CHAPTER 4

THE EPIDEMIOLOGY OF SMALLPOX

Contents

INTRODUCTION

Chapters 1 and 3 were concerned with smallpox as a disease of individual human beings, discussing such problems as how the virus entered the body and spread through it, how the body reacted and what symptoms were produced, and how the virus was shed. Since smallpox was an infectious disease, there is another dimension to its study besides its effect on individual patients—namely, its behaviour in human populations. This di-

mension constitutes the epidemiology of the disease, which involves examination of the incidence of smallpox and the mortality attributable to it, over time and in different countries and regions; the various determinants of its occurrence and spread; its maintenance as an endemic disease; and the causes of epidemics. These considerations were of fundamental importance in its control and eventual eradication.

THE MORBIDITY AND MORTALITY OF SMALLPOX IN THE 20TH CENTURY

In Chapter 5 we describe how smallpox spread throughout the world, first through Asia, beginning in the 1st century AD, and then into Europe and northern Africa from about AD 700 onwards. With European colonization the disease was carried to Central, South and North America and southern Africa in the 16th and 17th centuries. By the time vaccination was introduced, at the end of the 18th century, the distribution of smallpox was world-wide. It was endemic everywhere, except in remote areas with sparse populations, such as Australia, New Zealand and the islands of the Pacific, Atlantic and Indian Oceans. Periodically it caused disastrous epidemics in many smaller island communities and then died out, as, for example, in Iceland, the islands of the Caribbean, Hawaii, Tahiti, Mauritius and the smaller islands of what were then the Netherlands East Indies (Hirsch, 1883).

Secular Changes in the Global Occurrence of Smallpox

By the early years of the 20th century endemic smallpox had been eliminated from a few of the countries of northern Europe with small populations, although importations from more densely populated neighbouring countries occurred almost every year (see Chapter 8). However, until current statistics began to be published by the Health Organisation of the League of Nations in 1922 (Howard-Jones, 1975), there was no mechanism for systematically collecting and disseminating information on the incidence of smallpox in different countries. National data for the early years of the 20th century were compiled by Low (1918) and consolidated figures for the years 1920–1947 were published by the Interim Commission of the World Health Organization (Fabre, 1948).

Weekly and consolidated annual figures for reported cases of smallpox in different countries were published by the World Health Organization after 1948. These figures, supplemented by investigations carried out by the WHO Smallpox Eradication unit, were used for the tabulation of reported cases of smallpox by country and by WHO region provided in the *Final Report of the Global Commission for the Certification of Smallpox Eradication* (World Health Organization, 1980). Further supplemented by studies conducted by the authors of the present book, these data were used for the detailed tabulation of reported cases of smallpox in the larger countries of the world presented in Chapter 8. These official data reflect only reported cases, and, as will be shown in a later section, smallpox was grossly underreported in most countries. The figures convey an impression of the ebb and flow of the disease in various countries, but they give little idea of its true incidence.

More relevant in the present context is a global overview of secular trends in the numbers of countries in which smallpox was endemic during the period from 1920 until its eradication (Fig. 4.1). To obtain the data for this, all available sources of information were consulted, and the assumption was made that smallpox was persistently endemic between the 1920s and the 1940s in countries in which in the 1950s it appeared to be a long-established endemic disease, even though some of these countries had failed to report its occurrence to the Health Organisation of the League of Nations during that period. The data are plotted by 5-year intervals prior to 1958 and annually thereafter; they show for each continent the secular changes in the numbers of countries in which smallpox was endemic. In terms of the global eradication of smallpox, important administrative decisions were taken in 1959, when the World Health Assembly first launched a programme for global eradication, and in 1967, when the Intensified Smallpox Eradication Programme was initiated (see Chapters 9 and 10).

The period 1920–1958

In 1920 smallpox was endemic in most countries, being present in 124 and absent

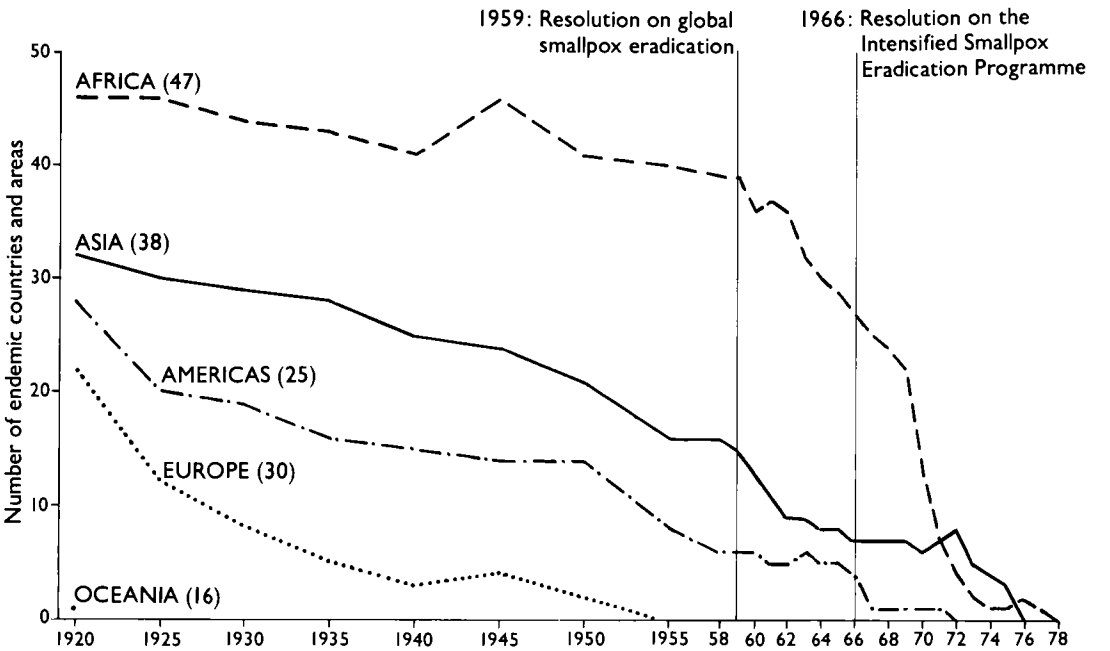


Fig. 4.1. Numbers of countries and territories in which smallpox was endemic between 1920 and 1978, arranged by continent. The figures in brackets indicate the numbers of countries and territories involved. Their names (as of 1986) are listed below.

Africa: Algeria, Angola, Benin, Botswana, Burkina Faso (Upper Volta), Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Libyan Arab Jamahiriya, Madagascar, Malawi, Mali, Mauritania, Morocco, Mozambique, Namibia (South West Africa), Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Sudan, Swaziland, Togo, Tunisia, Uganda, United Republic of Tanzania, Zaire, Zambia, Zimbabwe.

Americas: Argentina, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, USA, Uruguay, Venezuela.

Asia: Afghanistan, Bahrain, Bangladesh, Bhutan, Burma, China, Democratic Kampuchea, Democratic Yemen, Democratic People's Republic of Korea, Hong Kong, India, Indonesia, Islamic Republic of Iran, Iraq, Israel, Japan, Jordan, Kuwait, Lao People's Democratic Republic, Lebanon, Loro Sae (East Timor), Macao, Malaysia, Mongolia, Nepal, Oman, Pakistan, Philippines, Qatar, Republic of Korea, Saudi Arabia, Singapore, Sri Lanka, Syrian Arab Republic, Thailand, United Arab Emirates, Viet Nam, Yemen.

Europe: Albania, Austria, Belgium, Bulgaria, Cyprus, Czechoslovakia, Denmark, Finland, France, German Democratic Republic, Federal Republic of Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Turkey, USSR, United Kingdom, Yugoslavia.

Oceania: Australia, Fiji, French Polynesia, Guam, Kiribati, Mariana Islands, Marshall Islands, Nauru, New Caledonia, New Zealand, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu.

only from all the countries of Oceania and 16 countries in the other 4 continents. The only countries of Oceania with populations large enough to have supported endemic smallpox were Australia and New Zealand, which were protected by distance and an effective system of seaport quarantine from all but a very few importations, most of which were controlled at the port of entry.

By 1920 endemic smallpox in Europe had been eliminated only from Denmark, the Netherlands, Norway and Sweden. Subsequently the situation improved quite rapidly, so that by 1935 endemic smallpox had been eliminated from 25 countries, although it remained relatively common in Portugal, Spain, the USSR and the United Kingdom. The last endemic case in the USSR was reported in 1936 (see Chapter 8). Elsewhere in Europe the downward trend continued, and the continent was free of endemic smallpox by 1953.

In the Americas, tens of thousands of cases of smallpox were reported annually up to the late 1930s, variola major in Mexico and some South American countries and mostly variola

minor in other South American countries and the USA. Smallpox was eliminated from the Central American countries between 1920 and 1951 and from Mexico in 1951. Endemic variola major had been eliminated from the USA in 1926 but variola minor persisted until the late 1940s. Smallpox continued to be endemic in the larger countries of South America until 1950, when a steady decline began. In that year a regional eradication campaign for the Americas was initiated by the Pan American Sanitary Organization (later renamed the Pan American Health Organization) (see Chapter 9) and the incidence continued to fall until, by 1958, smallpox remained endemic in only 6 countries.

The situation was not nearly as good as this in Asia and Africa, the continents in which reporting was the least reliable. The number of endemic countries in Asia declined slowly, endemic smallpox being eliminated from Indonesia, Malaysia, the Philippines and Sri Lanka by 1938, only to be reintroduced into these countries during the disruption caused by the Second World War. After that there was a slight but steady improvement, mainly in the smaller countries of eastern Asia, but the disease appeared to be largely unchecked in the Indian subcontinent and was still endemic in some 40% of the countries of Asia in 1958.

In Africa progress was even slower, except for the gradual reduction in the number of reported cases and the elimination of endemic smallpox in the countries of northern Africa and some of the small sparsely populated countries in southern Africa. During this period successful country-wide elimination did not always mean that subsequent importations would be successfully contained. For example, after the elimination of endemic smallpox from Egypt in the mid-1930s, variola major was reintroduced during the Second World War and became endemic again, producing several thousand reported cases in 1943–1945 (Tulloch, 1980). There were similar exacerbations after the Second World War in Algeria, Libya and Morocco. In most countries in Africa south of the Sahara smallpox was apparently almost as common in 1958 as it had been two decades earlier.

The period 1959–1966

In 1959 the Twelfth World Health Assembly adopted a resolution introduced by the USSR calling for the world-wide eradication of smallpox (see Chapter 9), confident in the knowledge that eradication had by then been achieved in Europe and in North and Central America. The situation in South America appeared to be manageable, and indeed the number of endemic countries decreased until, by 1967, smallpox remained endemic only in Brazil. The real problem was posed by the developing countries of Africa and Asia. During the few years between 1959 and 1966 there were substantial gains in Asia, the most important of which was the elimination of endemic smallpox from China. This was achieved by 1961 and was due entirely to a national initiative. Smallpox, however, remained rampant in the Indian subcontinent. Some progress was made in western and southern Africa, but in 1966 the disease was still endemic in 27 of the 47 countries of Africa.

The period 1967–1978

As outlined in Chapter 9, by 1967 it was clear that—the Twelfth World Health Assembly resolution notwithstanding—the global eradication of smallpox could not be achieved without greater financial, administrative and scientific support. In that year the Intensified Smallpox Eradication Programme was instituted, supported by funds from the WHO regular budget, and a Smallpox Eradication unit was established at WHO Headquarters in Geneva. At the same time, the WHO regional offices responsible for countries in which endemic smallpox was present assumed an active role in organizing and coordinating country programmes. The rapid fall in the number of countries with endemic smallpox over the period 1967–1978 is illustrated in Fig. 4.1 and described at greater length in Chapter 10.

