediate investigation is required.

Scars in very young children and recent facial scars in persons of any age suggest the existence of an unrecognized focus of infection. An investigation should be instituted immediately. Studies in West Africa showed that about 70% of cases had scars detectable after 1 year, but these were less persistent in young children (Table 4). The frequency with which

TABLE 4. WEST AFRICA: RESIDUAL FACIAL SCARRING 1-4 YEARS AFTER SMALLPOX ^a

Age (years)	No. examined	No. with scars	% with scars
0-4	17	5	29.4
5-9	42	18	42.8
10-14	23	22	95.6
15-19	20	16	80.0
20-24	15	14	93.5
25+	17	15	88.3
Total (all ages)	134	90	67.1

^a Scarring is defined as 5 or more concentric, depressed, facial scars 1 mm or more in diameter.

persistent scars occur is assumed to be similar in Asia. However, the frequency is much lower in South America, although this has not been specifically quantified.

When each newly detected outbreak of smallpox can be traced to previously known and investigated outbreaks, experience has shown that the complete interruption of transmission is imminent.

Finally, when transmission is believed to have been interrupted, every suspected case should be treated as a public health emergency. Confirmation by fully competent staff through clinical, epidemiological, and laboratory investigation is vital. In non-endemic countries, because of the international implications of a case of smallpox, it is considered important that international staff should participate in the investigation of any outbreak.

12. LABORATORY DIAGNOSIS

In endemic areas and during epidemics in non-endemic areas, there should be no difficulty in the clinical diagnosis of all but occasional cases of smallpox. The few clinical puzzles presented by haemorrhagic or modified cases may be considered as smallpox and dealt with as such. However, in non-endemic countries and in countries or large provinces that are virtually free of smallpox, every case must be carefully investigated by a surveillance officer or team and confirmed in the laboratory.

Laboratory diagnostic services can now be provided by two WHO reference centres.¹ In larger endemic countries, a single national laboratory may assume the responsibility if its competence has been established and the continuous supply of fertile eggs is guaranteed. Because each specimen is important and because it is necessary to be sure that the procedures are correctly performed, it is strongly recommended that not more than one laboratory (or perhaps two in very large countries) be designated to undertake laboratory diagnosis. In non-endemic countries with a smallpox laboratory, specimens should be collected in duplicate and examined in both a WHO reference laboratory and the national laboratory so as to ensure accurate diagnosis and to permit the detection of unusual poxviruses, such as monkeypox.

The efficiency of all smallpox diagnostic laboratories should be assessed regularly by their success in reporting correctly on unknown test specimens supplied by a WHO reference laboratory.

12.1 Type and quantity of specimens needed

The surveillance team responsible for investigating the epidemiological aspects of each suspected case should also be responsible for and specifically trained in the collection of specimens. WHO has available for supply to the central surveillance authorities a simplified specimen-collecting kit consisting of a plastic, screw-capped tube containing a cotton swab mounted on a stick. The tube is inside a screw-capped container which itself is in another screw-capped container. Swabs are used to collect the contents of 5 or 6 pustules for each laboratory. When the patient's lesions have formed crusts, not less than 6 scabs should be obtained.

¹ Laboratory of Smallpox Prophylaxis, Research Institute of Virus Preparations, Moscow; and Center for Disease Control, Atlanta, Ga.

Where no active cases are found but where an outbreak has obviously occurred, sera may be submitted for examination. The patients should be bled by the usual method of venepuncture. Between 5 ml and 10 ml of blood should be drawn and allowed to clot, and the sera separated. The sera should then be sent in a leakproof container to a WHO reference laboratory where they can be tested by a variety of methods.

12.2 Despatch of specimens to the laboratory

The specimens must be regarded as highly infective and must therefore be enclosed in suitable containers. These are supplied as part of the WHO kit. Specimens should reach the laboratory promptly and, when possible, should be refrigerated. If they cannot be delivered by hand they should be sent by the most rapid means of transport available, and the receiving laboratory should be informed by telephone or telegraph of the estimated time of their arrival. Packages sent through the post should conform to national and international postal requirements.

With all specimens sent to the laboratory, details should be given of the patient's age, name, address, history of vaccination, date of appearance of rash, and date of collection of specimen. This requires the completion of the form supplied with each kit.

