Handbook for Smallpox Eradication in Endemic Areas (1st revision)
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AREAS OF PARTICULAR INTEREST FOR FIELD RESEARCH AND INVESTIGATION

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1. Introduction

In view of the proliferation of medical research during recent decades, it is perhaps surprising that much practical epidemiological information concerning smallpox is either lacking or is based on broad interpretation of incomplete or inadequate data. A number of significant aspects remain to be described and clarified. Many of these are basic to present concepts regarding smallpox eradication.

The patterns of occurrence of smallpox are known to differ, sometimes significantly, in different parts of the world. In many endemic countries little or nothing is known regarding the epidemiological behaviour of the disease. The changing and distinctive patterns of social organization in different countries and areas, coupled with variations in climatic patterns, nutrition and parasitism, indicate that experience and knowledge gained in one area cannot be fully extrapolated to another with respect to either the clinical or epidemiological behaviour of the disease.

Confronted with the problem of global eradication of smallpox, an improved epidemiological understanding of the disease assumes a very practical as well as a scientific importance. Such understanding can, in the long term, serve to focus the problem more sharply, to strengthen the operational structure and to shorten the time requisite to achieve full eradication.

The purpose of this section is to point out in general terms broad gaps in our present understanding of the occurrence and transmission of smallpox, and to outline ways in which the various concepts and approaches to eradication might be subjected to more critical scientific scrutiny. In addition, reference will be made to other areas where more information is needed concerning mass immunization practices. It is perhaps superfluous to add that the following descriptive list is only a partial one, and can be extended indefinitely by the inquiring mind.

Many of these studies can be carried out by one or a few individuals alert to the opportunities presented by epidemic circumstances (single cases with unusual epidemiological histories, etc.). Some, however, require the development of fairly sophisticated protocols with carefully selected subjects and controls, and may involve substantial laboratory work. The WHO Regional Office and WHO Headquarters staff should be kept currently informed regarding anticipated studies of a more elaborate nature as well as pertinent findings derived from all studies, to permit the maximum exchange of information, to prevent unnecessary duplication of efforts and, under appropriate circumstances, to assess the possibility of providing supplementary personnel and laboratory support, should this be required for particular studies.

2. Descriptive epidemiology of smallpox

A considerable amount of important information can be obtained simply from observation of the basic patterns of disease occurrence and the application of simple epidemiological analysis. The principal areas of interest are summarized below:

2.1 Seasonal patterns of occurrence in different climatic regions

2.2 Age and sex distribution of cases

Variations in smallpox incidence by age and sex may provide important clues to differences in acceptance or accessibility for vaccination or may relate to relative differences in type or frequency of exposure.

2.3 Urban versus rural disease concentrations

Principally, on logical grounds, it has been assumed that smallpox is a "crowd disease", that its endemic persistence is dependent upon adequate conglomerations of people. On the other hand, some health workers believe that in certain areas smallpox can persist in remote areas with only small, scattered population groups - its continued presence made possible by highly mobile populations. In the context of smallpox eradication, as distinct from mere control, it is obviously necessary in all areas that we know whether smallpox will disappear spontaneously in remote areas after urban foci are eliminated or whether such remote areas require the same degree of intensive vaccination. An analysis of the prevalence of smallpox in terms of urban concentration and descriptions of outbreaks in rural areas would provide such vital information on the endemic patterns of the disease.

2.4 Case fatality ratios

The establishment of case fatality ratios, in conjunction with appropriate virological studies, is required to ascertain the relative importance and frequency of variola major, variola minor, or disease possibly due to an intermediate strain in different areas. Although it is generally assumed that variola major exclusively is now present in South East Asia and variola minor in the Americas, the situation in Africa is quite unclear. Case fatality ratios in Africa appear to be intermediate between those normally observed with each of the two types of disease; some studies have suggested the presence of an "intermediate-type" strain. Whether variola minor is absent in Asia and variola major absent in the Americas needs to be more precisely determined. Unusually low case fatality rates have been recorded during some outbreaks in Asia, while in the Americas a number of cases of possible haemorrhagic smallpox have recently been recorded. These findings suggest that the assumed geographical distinctions may not be as definite as has been thought.