By the time that the Intensified Programme was launched, smallpox had been eradicated in South America, except for Brazil, in which the last case in the Americas occurred in 1971. Results were achieved rapidly in the countries of western and central Africa in a campaign which began in 1967. Steady progress occurred in eastern, southeastern and southern Africa. The biggest challenge confronting the Intensified Smallpox Eradication Programme was the eradication of variola major from the Indian subcontinent, a relatively slow process, which was, however, achieved by 1975. By 1976 the only remaining endemic country was Ethiopia, in

which variola minor persisted and spread to Somalia, eventually to be eradicated from the Horn of Africa, and the world, by the end of 1977.

Smallpox Incidence and Incidence Rates

General considerations

The countries and territories listed beneath Fig. 4.1 vary enormously in size and population, from China and India on the one hand, each with populations of several hundred millions, to Bahrain and Swaziland, with populations of a few hundred thousand, on the other.

The numbers of cases of smallpox reported annually to the international health authorities by the governments of different countries varied greatly in accuracy. Those obtained from non-endemic countries with well-established health services, reporting small outbreaks due to importations, were probably the most accurate, although even here distortions sometimes occurred, owing to the suppression of reports (see Chapter 23). The reported numbers of cases in endemic countries for the earlier years of the period under review—often countries with grossly inadequate reporting systems—greatly understated the true incidence of the disease. Even in countries in which smallpox was an important public health problem and there were reasonable health services, reporting was incomplete before and even after national eradication campaigns had been launched (see below). However, the incidence of reported cases (Fig. 4.2) provides some indication of the true incidence of smallpox in the countries in which it was endemic in 1967. At the start of the Intensified Smallpox Eradication Programme, the reported incidence amounted to perhaps 1–2% of the true figure.

During the Intensified Programme several efforts were made to determine what proportion of cases was actually reported in countries with endemic smallpox. Two kinds of assessment were made. The first contrasted the reported figures with the incidence as estimated by pockmark surveys carried out in selected age groups; the second was based on a comparison, in India and Ethiopia, of the reported incidence before and after efficient surveillance and case-reporting systems were established, during the late stages of the eradication campaigns in each country.

Assessment by facial pockmark surveys

First employed by Dr Jacobus Keja in Nepal and then in Indonesia (see Chapter 13), this method was later used by Foster (WHO/SE/72.34) and Hughes et al. (1980) for assessing the efficiency of reporting in western Africa and Bangladesh respectively. The method involved the examination of persons in appropriate age groups for facial pockmarks (Table 4.1). For survey purposes a

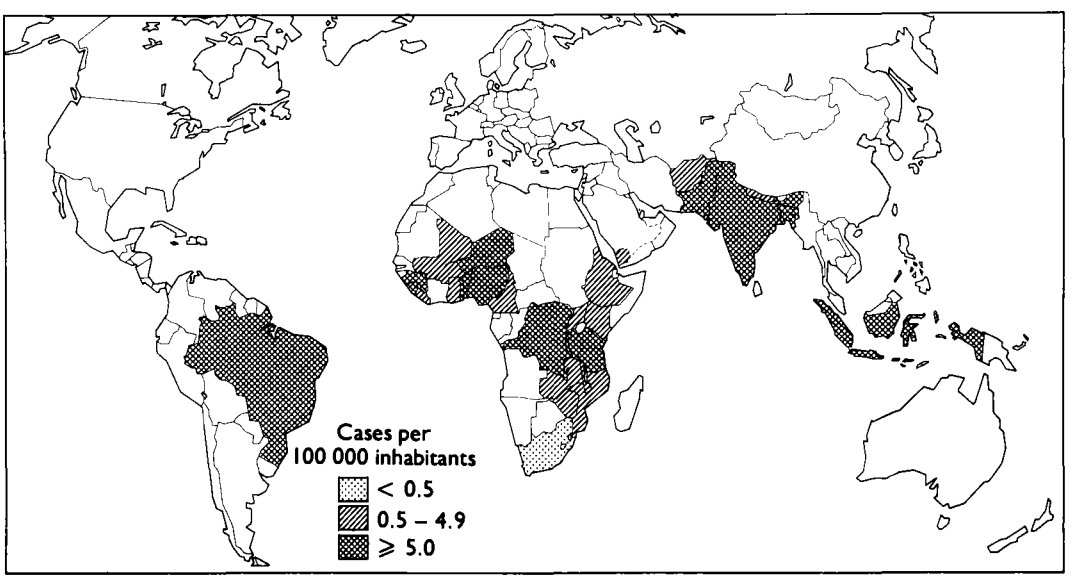


Fig. 4.2. Incidence of reported cases in the 31 countries and territories in which smallpox was endemic in 1967.

Table 4.1. Efficiency of reporting of smallpox in Kano (an urban area in Nigeria), as estimated from facial pockmark surveys in the age group 0–14 years[a]

(1) *Estimated population in the age group 0–14 years*
Total population—500 000, of which 223 000 (44.6%) were 0–14 years old.

(2) *Estimation of total number of cases of smallpox in the age group 0–14 years*
Observed frequency of smallpox pockmarks in a sample survey of the age group 0–14 years—3.7%.
Estimated number of children aged 0–14 years with facial pockmarks—3.7/100 × 223 000 = 8250.
Proportion of children aged 0–14 years who retained pockmarks for at least 1–4 years—55%.
Estimated number of children aged 0–14 years who had smallpox and survived—$\frac{8250}{55/100}$ = 15 000.
Smallpox case-fatality rate in children aged 0–14 years—13%.
Estimated total number of cases of smallpox in the age group 0–14 years—$\frac{15\,000}{87/100}$ = 17 250.

(3) *Estimation of total number of cases of smallpox during the last 15 years*
Proportion of smallpox cases which normally occur in the age group 0–14 years—50%.
Estimated total number of smallpox cases during the last 15 years—$\frac{17\,250}{50/100}$ = 34 500.

(4) *Calculation of the efficiency of reporting smallpox*
Reported number of smallpox cases during the last 15 years—2805.
Reporting efficiency—$\frac{2\,805}{34\,500}$ = 8.1%.

[a] Based on Foster (WHO/SE/72.34).

positive case was defined as one which had at least 5 characteristic round, depressed facial scars, a millimetre or more in diameter. By correcting for the observed rate of smallpox mortality in a selected age group, for mortality due to other causes and for the disappearance of facial scars over time (which varied according to the age at which the person acquired smallpox and was determined for each age group and area) it was possible to estimate the incidence rates of smallpox within the sampled population. The smallpox incidence in the entire population could be estimated by correcting for the age distribution of cases, and this figure could then be compared with the number of officially reported cases.

Using this procedure, Foster calculated that the efficiency of reporting was 1.3% in rural areas of Nigeria and 8.1% in Kano, an urban centre. Hughes et al. (1980), using a similar procedure, found that as late as 1972 reporting efficiency in Bangladesh was only about 12%, but rose in the succeeding years, when active searches for unreported cases were intensified, to over 80% (see Chapter 16, Fig. 16.9). The health services in Bangladesh and Nigeria were more extensive and better developed than those in most endemic countries at that time, so that these estimates reflect better-than-average situations.

Changes in the numbers of reported cases after improved surveillance

The highest numbers of cases for many years were often reported during the periods just before country-wide elimination was achieved, since by this time good surveillance systems were in operation. For example, the highest figure for India since the 1950s was 188 003 in 1974, the year before the attainment of eradication. The results of active searches in India in 1973 (Fig. 4.3), described in detail in Chapter 15, suggested that at that time the reporting efficiencies in the highly endemic states of Madhya Pradesh and Uttar Pradesh were less than 1% and 5% respectively—and this a decade after the launching of the Indian national smallpox eradication programme and 6 years after the initiation of the Intensified Smallpox Eradication Programme. Likewise, with the development of

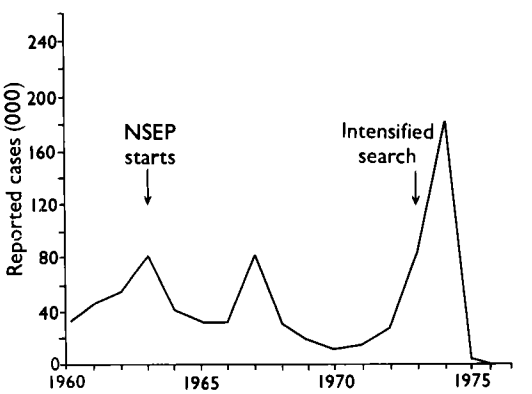


Fig. 4.3. Evidence of the underreporting of variola major. Increase in the number of reported cases in India following the introduction of active searches in the highly endemic states in 1973 (see also Chapter 15, Fig. 15.15). NSEP = National Smallpox Eradication Programme of India.

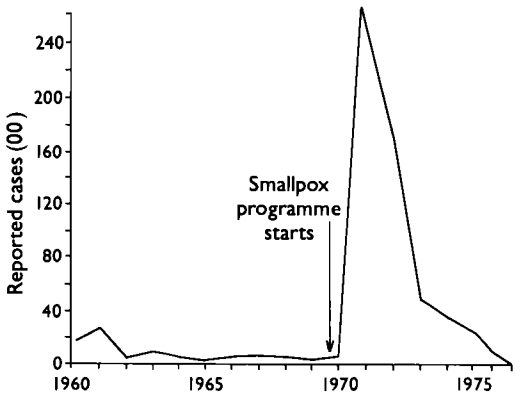


Fig. 4.4. Evidence of the underreporting of variola minor. Increase in the number of reported cases in Ethiopia following the initiation of intensified surveillance in 1971.

better surveillance in Ethiopia in 1971 (see Chapter 21), there was a dramatic increase in the number of reported cases, 722 being notified in 1970 and 26 329 in 1971 (Fig. 4.4).

For China, the most populous country in the world, with endemic variola major for centuries and poor vaccination coverage prior to 1950, the cases reported to the international health authorities were in the thousands only, the highest figure (68 101) being reported in 1951, just after the national eradication campaign had been launched.

The overall picture

It is clear that the reporting of cases of smallpox was the most efficient in countries in which the health services were well developed, which was usually where the disease was least common. It was very inefficient elsewhere. Since the countries in which reporting was good must have provided only a small proportion of the total number of cases in the world, it is not unreasonable to regard the official figures reported to WHO as representing only 1–2% of the true incidence—probably nearer 1% for the years before the initiation of the global eradication programme. In the early 1950s, 150 years after the introduction of vaccination, there were probably some 50 million cases of smallpox in the world each year, a figure which had fallen to perhaps 10–15 million by 1967, when the disease had already been eliminated in 125 of the 156 countries and areas listed in the legend of Fig. 4.1.

The Effect of Vaccination on the Incidence of Smallpox

As has been described in Chapter 1, an attack of smallpox in persons who had been vaccinated was usually less severe than in the unvaccinated. Much more important, from the point of view of the ultimate eradication of smallpox, was the fact that vaccination within the previous 5 years usually completely prevented disease. Some vaccinated persons experienced subclinical infections, as judged by their serological responses (Heiner et al., 1971a). These subjects did not transmit the disease to others, although the subclinical infection substantially increased their level of immunity. Even if their immunity had not been boosted by subclinical infection or revaccination, many vaccinated individuals were protected against clinical smallpox for a much longer period than 5 years. However, no data exist which allow an accurate assessment to be made of the proportion of those at risk who were protected against smallpox at various intervals after vaccination. Such data as are available suggest that vaccination in infancy protected most of those under 10 years of age and at least half of those aged 10–20 years from overt disease.