When specimens are sent by post, special precautions must be taken. The following is quoted from Article 120 of the requirements established by the International Postal Convention (Vienna, 1964).

Perishable biological substances consisting of living pathogenic micro-organisms or of living pathogenic viruses shall be enclosed in a bottle or tube of glass or plastic materials with thick sides, well stoppered, or in a sealed vial. This container shall be impermeable and hermetically sealed. It shall be surrounded with a thick and absorbent material (medicated cotton wool, swan's down cloth or flannelette) wrapped round the container several times and bound both above and below it so as to form a sort of cocoon. The container so wrapped shall be placed in a solid, well-fastened, metal box. The absorbent material placed between the inner container and the metal box shall be of sufficient quantity to absorb, in case of a breakage, all the liquid contained, or capable of being formed, in the inner container. The metal box shall be made and fastened in such a way as to make any contamination of the outside of the box impossible. The metal box itself shall be wrapped in cotton or spongy material and enclosed in its turn in a protective box in such a way as to prevent any movement. This outer protective box shall be hollowed out from a block of solid wood, or shall be of metal, or may be of a material and construction of equivalent strength, and furnished with a well-fitting lid fastened so that it cannot open in course of transmission. Special provision, such as drying by freezing or packing in ice, shall be made to ensure the preservation of substances sensitive to high temperatures. Air transmission, which entails changes in atmospheric pressure, makes it necessary that the packing should be strong enough to withstand these variations in pressure. Moreover, the outer box (as well as the outer wrapping if there is any) shall be furnished on the side which bears the addresses of the officially recognized laboratories sending and receiving the item with a violet coloured label with the following indication and symbol :



(Dimensions 62 × 44 mm)

12.3 Tests performed and the significance of results¹

12.3.1 *Precipitation-in-gel*

This is an immunodiffusion test for the recognition of poxvirus antigens. It is a reliable diagnostic test when sufficient material is used. False negative results are seen when too little material is employed. In this test, a suspension containing pustular material or an extract of 2 or 3 crusts and a highly potent antivaccinial serum are used. The test is done on microscope slides on which a layer of agar is prepared and reservoirs or cups are cut. The antiserum is placed in one cup and pustular fluid, crust extracts, and control materials are placed in surrounding cups. If the material is from a smallpox patient, precipitation lines should appear in the agar between the antigen and antiserum cups within 2 hours, linking with those in the positive control within 4–5 hours. If a weak serum or little antigen is present in the pustular fluid or crusts, a positive result may be delayed for 24 hours.

A positive result is strong presumptive evidence that the specimen contains virus material of the variola-vaccinia group, but vaccinia and variola viruses cannot be differentiated by this test. A negative result indicates that the patient may have had some other illness or that insufficient antigen may have been present in the specimen. Virus isolation must be done in confirmation and to identify the virus.

12.3.2 *Virus isolation*

Poxviruses may be isolated by inoculating material from the lesions of the patient on the chorioallantoic membranes of chick embryos. Normally, 72 hours are required for growth. Isolation of virus should always

¹ For a full description, see : World Health Organization (1969) *Guide to the laboratory diagnosis of smallpox*, Geneva, p. 19.

be attempted as a confirmatory test and to supplement other diagnostic methods. Variola, vaccinia, cowpox, monkeypox, and herpes simplex viruses produce different types of lesion and thus may be distinguished by this technique. Varicella virus does not grow on the chorioallantoic membrane. Failure of pock formation on the membrane may indicate that the suspected case is not smallpox or that the sample was inadequate or improperly handled before it reached the laboratory. The use of appropriate tissue culture in the diagnostic procedure may provide an additional indication of the specific virus infection.

When there are strong clinical grounds for diagnosing smallpox, the physician should not allow his judgment to be unduly influenced by failure to identify the virus. However, when very few cases of smallpox are occurring, isolation of the virus from a suspected case is welcome confirmation of the clinical diagnosis.

12.3.3 *Electron microscopy*

This is a quick and sensitive method of demonstrating a poxvirus in a specimen. It may equally rapidly identify varicella or herpes simplex viruses. The method requires not only an electron microscope—a very expensive and highly specialized instrument—but also a skilled and experienced investigator.