3. Specific epidemiological indices assessable without laboratory facilities

3.1 Index of infectivity

An index of infectivity of various diseases based on the "susceptible exposure attack rate" in families has been effectively used by Simpson [1]. This has permitted a comparison of the infectivity of various viral diseases in industrialized areas. Such a rate has never been adequately developed for smallpox in most presently endemic countries. Where smallpox is endemic, the opportunity presents itself to obtain such information based on the study of the disease in family units. This information would permit assessment of the relative infectiousness of smallpox under different circumstances and for different strains.

3.2 Incubation period

The incubation period of smallpox is felt to be quite consistently 12 to 14 days with comparatively little variation. Information regarding incubation periods is largely based on the average time interval between cases in outbreaks. This interval between cases can be due, however, not only to the incubation period but also to duration of infectivity. In most outbreaks, certain cases can be found which, through circumstances, result from "brief and only-possible" exposures. Such cases provide direct information on the incubation period and permit study of its variability. A series of as few as 15 to 20 well-documented incubation periods resulting from "brief and only-possible" exposures would permit a better determination of the range of incubation period of smallpox than now exists.

3.3 Duration of infectivity

Laboratory data suggest that smallpox may be potentially transmissible from the first 24 hours of illness until the last crusts are disposed of. However, the frequently observed intervals of 12 to 14 days between related cases in outbreaks suggest that the actual period of infectivity is substantially less than the potential one. Careful evaluation of cases in which the circumstances of contact with subsequent cases have been "brief and only-possible" exposures may provide more precise information on the effective infectivity of the disease. See Dixon[2] for a full discussion of this subject and Simpson[3] for the methodology of assessing the infectious period.

3.4 Type of contact resulting in transmission

Data from European and American outbreaks suggest that close personal contact is responsible for most smallpox virus transmission; the type of contact frequently documented is person-to-person contact as by family exposure or in hospital settings. There are, however, disturbing exceptions to the "close personal contact" exposure in which transmission has been explained only by long-range aerial spread. Verification in detail of apparent "jumps"

outside the limit of immediate, person-to-person contact must be documented. Such documentation would also permit evaluation of the relative importance of the contaminated environment, such as the household or hospital room, as compared to personal contact.

3.5 Duration of protection afforded by vaccination

More complete information regarding the average

~~Despite its enormous importance, the~~ duration of protection against smallpox following successful vaccination is ~~incompletely known~~ less reliable. Even more poorly understood is the effect of previous vaccination on the reduction of infectiousness in the person who develops modified smallpox, i.e. the secondary attack rate resulting from the case who had been previously vaccinated as compared to that resulting from the unvaccinated case. In any outbreak, careful documentation of the vaccinal status of cases and non-cases will provide evidence bearing on the question of the duration of vaccine effectiveness. Careful documentation of the vaccinal status of the first case in relation to secondary attack rates in household associates may provide evidence bearing on the comparative infectiousness of cases previously vaccinated and thus presumably partially immune.

3.6 Protection afforded by vaccination after exposure

Although it is known that primary vaccination or revaccination following contact exposure confers some degree of protection against smallpox, it is far from clear as to how effective this procedure is nor at what time in the incubation period vaccination must be carried out if it is to be effective. Serological evidence suggests a rapid response to revaccination which should occur early enough to prevent or modify smallpox in contacts even when administered moderately late in the incubation period. On the other hand, it is generally thought that vaccination or revaccination after the seventh day following exposure exerts no effect on the subsequent development of disease. In any outbreak, vaccination of contacts is likely to provide a ready-made situation for analysis of this effect. Careful documentation of dates of contact and dates of vaccination, coupled with evidence of previous vaccination status, should routinely be carried out.

3.7 Influence of social class and living conditions

As pointed out by Dixon[2] (p. 314), the principal influence of social class on the likelihood of disease transmission has been ascribed simply to the relative frequencies of vaccination in the various social groups. The influence of housing accommodation and crowding factors are not clearly understood. Opportunities should exist in many areas to document whether conditions of crowded or unusual housing arrangements influence the transmission of the disease.

3.8 The importance of human mobility in smallpox epidemiology

In a number of outbreaks in western nations, as well as in many instances in endemic countries, individual and group movements of various sorts have been shown to be responsible for the spread of disease from one area to another. Throughout most endemic countries, mobility is due to many factors: traditional pastoral nomadism, systematic seasonal migration by larger or smaller population units, itinerant traders, individual movement from rural to urban areas and back

again in search of work, and the ebb and flow of village people for social and marketing purposes. The relative importance of these types of movement in initiating and sustaining outbreaks must be determined.