Case-Fatality Rates in Smallpox

Data from the Indian subcontinent show that Asian variola major had always been a disease with a high case-fatality rate, of the order of 20% or more in unvaccinated persons. Higher case-fatality rates were observed in urban hospitals than in the population as a whole, as documented in Bangladesh (Koplan et al., 1978; see Chapter 1), and in cities than in rural areas (see Table 4.6). Historical documents suggest that high case-fatality rates had prevailed everywhere in the world for many centuries. Indeed, epidemics in previously unexposed, subsistence-farming populations appeared often to have produced much higher mortalities than those seen in Asia, owing to the social disruption and consequent starvation that they caused.

From about the end of the 19th century another variety of smallpox, variola minor, was recognized, which although it produced similar skin lesions had a case-fatality rate of only about 1% (see Chapter 1). Subsequently, observations made in Africa during the Inten-

sified Smallpox Eradication Programme suggested that smallpox of intermediate severity, with case-fatality rates of 5–15%, was endemic in many parts of that continent.

In addition to differences in the virulence of the virus, several other important variables can be identified that played a role in the observed variations in case-fatality rates: the age distribution of cases, the effects of previous vaccination, nutritional status, and the influence of reporting accuracy, since severe (hospitalized) cases and deaths were more likely to be reported than milder cases. Pregnant women were especially susceptible and showed higher case-fatality rates for both variola major and variola minor than did men and non-pregnant women of the corresponding age groups (see Chapter 1). Further, there were interactions between age and vaccination status, since in persons receiving only primary vaccination, susceptibility increased with the interval since vaccination and thus with age. Relevant data from India and from western and central Africa are set out in Tables 4.2 and 4.3.

Foege et al. (1975) noted that the age distribution of cases in western and central Africa in 1968 followed closely the age distribution of the population, reflecting the predominant occurrence of cases in isolated and poorly vaccinated rural areas. In India, on the other hand, with its much denser and more mobile population, smallpox was predominantly a disease of children (over 70% of cases in individuals under the age of 15 years: Table 4.2); the situation was similar in Bangladesh, Burma, Indonesia and Pakistan. Since the immunity produced by vaccination in childhood steadily waned, the majority of cases in vaccinated subjects occurred in older age groups (54.3% in persons over 14 years of age: Table 4.3), whereas in unvaccinated subjects 82.3% of cases occurred in children less than 15 years old. The age-related trends in case-fatality rates were similar in India and Africa, the rates being highest in the very young and in older persons. Children and adolescents (10–19 years of age) had lower case-fatality rates than any other age group, a feature which was accentuated when only

Table 4.2 Age distribution and case-fatality rates of smallpox in India and in western and central Africa[a]

India, 1974–1975[b]				Western and central Africa, 1968[c]			
Age group (years)	Cases		Case-fatality rate (%)	Age group (years)	Cases		Case-fatality rate (%)
	Number	%			Number	%	
<1	1 373	5.8	43.5	<1	102	4.8	29.4
1–4	5 867	24.9	24.5	1–4	417	19.6	11.5
5–14	9 501	40.4	11.4	5–14	494	23.2	7.7
15–39	5 698	24.4	9.0	15–44	1 009	47.5	15.2
40–49	695	2.9	20.1	⩾45	103	4.8	32.0
⩾50	412	1.7	37.4				
Total	23 546	100	17.4	Total	2 125	100	14.2

[a] Includes both vaccinated and unvaccinated subjects.
[b] Based on Basu et al. (1979).
[c] Based on Foege et al. (1975).

Table 4.3 Age distribution and case-fatality rates of smallpox in vaccinated and unvaccinated subjects in 6 states of India, 1974–1975[a]

Age group (years)	Vaccinated			Unvaccinated		
	Cases		Case-fatality rate (%)	Cases		Case-fatality rate (%)
	Number	%		Number	%	
0–4	114	13.3	10.5[b]	725	36.8	45.7
5–14	277	32.4	5.1	897	45.5	12.4
15–39	348	40.7	4.9	265	13.4	20.7
⩾40	116	13.6	8.6	84	4.3	29.8
Total	855	100	6.2	1 971	100	26.5

[a] Based on Basu et al. (1979).
[b] Thought to be cases vaccinated during the incubation period.

unvaccinated subjects were considered. However the data are analysed, the case-fatality rates were higher in India than in western and central Africa. Nevertheless, the age distribution of cases clearly influences the overall case-fatality rate for a particular geographical region, and critical comparisons of geographical variability in case-fatality rates would have to assess separately the figures for vaccinated and unvaccinated subjects and consider the age distribution of cases of smallpox. Unfortunately, there are very few large series of cases, from different geographical areas, that give such details; the analyses that follow are the best available.

Shafa (WHO/SE/72.35) analysed data from 11 areas for which he considered that reasonably reliable information was available, making adjustments for age-specific case-fatality rates by adjusting the data to a standard age distribution. The case-fatality rates for 9 areas in which variola major was endemic are shown in Table 4.4. They were always higher among infants and children aged 0–4 years than among individuals in older age groups.

Table 4.4 Case-fatality rates of variola major in different geographical areas for the total population and the age group 0–4 years[a,b]

Country or area	Age group	
	0–4 years (%)	All ages (%)
Bangladesh[c]	47	36
	26.8	18.5
India (Tamil Nadu)	43	26
Burma	23	17
Afghanistan	19	16
India (Punjab)	18	15
Indonesia (Jakarta)	18	13
Indonesia (West Java)	11	8
West Africa	14	13
Togo	10	8

[a] Based on Shafa (WHO/SE/72.35).
[b] Includes both vaccinated and unvaccinated subjects.
[c] More recent data (Joarder et al., 1980) suggest that the lower figures (26.8% and 18.5%) represent more accurately the true situation in Bangladesh.

The effect of age on mortality was even more pronounced in variola minor, in both Brazil and Africa, in which the case-fatality rate was much higher for infants (less than 12 months old) than for any other age group (Table 4.5). Indeed, in Brazil, in which data were available for infants less than 3 months old, the case-fatality rate in this group was 16.7%.

Geographical variations in crude case-fatality rates, based on data obtained during the Intensified Smallpox Eradication Programme, are shown in Table 4.6. There are striking differences between the case-fatality rates in large cities and those in the surrounding countryside (see Indonesia and Pakistan). This may have been due partly to the better recording of deaths and partly to the fact that data for the cities were derived in large measure from hospitals, in which more severe and neglected cases were more common (Koplan et al., 1978).

There are also large differences between the case-fatality rates in countries in which variola minor was endemic and those in other countries. Variola minor itself varied in severity, the form present in Botswana in 1972 (which may have been characteristic of "amaas" of southern Africa) being particularly mild. Smallpox other than variola minor was associated with case-fatality rates that varied in different geographical areas from slightly more than 5% to over 20%. There were suggestions in the mid-1960s that strains of virus from eastern African countries (Uganda and the United Republic of Tanzania) could be differentiated from Asian strains of variola major virus by laboratory tests, and it was suggested that the disease there should be called "variola intermedius". However, the "characteristic" laboratory reactions of "variola intermedius" were not invariable for strains from that area, and case-fatality rates only slightly higher than those found in eastern Africa were also recorded for Indone-

Table 4.5 Age-specific case-fatality rates in variola minor (data collected during the Intensified Smallpox Eradication Programme)

Age group (years)	Brazil (1968–1969)		Botswana (1971–1972)		Ethiopia (1971–1976)		Somalia (1977)	
	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)
<1	387	5.2	17	5.9	1 322	7.9	47	12.8
1–4	2 322	0.7	195	0.5	13 501	1.8	506	0.6
5–14	4 389	0.2	505	0.0	26 087	0.6	1 061	0.1
⩾15	2 683	1.0	365	0.0	14 081	2.5	1 408	0.1
Total	9 781	0.7	1 082	0.2	54 991	1.5	3 022	0.4

Table 4.6 Case-fatality rates of smallpox in different geographical areas (data from country reports submitted prior to certification of eradication of smallpox)[a]

Country or area[b]	Period	Number of cases[b]	Number of deaths[b]	Case-fatality rate (%)[b]
Variola major: Asia				
Bangladesh	1975	1 127	209	18.5
India	1974–1975	23 546	4 103	17.4
Afghanistan[c]	1969–1973	1 898	306	16.1
Pakistan (Sind Province)	1972–1974	17 491	1 646	9.4
Pakistan (Karachi)	1973–1974	*587*	*140*	*23.9*
Indonesia (West Java)	1969	11 966	930	7.8
Indonesia (Jakarta)	1968	*405*	*82*	*20.2*
Variola major: Africa				
West Africa	1967–1969	5 628	540	9.6
United Republic of Tanzania	1967	1 629	150	9.2
Uganda	1966–1970	1 045	54	5.2
Variola minor: South America				
Brazil	1966–1969	9 854	75	0.8
Variola minor: Africa				
Ethiopia	1971–1976	54 991	838	1.5
Sudan	1970–1972	3 019	35	1.2
Somalia	1977	3 022	12	0.4
Botswana	1972	1 059	2	0.2

[a] Includes both vaccinated and unvaccinated subjects.
[b] Data in italics refer to urban areas.
[c] Excluding cases due to variolation.

sia and western Africa. As has been suggested in Chapters 1 and 2, it is possible to differentiate between variola major and variola minor by considering clinical features and epidemiology and, for some strains, the laboratory characteristics of the virus, but it is not worth while to attempt to designate "variola intermedius" or to differentiate further between strains of variola major. The data shown in Tables 4.4 and 4.6 illustrate the fact that both variola major and variola minor were caused by strains of variola virus which differed in their virulence for man, and that some strains were predominant in some geographical areas and other strains in other areas.

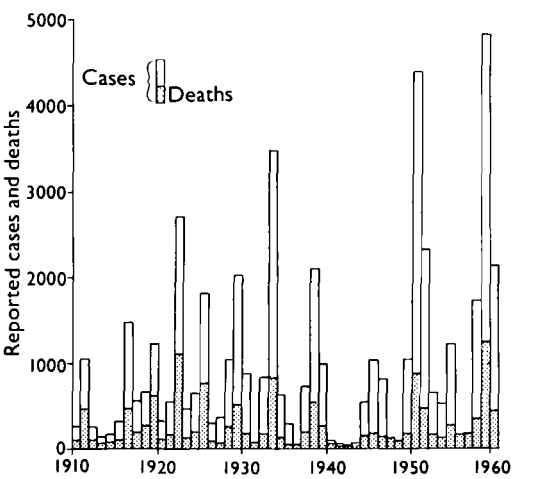
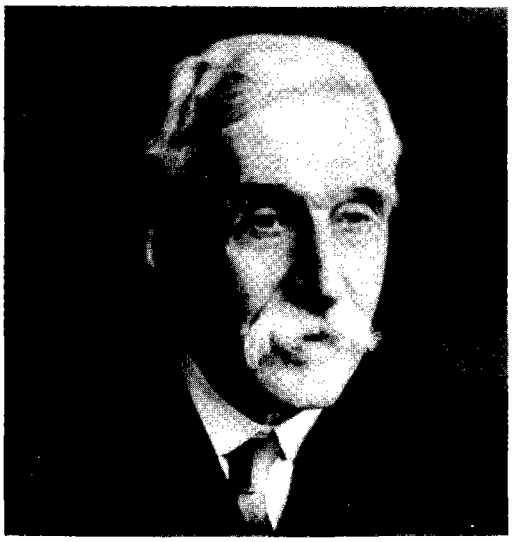


Fig. 4.5. Cyclic fluctuation in the incidence of smallpox in the city of Madras, India: annual numbers of cases and deaths between 1910 and 1960. (Based on Rao et al., 1960.) A similar cyclic fluctuation, with epidemics every 5–10 years, occurred in India as a whole and most other countries in which smallpox was endemic. (See Chapter 5, Fig. 5.2 and Chapter 6, Fig. 6.1.)