13. CONTAINMENT MEASURES

Containment measures consist in isolating the patient and vaccinating his contacts; epidemiological investigation to identify and interrupt the chain of transmission; and, in due course, disinfection of the patient's clothing and bedding. The measures to be taken in endemic and non-endemic countries are the same in principle. However, more intensive action, such as individual surveillance of all contacts of smallpox cases, is essential in a non-endemic country. This is not always feasible in an endemic country where large numbers of cases occur.

13.1 *Isolation and quarantine*

The patient should be isolated to the maximum extent possible throughout the infective period. This extends from about 24 hours before the appearance of rash and continues until all scabs have separated. Isolation is especially important during the first 2 weeks of rash, when the excretion of virus is greatest. In many endemic areas, isolation in the home is common practice. This can be satisfactory provided that the patient remains in the home, that all family members are vaccinated, and that visitors are prohibited.

Since there is no specific therapy for smallpox, admission to a hospital offers no special advantages except that it perhaps ensures more effective isolation. However, it can be hazardous to other patients as well as to visitors and hospital staff. In both endemic and non-endemic countries, smallpox has frequently been transmitted after contact between patients with smallpox—both recognized and unrecognized—and patients hospitalized for other reasons. Because of this hazard, all patients in and visitors to infectious disease hospitals in endemic countries should be routinely vaccinated on entry. In non-endemic areas, this should be done when an importation occurs. Extensive experience at the Madras Infectious Diseases Hospital as well as in other hospitals has shown this to be a safe and efficacious procedure. Every suspected smallpox patient should, of course, be vaccinated and isolated. Hospital staff should be vaccinated at 3-year intervals to ensure the maximum possible protection.

In non-endemic countries, contacts of the patient, in addition to being vaccinated, should be placed under daily surveillance. If any develops fever at any time from 7 days after the first exposure to 17 days after the last, he should be isolated until it can be determined whether or not the fever represents the prodromal illness of smallpox. In endemic areas, shortages of personnel and other facilities may not permit such intensive measures.

13.2 Contact and community vaccination

The appearance of smallpox calls for the immediate vaccination of all contacts of the patient and, following this, the vaccination of all residents in a village, or in a defined area of a town or city. In general, if from 500 to 1 000 contacts and persons in the immediate area are vaccinated, further transmission is stopped. Containment vaccination in the defined area should have as its objective the vaccination of every resident within 2–3 days. Failure to interrupt transmission has most frequently resulted from delays in completing the vaccination programme or from not vaccinating all residents. Since many people are absent from their homes during normal working hours, vaccinations must be performed in the evening or early morning, as well as during the day. The area should be revisited at least at weekly intervals to detect further cases, to examine vaccination responses among contacts, and to vaccinate recent arrivals. Such visits should be repeated for at least 6 weeks after the onset of the last case.

13.3 Disinfection

The object of disinfection is to destroy virus contaminating the patient's clothing, bedclothes, and room. Disinfection methods will depend on the facilities available. Destruction by fire is the most effective and is particularly recommended for disposing of discharges from the nose and throat.

Where chemical disinfectants or special equipment are not available, simple procedures are effective for the disinfection of premises, bedding, and other objects. Bedclothes and covers should be boiled. The room and all hard surfaces in it should be washed thoroughly with soap and water, and entry to the room should be prohibited for 48 hours. When possible, surfaces so treated should be exposed to direct sunlight for several hours.

Fabrics and other items should be soaked for 2–24 hours in solutions of disinfectants known to kill poxviruses. The disinfectant should be chosen from among the following groups of substances: chlorine preparations, such as chlorinated lime in concentrations that leave 25 ppm or more of free chlorine after the chlorine demand has been satisfied (N.B.: these are bleaching and oxidizing compounds); formaldehyde solution at a concentration of 1% or more; iodophores; or quaternary ammonium compounds, such as benzethonium, benzalkonium, and cetylpyridinium chlorides at concentrations of 1% or more. For the chemical disinfection of premises, floors and surfaces should be sprayed or mopped with one of the above-mentioned disinfectant solutions. The solution should remain in contact with the surface for at least 4 hours before final washing.