3.9 The relative importance of age group in transmission

Age as a determinant in the maintenance of smallpox transmission has been only vaguely referred to in the past. Yet there are suggestions in Indian outbreaks that children are more important as transmitters than are adults. The implications of this phenomenon for a mass vaccination programme are obvious. Data bearing on this question may be collected by a careful study of the course of spread of outbreaks and by assessment of secondary attack rates in households in relation to age of the first case. Less directly, but perhaps just as usefully, age-specific epidemic curves might be constructed for extensive outbreaks in order to determine whether one age group or another is involved earlier during the course of an outbreak.

3.10 Vaccination coverage necessary to interrupt transmission

Due to local factors, the response to the mass vaccination campaign is likely to result in variable proportions of coverage in different communities. Much of the theory of smallpox eradication is based on the assumption that a certain level of coverage, frequently stated to be 80 per cent., is adequate to result in interruption of smallpox transmission. This figure has not been substantiated in the field and presumably would vary according to the characteristics of the population approached. Although an analysis of this sort, as well as the assessment of transmission in a moderately large number of communities for which coverage data are available, will require imagination, it should be possible to ascertain minimum levels necessary for interruption of continual transmission according to community size. Such factors as the increase of susceptibles by migration, the level of the birth-rate, indices of crowding and environmental and climatic factors will have to be taken into consideration to make such an analysis meaningful. This problem is obviously the most difficult of those enumerated to resolve adequately. It is, however, also singularly the key to the ultimate success of the global programme.

4. Investigations requiring laboratory assistance

Since laboratory studies are time consuming and since an active field epidemiologist can readily provide sufficient specimens to keep even a well-staffed laboratory fully occupied, it is important, prior to initiating studies involving laboratory support, to discuss projects in detail with the supporting laboratory to assure that the work can be done. Where no facilities exist, arrangements may be developed through WHO in selected instances for processing of specimens at collaborating laboratories.

4.1 Smallpox virus types (variola major, intermediata and minor)

As alluded to in 2.4, little is known regarding the range of laboratory characteristics of smallpox viruses, particularly in Africa; also in Asia and South America. By characterizing viruses from patients in many smallpox outbreaks, and correlating these findings with the case fatality ratios among vaccinated and unvaccinated persons and the severity of non-fatal disease in these epidemics, a more complete picture of smallpox virus types can be derived.

4.2 Possible importance of simian pox virus diseases

It is generally accepted that man is the only natural host of smallpox virus. It is partially on this premise that the prospects for smallpox eradication are considered to be so optimistic. Experimentally, monkeys can be infected with variola virus by exposure to aerosols containing the virus. The disease course in monkeys is comparable to that in man. Viremia occurs, with vesicular and pustular lesions. In the experimental situation, disease is mild and death rare [4].

In nature, smallpox in monkeys has been reported several times but virological confirmation is lacking as virus culture techniques had not been developed at the time of these observations [5,6,7]. During an epidemic of human smallpox in Indonesia in 1949, smallpox was reported in an orangutan in a zoo.

While it is unlikely, based on present information, that variola occurs in monkeys under natural circumstances and while it is doubtful that monkeys can serve to transmit the infection to man, the possibility that monkeys might serve as reservoirs for smallpox virus cannot be completely dismissed. Wherever human smallpox occurs in association with monkey populations, animals should be obtained for examination and specimens collected for virological and serological studies. Furthermore, careful epidemiological and virological studies of vesicular-pustular diseases in monkeys need also to be carried out.

4.3 Neutralizing antibody response following vaccination

Only limited data are yet available regarding comparative neutralizing antibody responses among primary vaccinees and revaccinees in different age groups. Age groups of particular interest are infants less than six months of age, children, adults about 20 to 40 years old and adults over 40 years of age.

Studies now in progress in the South Pacific (Tonga) should provide a number of answers to questions in this area. Because it is difficult in endemic regions to obtain an adequate number of persons, particularly in the older age groups, who quite clearly have neither been vaccinated previously nor have experienced smallpox, only a few highly selected studies of this type can be contemplated in these endemic areas.