Smallpox Epidemics in Endemic Countries

It was widely observed that in countries in which smallpox was endemic there were periodic episodes of much higher incidence: "epidemic years". The history of smallpox before the 20th century is replete with accounts of great epidemics occurring against a background of endemic smallpox (see Chapter 5). An unusually complete series of data on smallpox incidence in the Åland Islands, Finland, extending from 1751 to 1890, showed a 7-year cycle of epidemics in the 18th century, which changed to an 8-year cycle, with a higher proportion of cases among adults, after vaccination became available in 1805 (Mielke et al., 1984). The phenomenon of epidemic years is well illustrated by more recent data from India. In the city of Madras, for example, Rao et al. (1960) found that there was a regular peaking of incidence every 4–6 years, epidemics extending over a period of 3 years, the middle year being the peak year (Fig. 4.5). This periodic

behaviour is a consequence of the size of the pool of susceptible individuals in the population and the rate of their removal by infection or vaccination. The phenomenon occurs in all common infectious diseases in which infection is followed by long-lasting immunity; it has been exhaustively analysed in measles (Bartlett, 1957) and is critically dependent on the rate of addition of new susceptible individuals to the population. A factor which lengthened the interval between epidemics of smallpox was that the occurrence of an epidemic led to greatly increased vaccination rates, because of increased activity by public health officials and increased demand for vaccination by the general public.



BRITISH MEDICAL JOURNAL

Plate 4.1. Sir Leonard Rogers (1868–1962). Distinguished British physician who worked in India for many years and was Professor of Pathology at Calcutta Medical College from 1900 to 1920. Besides making important contributions to many aspects of tropical medicine, he devoted particular attention to a study of seasonal effects on the incidence of smallpox.

Seasonal Variations in Incidence

Most infectious diseases show characteristic seasonal variations in incidence. In temperate climates, where there are pronounced seasonal differences in temperature, arbovirus infections usually occur in summer, enteroviral infections in summer and autumn, influenza and other infections of the respiratory tract mainly in winter, and measles, chickenpox and mumps mainly in winter and spring. Smallpox showed a seasonal incidence similar to that of measles and chickenpox; it was mainly a disease of winter and spring. For several of these diseases the seasonal variations are blurred in tropical climates, where the seasonal changes in temperature and humidity are often much less marked. However, smallpox showed a response to seasonal effects in many tropical regions; in Bangladesh the seasonality was so pronounced that smallpox was called, in Bengali, *guti bashunto*, the spring rash (Joarder et al., 1980).

The most detailed studies of the seasonality of smallpox were those reported by Sir Leonard Rogers, using mortality figures from British India (Rogers, 1926, 1948) and data on reported cases from England and Wales (Rogers, 1928) and certain parts of Africa (Rogers, 1948). Although many of his data were poor, comprising deaths rather than cases, both being grossly underreported, Rogers' observations of the seasonal incidence of smallpox have been confirmed by the more accurate data on case incidence obtained during the global smallpox eradication campaign.

Fig. 4.6 shows the monthly incidence of reported cases of smallpox in representative countries in the Northern and Southern Hemispheres and in the humid tropics. In Bangladesh the maximum reported incidence was in the period from January to the end of April; in Brazil, in the Southern Hemisphere, the maximum reported incidence occurred in the spring, from August to the end of October, with well-marked minima in September to the end of December and in February to the end of May. The maximum incidence in Indonesia occurred in January but thereafter the monthly incidence showed little variation. Bearing in mind the delays in reporting (see box), the maximum transmission rate probably occurred in December in Bangladesh and in June in Brazil—i.e., during the early winter. Old records for European countries (Low, 1918; Mielke et al., 1984) show that smallpox there was also mainly a winter disease.

Within India, Rogers (1928) observed that the seasonal fluctuation was the least marked and the incidence the most uniform from year to year in the State of Tamil Nadu (formerly Madras), in South India, which experienced little seasonal variation in temperature and humidity; these observations were confirmed for the city of Madras by Rao et al. (1960). Other countries in the tropics, which also

Interpreting Seasonal Fluctuations in Incidence

The analysis of seasonal factors in smallpox is based on curves of monthly incidence of reported cases or deaths, as illustrated in Fig. 4.6. The extent of reporting may affect such curves in a dramatic way, as illustrated during the "search weeks" in India (see Fig. 4.3) and after the initiation of the Intensified Smallpox Eradication Programme in Ethiopia (see Fig. 4.4). However, if it is assumed that the extent of reporting was reasonably uniform throughout each year, over a period of several years, clearly there were large differences in the incidence of reported cases at different times of the year. It is reasonable to ascribe such seasonal effects on the incidence of smallpox to factors, biological and/or social, that affect transmission. It is necessary, however, to determine the average time-lag between transmission and the recording of cases in the statistics.

As the WHO system reported smallpox cases by date of detection rather than date of occurrence, the observed pattern of disease represents a delay from actual transmission by periods of up to 2 months. Factors contributing to this time-lag include the incubation period, delays in case detection, and delays in reporting. As many outbreaks were not detected until the 2nd, 3rd or 4th generation of transmission, all cases detected on the initial investigation would have been recorded in that week—the week of detection.

experience less pronounced seasonal differences in humidity and rainfall—e.g., Indonesia and Zaire—likewise exhibited much less pronounced seasonal differences in the incidence of smallpox (Fig. 4.6). But where there were clearly distinguishable hot and cool seasons, with high and low absolute humidities respectively, the incidence was always much higher in the cool, dry season. Data on importations of smallpox into Europe during the period 1961–1973 support the findings in the endemic countries (see Chapter 23). There were 3 times as many importations during the months December–May as in the following 6 months, which is explained by the higher incidence of smallpox in the main "exporting" countries in the Indian subcontinent at that time. Further, each case imported during December–May gave rise to an average of 24 subsequent cases (median 4.5), whereas each case imported in the period June–November gave rise to an average of 1.6 cases (median 1.0) (Henderson, 1974).

A variety of factors can be envisaged that could have contributed to the seasonal incidence of smallpox: viability of the virus in an infectious state, social factors and possibly the physiological susceptibility of the host.

Viability of the virus

Experiments described in Chapter 2 show that the viability of variola and vaccinia viruses was less prolonged at high than at low temperatures and at high than at low humidities. This was true with virus in scabs (Huq, 1976), on raw cotton (MacCallum & McDonald, 1957) and in an aerosol (Harper, 1961). The correlation of low temperature and humidity with a higher incidence of smallpox was observed in many different countries—e.g., India (Rogers, 1928; Basu et al., 1979), Bangladesh (Joarder et al., 1980), western and central Africa (Foege et al., 1975), Brazil (Morris et al., 1971), the USSR (Low, 1918) and Nyasaland (Malawi) (Rogers, 1948)—suggesting that the effect of environmental conditions on the viability of variola virus was probably an important factor in determining the seasonal incidence of smallpox. In some situations, this physical effect was supplemented and amplified by social events that increased opportunities for transmission during the dry season (see below).

Changes in susceptibility of the host

Another possibility, often invoked to explain the winter incidence of influenza, is that there may be seasonal changes in individual susceptibility, due perhaps to changes in mucous membrane permeability or to alterations in resistance associated with dietary changes. There is no convincing evidence that such factors were important in smallpox.

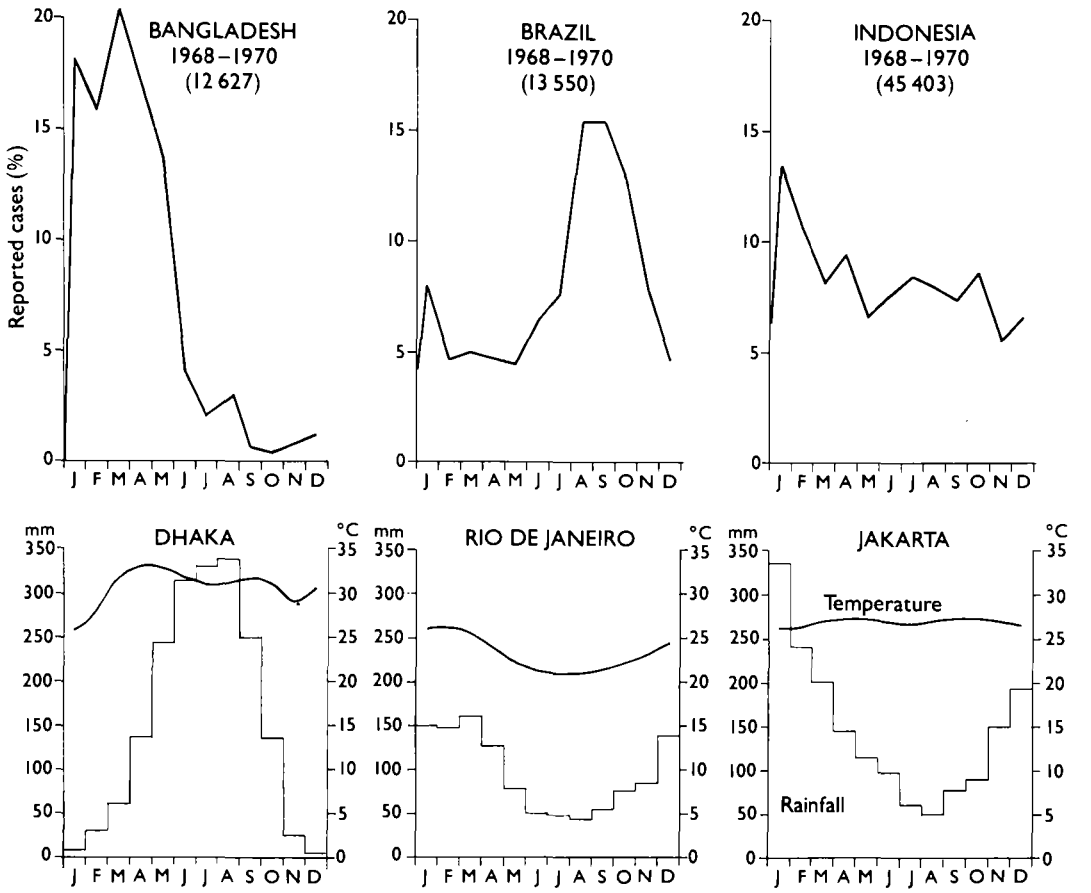


Fig. 4.6. The monthly incidence of reported cases of smallpox in countries situated in the Northern Hemisphere (Bangladesh), mainly in the Southern Hemisphere (Brazil) and in the tropics (Indonesia), as observed during the Intensified Smallpox Eradication Programme. Figures in brackets indicate numbers of cases. The lower graphs show the average monthly rainfall (mm) and maximum temperatures (°C) for Dhaka (Bangladesh), Rio de Janeiro (Brazil) and Jakarta (Indonesia). There was a pronounced seasonal incidence in countries with well-marked wet and dry seasons, but this feature was not as obvious in localities in tropical countries with sustained high humidities, such as Java (Indonesia), or Madras (India).

Social factors

Social factors of various kinds amplified the effects of temperature and humidity on the viability of variola virus. In western and central Africa, Foege et al. (1975) observed that the seasonal variation—low in the rainy season (September, October) and reaching a peak in the late dry season (March and April)—was less marked in the humid coastal areas and more pronounced in the dry savanna or Sahel. They suggested that in part, at least, this was due to the effects of climate on social activities. Planting during the rainy seasons resulted in the dispersion of the population in the fields, whereas in the dry seasons there were festivals and many more social contacts in the agricultural areas and the long-distance movement of nomads in the sub-Saharan areas. These activities facilitated the dissemination of the virus.