When fumigation is required, spaces can be disinfected by exposure to formaldehyde vapour for 6 hours. This can be accomplished by boiling commercial formalin in 2 volumes of water (500 ml of formalin plus 1 litre of water per 30 m³), or by adding potassium permanganate to commercial formalin in large jars (170–200 g to 500 ml of formalin plus 1 litre of water per 30 m³).

13.4 Antiviral agents

Many antiviral drugs have been tested for the chemoprophylaxis of smallpox. Only one—*N*-methylisatin 3-thiosemicarbazone (metisazone)—has been found to be of some value. A few studies have shown that this drug confers considerable protection,¹ but well controlled trials have not confirmed this.² The level of protection offered is less than that afforded by vaccinia immune globulin. Metisazone has the further serious disadvantage that it induces nausea and vomiting in a substantial proportion of those receiving it and is therefore unsuitable for administration on a large scale. In addition, this drug is not widely available. The most practical approach to the control of outbreaks continues to be the vaccination of all contacts. Vaccinia immune globulin, when it is available, may be used to protect those for whom vaccination is contraindicated.

¹ Bauer, D. J., St. Vincent, L., Kempe, C. H., Young, P. A. & Downie, A. W. (1969) *Amer. J. Epidem.*, **90**, 130.

² Heiner, G. C. et al. (1971) *Amer. J. Epidem.*, **94**, 435.

14. MAINTENANCE OF SMALLPOX-FREE STATUS

In the world of today, when travel is extensive and rapid, there can be no assurance that freedom from smallpox, once it has been achieved in a country, will be permanent. Special efforts are required if a country is to remain non-endemic. The nature of the effort will vary from one country to another, depending on the risk of importation of smallpox as well as on the capacity of the existing health services to detect and contain importations if they occur.

All countries must expect possible importations. However strictly the International Health Regulations may be applied to ensure that travellers have valid international certificates of vaccination, illegal immigrants, individuals with forged vaccination certificates, and other unprotected travellers may introduce infection. When smallpox has been introduced, the possibility always exists that further transmission of infection will occur, since no vaccination programme, however extensive, can assure complete and continuing protection against smallpox.

The principal defence against the re-establishment of endemic smallpox is necessarily based on detection of the infection as early as possible, appropriate epidemiological investigation, and containment of the outbreak. Because smallpox outbreaks usually develop comparatively slowly and cases tend to occur in isolated clusters, this approach has been found to be fully effective, even though several weeks may elapse between the initial introduction of the outbreak and its discovery.

A well defined reporting system is essential. As with smallpox surveillance programmes in endemic countries, specific reporting posts should be established that report immediately if a suspected case of smallpox is detected, and weekly regarding the presence or absence of smallpox as well as other specific diseases of national concern. Regular completion of the weekly report provides evidence that the reporting posts recognize the need to notify a higher authority.

The notification of a suspected case constitutes a public health emergency. If the case is one of smallpox the country as a whole is threatened, and national authorities must ensure that all possible measures are taken to contain the outbreak. To entrust these activities to local authorities with little or no training or experience is to invite disaster. A well trained surveillance officer or unit at the national level should be available immediately for investigation and control. Such an officer or unit may constitute part of an epidemiological unit or system dealing with a variety of diseases, but the need for immediate attention to a report of suspected smallpox must be recognized. In countries having common borders with an endemic country, the surveillance unit should be concerned full-time with smallpox, for experience has shown that importations occur more frequently there

than in other countries. In such countries there must also be a continual, active search for cases, particularly in border districts.

Each suspected case must be confirmed by clinical, laboratory, and epidemiological investigations, and immediate containment measures must be taken. Detailed information regarding the source of the imported infection should be sent immediately to WHO, Geneva, and to the country where the infection originated. Laboratory specimens may be processed locally but duplicate specimens must be despatched immediately by air to WHO, Geneva, for further confirmation.

The transmission of infection following importation will be slower and less extensive in a more highly immune population than in one that is fully susceptible to the disease. Countries with less adequately developed health services may not detect imported smallpox for a considerable time. It is therefore particularly important to maintain a high level of immunity through a continuing vaccination programme in such countries.