4.4 Correlation of smallpox antibody levels with protection

The relative role of humoral antibodies in conferring protection against smallpox has not been defined although it is generally agreed that levels of serum neutralizing antibody should correlate to some degree with the level of protection. The observation that hyperimmune globulin confers some protection when administered to contacts following exposure is further suggestive evidence [8].

Reasonably definitive answers to this question might be obtained by taking blood specimens from household contacts of smallpox cases. By careful follow-up of these contacts to determine which did and which did not develop smallpox and by correlation of this information with the neutralizing antibody titres obtained, more definite answers regarding protective titre levels should be forthcoming. However, since vaccination of household contacts at the time of recognition of a case is customary practice and since vaccination itself induces increased neutralizing antibody levels, this type of study would require collection of detailed epidemiological data and, undoubtedly, a substantial number of blood specimens to permit interpretation of the results. In the context of this study, the types of cutaneous responses to vaccination among contacts may be assessed to determine if a correlation exists between the type of response and the probability of the development of clinical smallpox.

Since these studies are of major importance to the entire eradication programme, it is hoped that co-operative studies employing a common protocol can be developed in several areas.

5. Multiple antigen administration

The economy involved in being able to administer, with safety and efficacy, several antigens simultaneously is self-evident. This is of particular importance in countries in which funds are limited and trained medical and paramedical personnel in short supply.

From available data, there is reason to believe that a number of antigens (DPT (diphtheria-pertussis-tetanus), typhoid, poliomyelitis, measles, smallpox, yellow fever and BCG vaccines) might be administered simultaneously with acceptable results from the standpoint of both safety and efficacy. Careful field evaluation and appraisal is required, however, before this can be done.

As summarized by Karzon and Henderson [9] and in the WHO Report on Virus Vaccines [10], there are reasonable data demonstrating the safety and efficacy of simultaneous administration of measles/smallpox, smallpox/BCG, yellow fever/smallpox and smallpox/inactivated vaccines. Definitive field evaluations are required for more elaborate combinations. Such studies will require careful serological appraisal of vaccinees and close follow-up for frequency of febrile

responses and other untoward reactions in progressively larger numbers of vaccines. If such studies are contemplated, the study designs and protocol should be discussed with individuals particularly knowledgeable in the area of vaccine studies.

6. Suitable strains of vaccinia virus for vaccine production

Although the precise history of vaccinia strains now used for vaccine production is unknown, it is certain that each of the strains used in the different production laboratories has been passed with different frequencies and in different animals and tissue culture media. From available data with respect to the relative frequencies of complications following vaccination [11,12,13], as well as from laboratory studies [14,15], it is clear that the different strains differ from each other with respect to a number of characteristics. Additional laboratory and field studies are required to compare the relative efficacy and reactogenicity of the different strains and to relate these to laboratory characteristics. Such studies would permit the development of recommendations with respect to the most suitable vaccine strain, or strains, which might be employed for vaccine production purposes.

7. Chemoprophylactic and chemotherapeutic agents

Several studies have been conducted to evaluate the comparative efficacy of chemoprophylactic agents given to contacts after exposure. The thiosemicarbazones ~~appear to~~ confer some degree of protection [16,17], but ~~the various studies are not in agreement with respect to the relative degree of protection conferred.~~ not all equally effective. Little information is available as to the relative efficacy of the drug administered at different intervals following exposure. Methisazone itself so frequently induces severe vomiting as to raise the question regarding its applicability as a practicable control measure. Further studies of this and other chemoprophylactic drugs could profitably be undertaken.

Recently, a number of chemotherapeutic drugs have become available including iododesoxyuridine (IUDR) and azauricilriboside, both of which appear to be of therapeutic value in the treatment of certain viral infections, including herpes simplex. Their potential value in treatment of smallpox remains to be evaluated.

8. Operational and sociological studies

Operational studies to assess the comparative costs of conducting large-scale vaccination programmes conducted in different ways, optimal methods of "selling" the programme to the general public, approaches to overcome resistance in the groups resistant to acceptance and other studies of this general character are of considerable practical value to the evolution of the programme in countries throughout the world. Consideration should be given to the incorporation of operations research specialists, sociologists, anthropologists, economists, etc. in approaching problems in this general area.

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