In Tamil Nadu (Madras), where the seasonal variation in the incidence of smallpox was not pronounced, Rao (1972) suggested that such variation as was seen was more "man-made" than natural. For example, two population groups belonging to two different communities and professions (Harijans and Gounders) lived very closely together in the same villages, but an outbreak of smallpox was limited to the Gounders (WHO/SE/68.6, Rao). Also, there was greater crowding and, because of the seasonal fluctuation in births, greater numbers of unvaccinated infants in the winter and rainy months, which Rao believed was enough to explain the limited seasonal fluctuation in incidence seen in

Forecasting Epidemic Years

The prime motive for Roger's studies was to forecast years when smallpox might cause major epidemics. Bearing in mind that seasonal conditions alone were not sufficient to produce epidemics, which could not occur if the pool of susceptible individuals was substantially reduced by recent epidemic prevalence, Rogers (1928, 1948) found a remarkably good association between failure of the monsoon rains and consequently low absolute humidity during the rainy season and epidemic prevalence in the following dry season. Transmission always continued through the rainy season, but there were more chains of transmission when the monsoon rains were poor than with a good monsoon and sustained high humidity. Thus, if the monsoon failed, the population was already extensively seeded with virus when the cooler dry season began, and the stage was set for a major epidemic. Using this criterion, Rogers (1948) found that the great majority of major epidemics could be correctly predicted; most exceptions were satisfactorily explained by the arbitrary nature of his criterion of "epidemic levels". Murthy et al. (1958) noted that in Uttar Pradesh more severe epidemics were likely if an unduly high incidence of smallpox occurred in the post-monsoon months of October and November.

Another factor, on which Rogers did not comment, was that when the monsoon rains were poor, the harvests were also poorer and hunger was more widespread. The extensive movements of refugees and others in search of food led to increased opportunities for the transmission of smallpox.

Madras city. On the other hand, in Pakistan, Mack et al. (1972b) found that there was no seasonal variation in the incidence of transmission within compounds; almost all susceptible subjects were infected when exposed to a case of smallpox, regardless of season. The interval between successive generations of cases was about 3 days longer in the cool season, a result compatible with longer viral survival but not explained by changes in social activity.

Seasonal variation in incidence in relation to eradication

Whatever its causes, the seasonal variation in the incidence of smallpox was an important factor in the planning of national eradication campaigns. For example, in India before 1973 it had been customary to utilize the end of the monsoons and the beginning of the cool season (September–October), when relatively little transmission occurred and there was no public pressure on health workers to vaccinate, as the leave period for smallpox programme workers. With the intensification of the eradication programme in 1973, rather than merely reacting to the high frequency of disease during the dry season, the policy was changed to concentrate on reducing the foci of infection during the wet season, when cases were the least numerous. In several countries, the efforts of smallpox workers during the rainy season were concentrated in the urban areas, where smallpox foci were the most numerous. When the rural areas became more accessible at the end of the wet season, efforts were made to eliminate persistent foci of infection during the seasonal lull in transmission.

INFECTION AND INFECTIVITY

Routes of Exit and Entry of Virus

The pathogenesis of smallpox, outlined in Chapter 3, is concerned in the main with how variola virions moved between different cells, organs and tissues within the human body and how the body responded. Epidemiology is concerned with the movement of virus particles between human beings—i.e., with the spread of infection in populations.

There are three principal routes of viral infection, corresponding to the three principal surfaces of the body: the respiratory tract, the alimentary tract, and the skin. Minor routes of infection include the urinary and genital tracts and the conjunctiva. Although congenital infection occasionally occurred in

smallpox (see Chapter 1), it was of no epidemiological importance and will not be discussed further in this chapter.

There is no evidence that infection ever occurred via the alimentary tract in smallpox. In experiments in monkeys, A. R. Rao (personal communication, 1981) fed concentrated suspensions of variola virus in food, or introduced concentrated viral suspensions directly into the stomach with a stomach tube. The monkeys were not infected, nor could virus be recovered from their stools. The latter result may have been due to the fact that variola virus probably behaves like vaccinia virus, which is rapidly inactivated in sewage (K. R. Dumbell, personal communication, 1982).

Mechanical transmission by arthropods is important in some poxvirus infections (myxoma virus in rabbits, fowlpox virus in birds). Sarkar et al. (1973c) showed that mosquitos could contaminate their probosces with variola virus by feeding on viraemic mice, and they speculated about the relevance of this to human smallpox. Houseflies could and probably did transport variola virus mechanically, especially in tropical countries, but their importance was probably trivial compared with other sources of infection and in any case there is no evidence that the ingestion of virus-contaminated food would produce smallpox. There is no epidemiological evidence to suggest that arthropods of any kind were involved in the transmission of smallpox.

Natural infection in smallpox usually occurred via the oropharynx or nasopharynx, sometimes via the lower respiratory tract, in special cases (inoculation variola and variolation) via the skin, and possibly, but in any case very rarely, via the conjunctiva. Before describing the processes of infection by these routes it is useful to consider how variola virions were shed from the infected patient and entered the environment and the way in which their mode of exit from the patient may have influenced their infectivity for man.

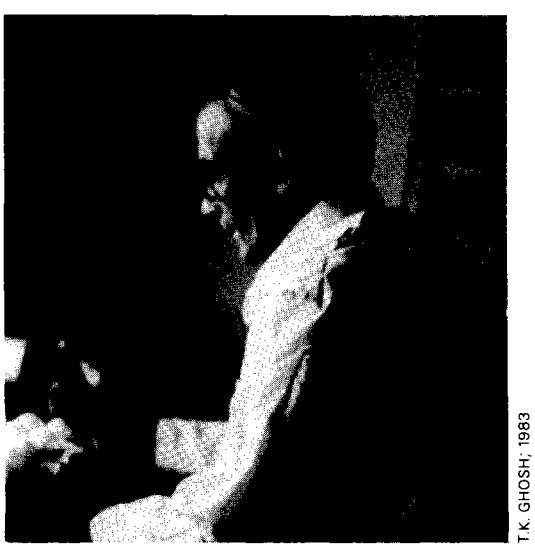
Shedding of Variola Virus

As we have shown in Chapters 1 and 3, after an incubation period of 12–14 days during which there was no evidence of viral shedding, lesions developed in the skin and the mucous membranes of the nose and mouth.

Oral, nasal and pharyngeal secretions

Because there is no tough stratum corneum in the mouth and pharynx, the lesions there ulcerated very soon after their formation (see Chapter 3, Plate 3.7) and released large amounts of virus into the oral and pharyngeal secretions. Several reports are available on the viral content of oropharyngeal secretions in variola major, all carried out with material obtained from cases occurring in the Indian subcontinent (Madras: Downie et al., 1961a; Calcutta: Sarkar et al., 1973a; Bihar: Kitamura et al., 1977b; Karachi: Shelukhina et al., 1973). Table 4.7 sets out the results of the two most extensive studies. The higher proportion of positive results recorded by Sarkar et al. (1973a) probably reflects the different modes of collection of the specimens in the two studies: throat swabs in Sarkar's series (of which the whole extract in 1 ml of fluid was assayed) and 5 ml of mouth washings (of which only 0.2 ml or 0.3 ml was assayed) in Downie's series. Besides the volumetric differences, throat swabs could be expected to detach virus particles from superficial lesions as well as including those free in the saliva. Both groups of investigators recorded positive results throughout the period of rash (3rd–14th days).

The results of titrations carried out by Sarkar et al. (1973a), shown in a condensed



T.K. GHOSH, 1983

Plate 4.2. Jaladhi Kumar Sarkar (b. 1916). Formerly Professor of Virology and Director of the School of Tropical Medicine, Calcutta, India. He carried out many investigations into the virology and epidemiology of smallpox as it occurred in Calcutta.

Table 4.7 Variola virus in the oropharyngeal secretions and urine of cases of variola major

Day of disease (from onset of fever)	Oropharyngeal secretions				Urine			
	Downie et al. (1961a)		Sarkar et al. (1973a)		Downie et al. (1965a)		Sarkar et al. (1973a)	
	Number tested	Number positive	Number tested	Number positive	Number tested	Number positive	Number tested	Number positive
1	1	0	–	–	–	–	–	–
2	4	0	2	2	–	–	–	–
3	8	4	10	10	–	–	5	5
4	20	8	22	22	–	–	9	9
5	39	18	20	20	1	0	16	15
6	49	32	22	22	3	1	14	12
7	51	33	22	21	5	3	10	6
8	39	24	18	14	4	2	9	6
9	34	22	18	11	3	2	8	6
10	10	0	13	7	4	2	5	4
11	15	4	10	6	3	2	5	4
12	12	3	8	4	5	2	3	3
13	12	1	9	4	1	1	4	4
14	5	1	5	4	2	1	–	–
15	3	0	2	0	1	0	3	3
16	1	0	1	0	1	1	1	0
17	2	0	–	–	–	–	2	1
18	4	0	–	–	–	–	1	0
19	–	–	–	–	–	–	2	1
20	–	–	–	–	–	–	1	0

Table 4.8 Variola virus in the oropharyngeal secretions of cases of variola major[a]

Day of disease (from onset of fever)	Results			Number of positive specimens with titre of:[b]					
	Number tested	Positive							
		Number	%	10	10^2	10^3	10^4	10^5	10^6
2	2	2	100	–	–	–	1	1	–
3	10	10	100	–	–	2	1	6	1
4	22	22	100	–	–	7	7	8	–
5	20	20	100	–	–	10	7	3	–
6	22	22	100	1	8	7	6	–	–
7	22	21	95	2	8	9	2	–	–
8	18	14	78	2	7	3	2	–	–
9	18	11	61	1	7	3	–	–	–
10	13	7	54	3	3	1	–	–	–
11	10	6	60	1	4	1	–	–	–
12	8	4	50	1	3	–	–	–	–
13	9	4	44	4	–	–	–	–	–
14	5	4	80	2	2	–	–	–	–
15	2	0	0	–	–	–	–	–	–
16	1	0	0	–	–	–	–	–	–

[a] Based on Sarkar et al. (1973a).
[b] Titres expressed as pock-forming units per ml.

form in Table 4.8, reflect the high viral content of the oropharyngeal secretions during the first week. The viral titres reached their highest level on the 3rd and 4th days of the disease (i.e., just after the appearance of the rash); they were highest and persisted for the longest period in the most severe cases (confluent, which in Sarkar's terminology included confluent ordinary-type and flat-type smallpox). In fatal cases virus was usually still present in the throat swabs at the time of death; in non-fatal cases it was found for as long as the 14th day from the onset of fever in confluent ordinary-type smallpox and until the 7th–9th days in discrete ordinary-type smallpox.

Skin lesions

The titres of virus in vesicular fluid and in scabs were assayed by Mitra et al. (1974) and Kitamura et al. (1977b). On about the 18th day of the disease (15th or 16th day of rash) the skin lesions scabbed and subsequently the scabs separated. Assay of the viral content of such scabs revealed that they contained a large

amount of virus and that the viral titre, as assayed by extracting the scabs in saline, remained at a high level throughout convalescence (Mitra et al., 1974).

Epidemiological observations, described below, abundantly confirmed the higher frequency of infection after face-to-face contact with a patient during the 1st week of rash. Exposure to patients in the late stages of the disease, when large amounts of virus were being released into the environment in the scabs, was much less likely to produce infection in susceptible contacts. The reasons for this difference in frequency of transmission were difficult to study experimentally. Oropharyngeal secretions expelled early and scabs released late in the disease contained virions that were equally infectious by ordinary assay methods, which involved suspending material from swabs in saline, or homogenizing the scabs by grinding, and assaying the suspension or the homogenate on the chorioallantoic membrane or in cultured cells. Perhaps the main reason for the differences observed lay in the physical state of viral particles shed by the patient from the enanthem and in scabs.