As an index of the efficiency of a programme, the Committee proposed that, in countries bordering endemic areas, at least 80% of persons in each of the age groups 0-4 years, 5-14 years, and 15 years and older should bear a scar of primary vaccination. When such a level has been reached in the 0-4-year age group, the total prevalence of vaccination scars will exceed 90%. In other countries located in endemic continents, at least 80% of the population as a whole should bear a scar of primary vaccination. Scar surveys should be conducted periodically to make sure that these objectives are being met.

To sustain the high levels of immunity necessary in countries at unusual risk, special vaccination programmes are required. When vaccination is confined to health centres or other permanent locations, the extent of coverage in the immediate area of the centre itself rarely exceeds 75% and decreases sharply beyond 2-3 km from the centre. The use of multipurpose workers has been attempted in some areas and has been found to be both ineffective and costly, as well as entailing considerable wastage of vaccine.

Countries that have recently become non-endemic after systematic vaccination programmes have adopted various approaches to maintaining immunity. In some, mobile teams have continued their activities, at the same time administering BCG or other vaccines in addition to smallpox vaccine to all children up to 10 years old. By limiting vaccination to this younger age group, the teams are able to cover larger populations, as children in this age group are readily accessible and rarely resist vaccination, as adults tend to do.

In another approach, vaccinators continue to administer smallpox vaccine only to newborn infants and to persons not previously vaccinated. Revaccination is provided at the time of school entry. The relative efficacy of this approach, as measured by scar surveys, has not been fully appraised. In still another approach, vaccination is given on a "vaccination day" on

one day of the week or month at existing health centres. In addition, all children are vaccinated during the year of school entry and during the last year of primary-school attendance. This system requires independent assessment by scar survey.

Just as health services and epidemiological requirements differ from one country to another, so must the design of continuing vaccination programmes.

15. STRATEGY AND FUTURE DEVELOPMENT OF THE SMALLPOX ERADICATION PROGRAMME

At the end of 1971, smallpox was confined mainly to 4 endemic countries: Ethiopia, India, Pakistan, and Sudan. Residual foci of transmission outside these countries are believed to be limited in extent and highly susceptible to eradication. However, the difficulties of interrupting transmission in the remaining principal endemic areas should not be underestimated. The fact that transmission persists in these areas, whereas most of the world has become smallpox-free, implies special problems that will demand an effort at least equal to that made in the past 5 years. Nevertheless, with a full commitment to this programme by the endemic countries, supplemented by necessary bilateral and multilateral support and co-ordination, there is every reason to believe that the goal of global eradication could be achieved within a few years.

The experience of the past 5 years clearly demonstrates that surveillance is the essential element in the strategy for eradication.

Reporting must be strengthened everywhere. Every suspected case must be investigated at once, its source of infection traced, and containment measures instituted promptly. With regard to the 4 principal endemic countries, the surveillance efforts in Ethiopia and in 4 of the 5 provinces of Pakistan appear to be progressing well; several of the states of India also are making satisfactory progress. However, in one province of Pakistan, surveillance has barely begun, and surveillance in Sudan needs to be strengthened considerably. India presents special problems: not only is there inadequate surveillance in many states, but the reporting of smallpox at all levels, notably from the state to the national level and from the national level to WHO is significantly delayed and often incomplete. The importance of national co-ordination in India, as in the other endemic countries, must not be underestimated.

In countries sharing borders with endemic areas, the risk of importing smallpox is particularly high and necessitates a continuing programme of surveillance with an active search for possible foci by special surveillance

teams. Continuing intensive vaccination programmes in these countries, especially in border districts, is strongly recommended in order to maintain high levels of immunity.

As for countries into which smallpox has been imported during the past 2 years, only intensive surveillance programmes will assure that residual foci have not persisted. From some countries, information regarding smallpox is regrettably incomplete. Most of these countries are in southern Africa and include specifically Angola, Botswana, Lesotho, Mozambique, South Africa, and Swaziland. The same may be said of the countries of the Arabian peninsula and Iran. During the past few years, many of these countries have recorded cases that have been attributed to importations, but epidemiological information is too scanty to permit definite conclusions to be drawn. In addition, it is most important to obtain detailed information regarding the smallpox situation in continental China. China was reported to be free of smallpox following an intensive programme more than 10 years ago, but confirmation of this fact is critical, particularly now that the goal of eradication in other parts of the world is within reach.

In other apparently non-endemic countries in the continents of Africa, Asia and South America, programmes of vaccination and surveillance should be continued until global eradication has been achieved. Except in a few countries at low risk and with highly developed health services and adequate surveillance, vaccination programmes should not yet be discontinued. Every case of smallpox that occurs in a non-endemic country is important: it could signify an unrecognized persistent focus of imported infection. Because the eradication programme is a global undertaking, each case in a non-endemic country is of international concern. The Committee therefore strongly recommends that all cases of smallpox in presumably non-endemic countries should be investigated promptly by national staff assisted by experienced WHO smallpox staff, in order to facilitate international co-ordination and co-operation in eliminating residual foci of infection.

All cases of smallpox should be notified immediately to WHO, as required by the International Health Regulations. Failure to do this has been exceptional, but the Committee strongly deplored that a few instances have been known. Since such omissions may seriously jeopardize the global effort, it is recommended that, when failure to report is suspected, representations should be made at the highest level to the government of the country concerned.

One of the most difficult aspects of the programme is to make sure that no endemic foci of the disease still remain in a country. It is obviously impossible to examine an entire population at any one time. The problem is to devise appropriate means of obtaining this assurance within each country through contact with a portion of the population. Examples of

effective approaches are those in Afghanistan and Zaire, where specially designated and trained surveillance teams travel systematically throughout the country as part of a continuous programme. During their travels they contact schools, health units, and civic leaders to enquire about the existence of possible smallpox cases and to encourage reporting.

Another approach that may be recommended is that used in Paraguay: malaria eradication staff enquired about smallpox in all houses visited during their monthly spraying tour; health units enquired about smallpox in a sample of schools in each area; and a special team visited all schools, health units, and principal civic officials in areas where information was scanty. Scar surveys were also made by the special team to detect facial scars of smallpox in young children. All suspected cases were investigated: none was smallpox. As a result of this survey, which lasted 2 months, it could be stated with reasonable certainty that smallpox was no longer endemic in Paraguay.

At this stage in the eradication programme, it is essential for WHO to intensify its efforts to support and co-ordinate all programmes. Although fewer resources are required in some areas, more will be needed in others to deal with difficult residual problems. The demand for large supplies of freeze-dried vaccine of the required standard will continue. Further assistance to already existing vaccine production laboratories will be needed, as well as substantial donations of vaccine from member governments. Assistance to established diagnostic reference laboratories will be increasingly important.

It would be prudent to continue an active programme of research in a number of important fields, including the ecology of monkeypox and related viruses; improved rapid diagnostic methods; the genetic inter-relationships of poxviruses of the variola-vaccinia-monkeypox group; the mechanism of immunity in poxvirus infections; and, finally, improved and simplified methods of applying other vaccines simultaneously with smallpox vaccine.

When countries become free of smallpox and systematic programmes of vaccination have been completed, due consideration should be given to the possible extension of responsibilities of programme staff in further supporting the general health services. The existing health services of previously endemic countries and those considered to be at high risk should be encouraged to continue routine vaccination to the greatest extent possible. Because systematic vaccination programmes have been specially effective in achieving high rates of acceptance, many non-endemic countries have extended the responsibilities of vaccinators to include BCG, measles, cholera, and yellow fever vaccinations (see also section 10.7). This approach has been effective and, at the same time, has maintained smallpox immunity. Further exploration of this combined approach is most important since several problems remain to be solved. Provision of the various vaccines of assured potency and at a reasonable cost is a major problem.

New techniques for vaccine administration must be investigated, since conventional needle-and-syringe techniques are not suitable for the large scale administration of vaccines, and jet injectors are expensive and difficult to maintain. The very useful bifurcated needle might, for example, prove suitable for administering yellow fever, measles, and BCG vaccines. Simplified vaccination schedules must be evaluated in the field.

Long-term technical and material assistance should be given to all countries for the support of surveillance programmes to verify continuously that smallpox transmission has been permanently interrupted. As smallpox incidence decreases to zero in all countries and the absence of the disease is beyond doubt, surveillance programmes should undertake increasing responsibilities for the surveillance of other communicable diseases.