Virions released from lesions of the enanthem into the oropharyngeal secretions in the early stages of the rash were expelled by the patient in liquid droplets of various sizes, which might be inhaled by persons in close contact with the patient or transferred directly to the nose or oropharynx by fingers or objects contaminated with infected saliva or nasal secretions (Knight, 1973; Gwaltney & Hendley, 1978). Many of the large droplets would rapidly fall and dry on the bedclothes or the floor, being readily dispersed again in the immediate vicinity of the patient. Virions transferred in these ways would readily come into contact with susceptible cells. In hospitals in non-endemic countries, nurses who made up the beds of patients suffering from undiagnosed smallpox were often infected; others were protected by vaccination but developed "smallpox-handler's lung" due to the inhalation of virus.

In contrast, virions in scabs were enclosed within the inspissated pustular fluid and were present in flakes which contaminated the patient's skin and bed-linen and the dust on the bed and the floor of the room. It is likely that virions in scabs would rarely have come into direct contact with susceptible cells, since inspired particulate matter of this kind is usually swept up in the mucous secretions of the oropharynx and swallowed, or expelled again into the environment. However, such virions could retain infectivity for long periods, as judged by laboratory assay.

In spite of this virological evidence, the policy of isolating patients adopted during the Intensified Smallpox Eradication Programme followed that traditionally taught—i.e., patients were not removed from isolation in hospital or at home until the last scab had separated. As smallpox eradication became imminent in Bangladesh and India, villages were considered to house infective persons for 6 weeks after the onset of the last recognized case. This policy of isolation and surveillance provided a safety margin, since sometimes infants or other persons became infected and were hidden from surveillance officers, thus constituting a missed generation of cases.

Several studies have been made of the presence of variola virions in the air and on fabrics and skin in the vicinity of smallpox patients. In evaluating these reports it must be borne in mind that the ventilation rate of adult human beings is about 10 litres per minute, so that the air-sampling device would have had to test a volume of about 600 litres in order to be comparable to an hour's exposure of a susceptible adult person. Unfortunately, rather inefficient methods of air sampling were used in the earlier studies. Using small glass funnels tightly packed with dry cotton wool through which air was drawn, Meiklejohn et al. (1961) obtained only one positive result in the wards of the Infectious Diseases Hospital in Madras. Subsequently, Downie et al. (1965a) analysed the immediate environment of smallpox cases in the same hospital using three devices: (1) a fluid impinger which excluded particles of 18 μm or more in diameter, held near the patient's mouth for periods of 10–15 minutes that included talking and coughing; (2) settling-plates placed below air samplers; and (3) swabbing of skin and bedclothes. The results, summarized in Table 4.9, show that virus was rarely found in the small airborne droplets or droplet nuclei, although the saliva and the patient's pillow covering were heavily contaminated.

Westwood et al. (1966) studied the problem experimentally by assaying the air in the environment of rabbits infected with rabbitpox virus with sampling devices similar to those used by Downie et al. They recorded some positive results, but sampling was often negative at times when the rabbits were clearly infectious. Thomas (1970a) repeated

Table 4.9 Recovery of variola virus from the vicinity of patients with variola major[a]

Source of sample	Number of patients	Number of specimens	Positive	
			Number	%
Impinger, near mouth	29	47	5	11
Settling-plates, near mouth	13	30	12	40
Circumoral swab	32	58	42	72
Pillow swab	40	67	41	61
Impinger, near bedclothes	9	15	5	33
Settling-plates, near bedclothes	13	20	11	55
Bedclothes swab	11	16	15	94
Back swab	35	66	25	38
Urine	16	34	17	50

[a] Based on Downie et al. (1965a).

these experiments using a slit sampler (Andersen, 1958; Thomas, 1970b) that sampled a larger volume of air and did not discriminate against the collection of larger particles from a heterogeneous aerosol, as did the fluid impinger and electrostatic precipitator. As might be expected, he obtained more frequent positive results and recorded higher titres of virus than the earlier workers. Subsequently Thomas (1974) compared impingers and sedimentation plates of the type used by Downie et al. (1965a) and a slit sampler like that used in his rabbitpox experiments in the sampling of the air in a hospital in England. His subjects were a few patients in a ward who were recovering from variola minor, a situation in which much less environmental contamination with virions would have been expected than in the Infectious Diseases Hospital in Madras. The impingers gave uniformly negative results, but virus was detected with the slit sampler in air near the bed on several occasions, associated with the physical activity of patients with active lesions. Sedimentation plates exposed for some hours about 20 feet from the occupied beds also yielded virus on several occasions.

An important feature of smallpox in relation to long-distance airborne spread was that patients with uncomplicated smallpox usually had no respiratory signs or symptoms; coughing and sneezing, which generate large clouds of infective aerosols in the acute stages of measles, for example, rarely occurred. When they did, as in the index cases in the Monschau and Meschede Hospital outbreaks (Anders & Posch, 1962; Wehrle et al., 1970; see later in this chapter) airborne infection within buildings could occur.

Urine

The urine was examined for variola virus by Downie et al. (1965a) and Sarkar et al. (1973a), with the results shown in Table 4.7. Sarkar et al. recorded the titre of virus in cases which at some time had viruria (21 out of the 39 cases examined). The titre was highest early in the disease (days 5 and 6); it was higher and more persistent in severe cases (haemorrhagic smallpox and those with a confluent rash) than in milder cases. No virus was detected in the urine of some cases whose severity was comparable to that of cases with viruria. Shelukhina et al. (1973) reported that a few patients excreted small amounts of virus in the urine during convalescence (23rd and 25th days of the disease). However, both because of the small quantities of virus involved and because of the mode of excretion, it is unlikely that urine was an important source of infectious virus.

Routes of Infection

Variola virus usually gained entrance to the body via the oropharynx or respiratory tract, and occasionally through the skin, usually by direct inoculation, as practised in variolation.

Entry via the respiratory tract

Particles enter the nose or mouth, other than in food or drink, either by inhalation, or by implantation on the oral or nasal mucous membrane by contact with contaminated fingers. A great deal of experimental work has been carried out on the fate of inhaled bacteria and viruses (reviewed in *Bacteriological reviews*, 1966; Gregory & Monteith, 1967; Hers & Winkler, 1973). Some relevant aspects can be summarized as follows. The ventilation rate of an adult human being is about 10 litres per minute. Most particles larger than 15 μm in diameter and about half those 6 μm in diameter are retained in the nose. Large particles deposited in the nasal cavity or oropharynx are usually carried to the back of the throat and swallowed. Particles deposited in the lower respiratory tract may be trapped in the mucus and borne upwards from the lungs to the back of the throat by ciliary action. However, smaller particles may reach the lungs, those 1 μm or less in diameter reaching the alveoli, where they may cause

infection of cells of the alveolar walls, or alveolar macrophages.

Size and physical state are also important in determining whether expelled particles fall quickly to the ground or remain airborne for a long time. Large particles—particularly scabs—fall quickly to the ground. Smaller liquid particles dry rapidly and float for a long time in the air, thus increasing the chance that they may enter the respiratory tract. The vigorous shaking of heavily contaminated bed-linen may disperse clouds of small particles of infected "dust" in the air (Duguid & Wallace, 1948).

The other critical factor in determining the infectivity of both large- and small-particle aerosols generated by talking, coughing and sneezing is the concentration of virus in the secretions of the nose and mouth. Experiments with bacteria showed that many of the expelled particles were sterile unless the concentration of bacteria in the secretions reached 10^6 per ml or more (Duguid, 1946).

Organizations that some years ago were concerned with research on biological warfare carried out a great deal of work on respiratory infection with viruses, including orthopoxviruses; some investigations of this kind have also been conducted in other laboratories (Noble & Rich, 1969). Relevant publications on the subject deal with two systems: rabbitpox virus in rabbits (Westwood et al., 1966; Lancaster et al., 1966; Thomas, 1970a) and variola virus in monkeys (Hahon & McGavran, 1961; Noble & Rich, 1969). These experiments were described in more detail in Chapter 3; their importance in the present context is the demonstration that susceptible laboratory animals can be readily infected by aerosols of orthopoxvirions. However, neither in smallpox nor in the experimental infection of animals with orthopoxviruses has evidence of a primary lesion been found in either the oropharynx or the lower respiratory tract; it seems likely that infection could occur at any site from the nasal mucosa to the alveoli, but that no "local lesion" developed.

Inoculation through the skin

For the genus *Orthopoxvirus* as a whole, the skin is a relatively common portal of entry, usually through breaches in the surface, which may be minute. It is the usual portal of entry of ectromelia virus in mice (Fenner, 1947b), as well as the common route of infection with cowpox virus in both cows and humans, and was deliberately used for inducing vaccinia infection in man—i.e., vaccination against smallpox. Infection through the skin with variola virus occupied a special position in the history of smallpox. Accidental inoculation with variola virus occurred in certain occupational groups—e.g., among hospital personnel or mortuary attendants dealing with unrecognized smallpox. However, a much more common situation for centuries in India and China, during the 18th century in Europe, and up to recent times in some parts of Asia and Africa (see Chapters 6, 14 and 21), was the practice of variolation, or "inoculation" as it was called before the introduction of vaccination (Miller, 1957). In China a "snuff" of dust containing variola virus was originally used, but in other countries, and in China since the early 19th century, the virus was introduced into the skin.

Inoculation smallpox showed important differences in pathogenesis and symptoms from smallpox acquired by the respiratory route (see Chapters 1, 3 and 6). In the case of the former, there was always a local lesion at the inoculation site; "daughter pustules" often developed in the skin near the inoculation site; the generalized rash appeared two or three days earlier and the course of the disease was usually much less severe than in naturally transmitted smallpox. However, oropharyngeal lesions occurred as part of the generalized disease and these lesions, in particular, constituted sources of infection of contacts.

The Infectious Dose of Variola Virus

During the 1940s and 1950s substantial experimental work was undertaken to determine the number of particles of vaccinia virus needed to infect selected cells or animals by various routes of inoculation. It was found that for a highly susceptible animal or cell system, a single viable virus particle could initiate infection (Parker, 1938), although usually the ratio of particles to "takes" was much more than 1 to 1 (Sharp, 1965). In contrast, in man a relatively high concentration of vaccinia virus was needed to produce consistently successful primary vaccination takes. It was recognized that only a very small proportion of the virus in the inoculum was actually introduced into the epithelium by scarification or multiple puncture vacci-

nation. However, in assays by scarification, the 50% infectious dose was found to be 3×10^5 pock-forming units per ml for the Lister strain (Cockburn et al., 1957) and about 10^7 pock-forming units per ml for the attenuated CVI strain (Cherry et al., 1977).

Man was the natural host of variola virus, and *a priori* it might be expected that a single viable virus particle, lodged in an appropriate site, could be infectious, although because of non-specific protective mechanisms a larger dose would usually be required. However, assays could obviously not be carried out and this must remain a supposition based on analogy with vaccinia virus in highly susceptible hosts.

The form in which the infectious virus was presented to susceptible cells was a more important factor than the actual viral content in determining whether virus in various excretions or secretions would cause infection. For example, when variola virions were present in fresh oropharyngeal secretions, there was a high probability that unvaccinated subjects, exposed by inhalation or direct contact, would be infected. On the other hand, much larger amounts of infectious virus (as judged by laboratory assay of scab extracts) enclosed within inspissated pus in scabs usually failed to produce infection. Such fragments were handled as foreign bodies by the mucociliary cleansing apparatus of the respiratory tract and excreted or swallowed, without causing infection.

The Incubation Period of Smallpox

It was difficult to measure the incubation period accurately in situations in which smallpox was endemic, for exposure usually occurred over a period of several days. However, precise observations were possible in importations of smallpox into Europe. Downie (SE/72.3) summarized data from 16 outbreaks of variola major and 2 outbreaks of variola minor, occurring in several European countries between 1927 and 1960 and involving 898 cases. Among these the exact incubation period (from a single exposure up to the 1st day of fever) could be determined in 83 cases. Mack (1972) investigated 49 importations of smallpox into Europe over the period 1950–1971 and published histograms of the incubation periods (to the onset of symptoms) for individuals whose possible exposures extended over 1, 2 or 3 days. Subsequent to these

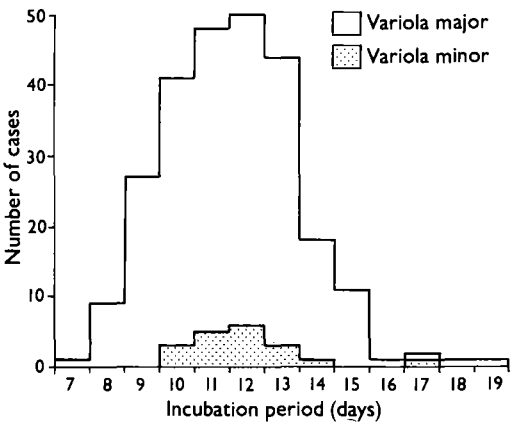


Fig. 4.7. The incubation period of variola major and variola minor, from day of exposure to the onset of symptoms. (Based on data from SE/72.3, Downie; Mack, 1972; and WHO/SE/73.57, Litvinjenko et al.)

analyses, the 1972 epidemic in Yugoslavia (WHO/SE/73.57, Litvinjenko et al.; Stojkovic et al., 1974) provided data for the calculation of the incubation period in 171 persons with variola major. Fig. 4.7 is a histogram based on the information provided by Mack for 1-day exposures in outbreaks occurring over the period 1950–1971, on Downie's data prior to 1950, and on data from the Yugoslav outbreak. In all cases the incubation period was taken as the interval between exposure and the onset of symptoms, rather than the time of appearance of the rash, which was usually 2–3 days later.

These precise data support the widely expressed opinion that the incubation period was usually 10–14 days but, in rare instances, as short as 7 or as long as 19 days. Downie concurred with the observation that acute fulminating cases of smallpox, especially haemorrhagic-type smallpox, may have had a shorter incubation period than the average, but he did not believe that previously vaccinated individuals had unusually long incubation periods, as some writers have suggested.

Variola minor appeared to have had essentially the same incubation period as variola major.

The incubation period in inoculation variola (variolation) was about 2 days shorter than in contact infection—i.e., 8 or 9 days to the onset of fever; or 5 days if the production of a local skin lesion at the inoculation site was taken as the first sign of disease (Dimsdale, 1767).

The Infectivity of Cases of Smallpox

Smallpox patients, especially those with a severe rash and enanthem, were surrounded by their infected oropharyngeal secretions and later by scabs, both of which contaminated their skin, bedclothes and to a lesser extent the air in their immediate vicinity. Susceptible individuals could be infected by coming into direct contact with the patient and his contaminated bedclothes or by inhaling infective droplets; or, more distantly, laundry workers could sometimes be infected after handling contaminated bed-linen. Very rarely, longer-range airborne infection occurred, when the contaminated droplets originating in the mouth and pharynx were smaller and more numerous, because the patient coughed or sneezed, and air currents transported infective droplet nuclei away from the immediate vicinity of the patient.

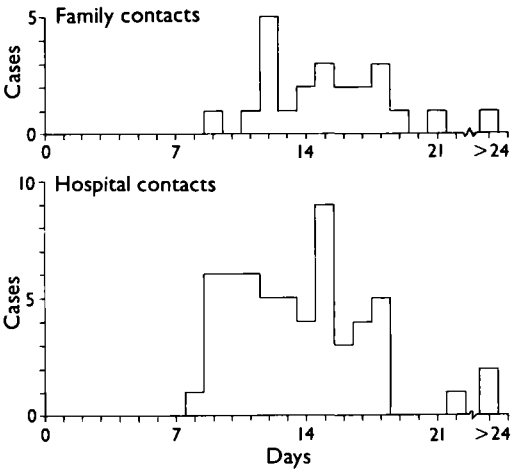


Fig. 4.8. The interval between the first possible exposure to a case of smallpox imported into Europe by air and the onset of symptoms in first generation indigenous cases, in family and hospital environments. (Based on Mack, 1972.)

Period of infectivity

The maximum infectivity of cases of smallpox was during the 1st week of rash, corresponding to the period when the lesions of the enanthem had ulcerated and were releasing virus into the secretions of the mouth and pharynx (see Table 4.8). At this stage the skin lesions were intact; the large amounts of virus later shed from the skin were not highly infectious because of the physical state of the virus particles, enclosed within hard dry scabs. For example, Mack (1972) found that the vast majority of cases infected after contact with cases of smallpox who had arrived in Europe from endemic countries while incubating the disease occurred within 3 weeks of the initial time of exposure (Fig. 4.8). In the hospital environment, the mean interval between the point at which a case first became infectious and the onset of symptoms in contacts was in the same range as estimates of the incubation period. In households, transmission took place a few days later, but in both situations the great majority of cases appeared within 3 weeks of the initial exposure.

It was difficult to obtain evidence of the infectivity of patients during the latter part of the incubation period or during the pre-eruptive fever; one series of assays of the oropharyngeal secretions of case contacts (see below) suggested that occasionally virus was present before the eruptive stage. However, epidemiological experience suggested that transmission very rarely occurred before the 1st day of rash. For example, in rural Pakistan Mack et al. (1972b) found no evidence of significant transmission during the prodromal period. Theoretically, cases remained infectious until the last scab had separated (usually from the soles of the feet) but the level of infectivity fell off greatly as the lesions of the enanthem healed during the latter part of the 2nd week of the disease.

The relative infectivity of different clinical types of smallpox

Two distinct variables were involved in determining the relative infectiousness of different cases of smallpox: the quantity of virus excreted in the oropharyngeal secretions and the number and extent of the face-to-face contacts between the patient and susceptible persons, especially during the period when large quantities of virus were being excreted. Cases with a severe rash and enanthem were more infectious than those with a slight rash and enanthem, which was why most cases of modified-type smallpox were not highly infectious. However, cases with early severe toxaemia—that is, most cases of variola major in unvaccinated persons—were usually confined to bed during the prodromal stage and were thus segregated from the community. On the other hand, although patients with modified-type variola major excreted less virus, they often moved about the community relatively freely and were thus in contact with

Table 4.10 Frequency of transmission of smallpox to household contacts in villages in Pakistan by cases occurring in unvaccinated and vaccinated subjects[a]

Status of index case	All contacts			Vaccinated contacts		
	Number	Contracted smallpox	%	Number	Contracted smallpox	%
Unvaccinated	390	83	21.3	271	15	5.5
Vaccinated	52	3	5.8	48	1	2.1

[a] Based on Heiner et al. (1971b).

many more persons. Such cases were frequently blamed for importations into the United Kingdom in the period after the Second World War, and in the 1972 outbreak in Yugoslavia 2 mild ambulant cases, not recognized as smallpox, generated 11 and 16 secondary cases respectively (Stojkovic et al., 1974). In general, however, persons who were infected despite previous vaccination were only one-fourth as likely as unvaccinated cases to transmit infection to household contacts (Table 4.10).

Rao (1972) found that the most highly infectious cases in Madras were those of ordinary- and flat-type smallpox in unvaccinated subjects. Studies in rural Bangladesh (Thomas et al., 1971b) showed that patients who died had been more infectious to family contacts during their illness than those who survived, and in rural Pakistan Mack et al. (1972b) found that while almost all susceptible persons within the relatively confined environment of compounds were infected, regardless of the severity of the index case, spread between compounds was much greater if the index case was severe.

Because the toxaemia was so much less in variola minor, cases often remained ambulatory during their period of highest infectivity and were thus likely to spread smallpox in the community, a feature which partially explains the persistence of endemic variola minor in Brazil, Great Britain and the USA after variola major had been eliminated from those countries.

Absence of recurrent infectivity

Another important epidemiological feature of smallpox was that recovery from an acute attack was followed by elimination of the virus; recurrence, with excretion of virus, never occurred (see Chapter 3). The epidemiological importance of this aspect of the pathogenesis, in relation to eradication of the disease, can be judged by comparing this situation with the recurrent infectivity found in varicella-zoster and herpes simplex infections, which accounts for the survival of these diseases in remote and isolated populations (Black et al., 1974).

The Infectivity of Case Contacts not Exhibiting Disease

Epidemiological observations before and during the eradication programme gave rise to a widely held belief that subclinical cases, patients still incubating the disease, and contacts of cases did not constitute important sources of infection. Although infection was sometimes associated with handling inanimate objects (fomites) and, rarely, seemed to be airborne over a considerable distance (see below), the vast majority of cases of smallpox could be traced to face-to-face contact of a susceptible person with a patient with overt disease, usually during the 1st week of rash. However, careful laboratory studies by Sarkar et al. (1973b, 1974) showed that about 10% of household contacts of cases of smallpox harboured detectable amounts of variola virus in their oropharyngeal secretions. Only about 10% of such carriers subsequently developed smallpox. These authors cautioned against too ready an acceptance of the view that asymptomatic carriers were not a significant factor in the epidemiology of smallpox.

Looking at the situation after smallpox has been eradicated, it seems probable that infection might occasionally have occurred from case contacts or those incubating the disease. Such events might have been responsible for what appeared to be abnormally long or short incubation periods. Nevertheless, the opinion of epidemiologists engaged in the global eradication campaign is that the vast majority of cases could be traced to close contact with a patient with an overt smallpox rash; had it been otherwise eradication of the disease from populous countries such as Bangladesh and India would have been much more difficult than proved to be the case.

Use of the Word "Contact" in Epidemiology

To clarify the discussion which follows it is useful to review the definitions used by epidemiologists for infection via the oropharynx or respiratory tract. Different conventions exist in different countries. In some countries the word "contact" is used only where true physical contact has occurred. In most English-speaking countries the word is used more broadly (Langmuir, 1973), and this was the common usage by epidemiologists engaged in the Intensified Smallpox Eradication Programme. According to this convention, infection which occurs only or mainly at short range, owing to the implantation of infectious droplets expelled from the mouth or nose of the patient during talking, coughing or sneezing, is said to occur by contact, even though physical contact does not occur. Thus "contact" includes physical contact either direct or via the fingers, as well as the direct implantation of large-particle aerosols on the oral, nasal or pharyngeal mucosae or the inhalation of small particles into the alveoli, as long as the infector and infected are in face-to-face contact.

If infection occurs at longer ranges, between persons not in sight of each other, it is regarded as being caused by airborne "droplet nuclei"—the dried particles that result from the evaporation of water from droplets that remain suspended in the air for a period. This is called "airborne infection".

However, the most common use of the word "contact" in this book is to signify a person who has been exposed to the risk of infection with smallpox, whether as a member of a household with an infected case, as a casual visitor to a hospital ward or as a co-traveller in an aeroplane, bus or train.

TRANSMISSION

The shedding of virus from an infected subject and its transfer to a susceptible person together constitute the transmission of smallpox. Transmission was ordinarily direct, by the implantation of infective droplets on to the nasal, oral or pharyngeal mucous membrane, or the alveoli of the lung, or less commonly indirect, as an airborne infection or from fomites.

Contact Infection

Contact infection could result from the inhalation of either large-particle aerosol droplets or droplet nuclei at close range or from transfer via the fingers or various objects.

Epidemiologically, the important question was the relative frequency of infection of very close contacts of the patient and infection, by aerosol, at short distances, such as occurs in tuberculosis (e.g., schoolroom epidemics) and influenza. Comparison of the intrafamilial and extrafamilial spread of smallpox (e.g., Rao et al., 1968a; Thomas et al., 1971a,b, 1972) demonstrated that the overwhelming majority of secondary infections occurred in close family contacts of overt cases of smallpox, especially in those who slept in the same room or the same bed. Next in frequency were those who lived in the same house; residents of other houses, even in the same compound (who would often have visited the house of the patient), were much less likely to become infected.

Negative evidence was also important. Especially in India, long-distance movements by train or bus of patients suffering from smallpox, with an overt rash, used to occur frequently, yet infection of casual fellow-travellers was rare indeed—so rare that instances of it were deemed worthy of special report (e.g., WHO/SE/72.41, Suleimanov & Mandokhel).

Indirect Transmission

Rather than being propelled direct from the patient on to the oropharynx or nasal mucosa of a susceptible contact or transferred by contaminated fingers or various objects (contact infection), infective particles may reach the same sites by indirect routes, after travelling considerable distances either in the

air or on fomites. Because experience had shown that most patients had been infected by face-to-face contact, indirect transmission was implicated only after all possibilities of such contacts had been eliminated.

Airborne infection

There is good epidemiological evidence that some viral infections, usually those associated with coughing and sneezing, are spread by aerosol over short distances (Coxsackievirus disease: Couch et al., 1970; influenza), while a few, notably foot-and-mouth disease, may be spread by the wind over distances of several kilometres (Donaldson, 1979; Gloster et al., 1982). Towards the end of the 19th century there was a great controversy in Great Britain about the siting of smallpox hospitals, based on the view propounded by some (e.g., Power, 1886; Buchanan, 1905) that infection could be carried by aerial spread for considerable distances from such hospitals. Collie (1912) and Dixon (1962), in reviewing the evidence, pointed out the difficulty of proving the occurrence of this type of spread in situations in which smallpox was endemic or not under control; mechanisms other than aerial spread could have been responsible in most instances. However, Christie (1980) describes a particular case which he claims is best explained by aerial spread from a hospital situated 400 yards (about 365 metres) away.

In India also it was sometimes said that the hospital was the focus from which the wind-borne spread of smallpox occurred. Hospitals were usually located in densely populated areas inhabited by persons of low income, whose vaccination status was often poor. Careful investigation showed that outbreaks of smallpox in these communities were associated with importations from outside the area—e.g., from distant construction sites—and not with spread from the hospital. In Madras, A. R. Rao (personal communication, 1981) noted that the hospital was surrounded by a zone relatively free of smallpox, probably because of more efficient vaccination in that locality. Further, Rao (1972) noted that, although wards for infectious diseases other than smallpox and corridors used by patients with such diseases were located within a few feet of the smallpox wards of the Madras Infectious Diseases Hospital, only 7 cases of smallpox presumably infected in the hospital occurred among 130 000 non-smallpox patients over the 10 years 1959–1968.

Nevertheless, airborne infection over short distances did sometimes occur. Two hospital outbreaks in the Federal Republic of Germany, at Monschau (Anders & Posch, 1962) and Meschede (Wehrle et al., 1970), seem certainly to have been airborne. In the Meschede outbreak an electrician who had just flown back to the Federal Republic of Germany from Karachi, Pakistan, and who, it transpired, had never been successfully vaccinated, was admitted 10 days later to the isolation ward of a large general hospital with a feverish illness that was suspected to be typhoid fever. He was confined to his room, and 3 days after admission developed a rash. Smallpox was confirmed by electron microscopy 2 days later and the patient was then transferred to the smallpox hospital. In spite of rigorous isolation of the patient (because of the suspicion of typhoid fever) and, after smallpox was suspected, the vaccination of all patients and nurses in the general hospital (in several cases with inactivated vaccine), or inoculation with vaccinia-immune globulin, 19 further cases of smallpox occurred there, on all three floors of the building in which the index case had been nursed. The dates of onset of these cases are shown in Fig. 4.9A. Seventeen cases occurred within one incubation period, counting from the 3 days during which the index case was in the hospital and infectious; the last 2 were room contacts of earlier cases, as indicated. The locations of these patients within the hospital are given in Fig. 4.9B, which also shows the results of tests on the carriage of smoke through the hospital. A number of circumstances favoured the airborne transmission of variola virus in this episode:

(1) the index patient had a densely confluent rash and severe bronchitis and cough;

(2) the relative humidity in the hospital was very low, a situation that promotes the survival of vaccinia virus (Harper, 1961) and presumably therefore of variola virus; and

(3) the design of the hospital led to the raising of strong air currents when the building was heated, as it was during the winter, when the episode occurred.

A visitor to the hospital during the period in question (Case No. 8) spent only 15 minutes inside the hospital, away from the patient care areas and the isolation unit corridor, but he nevertheless developed smallpox with onset of fever 11 days after this visit. Case No. 15 was a nurse who was located on the top floor;

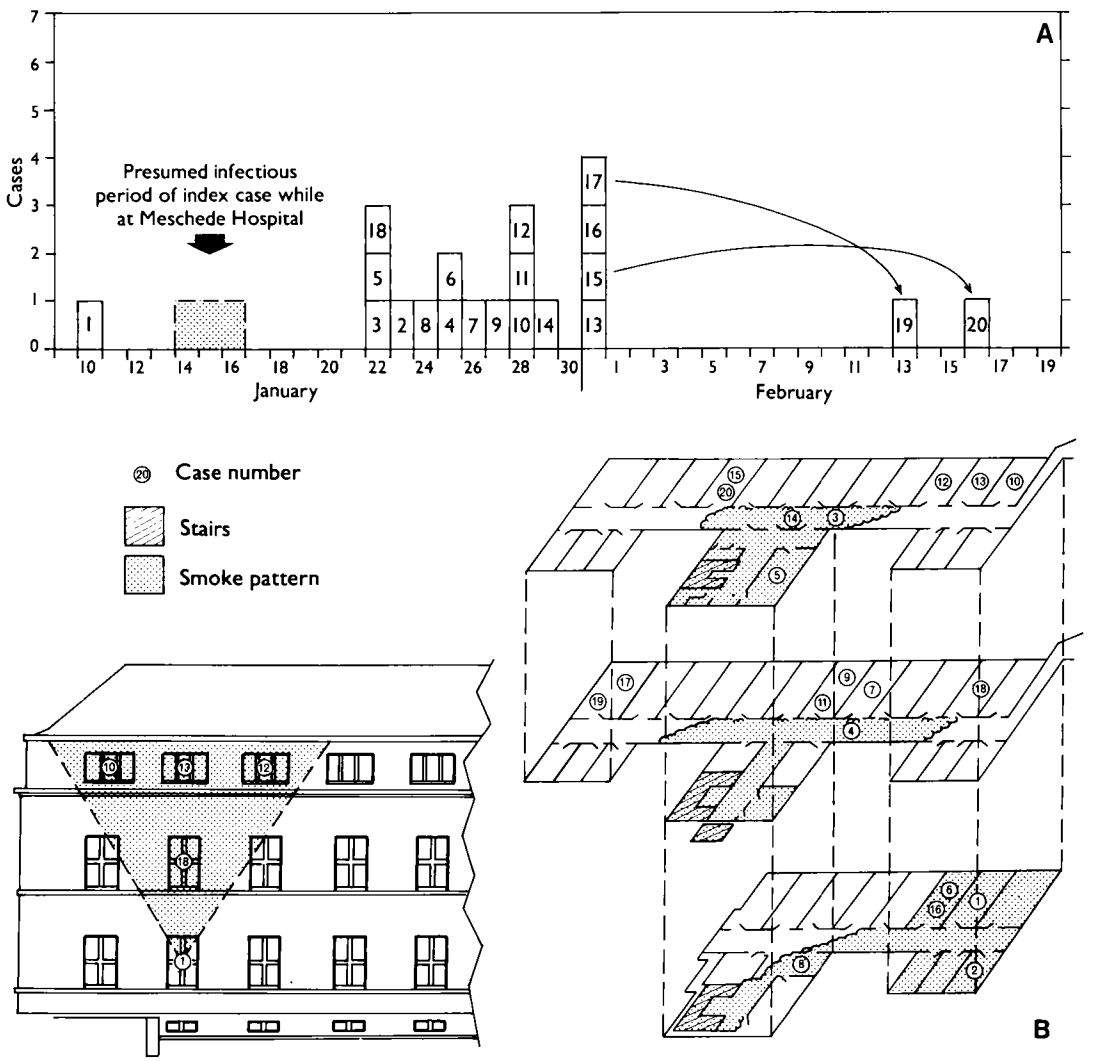


Fig. 4.9. Airborne spread of smallpox in the Meschede Hospital, Federal Republic of Germany, in 1970. **A**: Sequence of infections. The numbers in the histogram indicate case numbers, representing patients who were located as shown below. No. 1 was the index case, No. 8 was a visitor who had spent no more than 15 minutes in a ground-floor office, and No. 19 and 20 were second generation cases who had been in contact with No. 17 and 15 respectively. **B**: Floor plan and rear elevation of the hospital building, showing the location of all cases of smallpox. The shaded area indicates the movement of a cloud of smoke generated in the room in which the patient who was the index case (No. 1) had been nursed before being recognized as having smallpox. (Based on Wehrle et al., 1970.)

she had not left her sick-room while the index case was in hospital nor had she been in contact with persons other than those involved with her case, but she contracted the disease, which manifested itself after an incubation period of about 16 days. Case No. 20 was infected after contact with this patient.

There is no reason to doubt that airborne infection, sometimes over considerable distances, did occur, but it appears to have been very rare. Short-range aerosol infection was probably responsible for most non-familial cases apparently infected in hospitals, buses and trains. Many laboratory manipulations, such as blending, centrifugation and pipetting, can generate substantial clouds of aerosols; airborne infection from a laboratory is suspected to have been the cause of the last outbreak of smallpox in the world, in Birmingham, England, in August–September 1978 (Shooter, 1980; see Chapter 23).

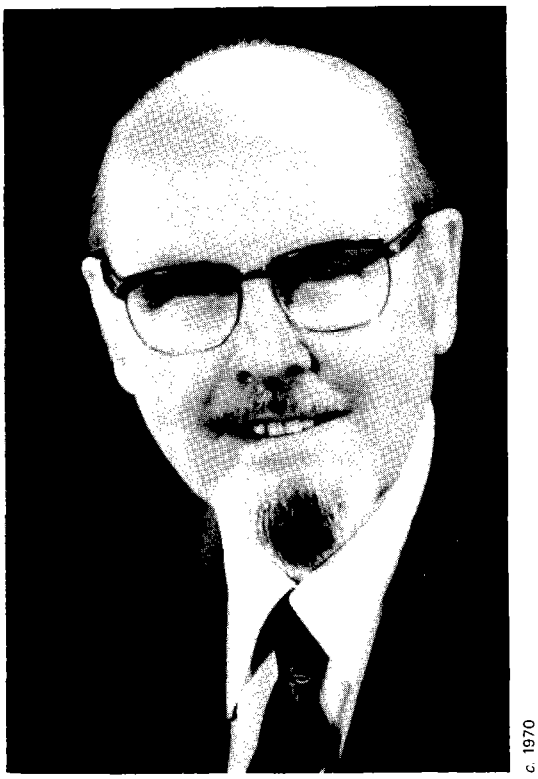
Infection via fomites

The clothing and bed-linen of cases of smallpox were heavily contaminated with virus derived from oropharyngeal secretions and later from ulcerated pustules or scabs (see Table 4.9). Such objects sometimes served as a secondary source of infectious virus for case contacts. There are several documented instances of the infection of laundry personnel whose work-places were located at some distance from the homes or hospitals in which smallpox patients had been nursed, and of chambermaids in hotels (Stallybrass, 1931). Dixon (1962) has summarized reports on infection via fomites and commented that for laundry workers the risk of infection was greatest among those who sorted the incoming laundry and could thus inhale contaminated dust; once wetted the garments and bed-linen were not infectious.

Rao (WHO/SE/72.40) carried out experiments on the persistence of infectivity of variola virus on various objects that had been deliberately contaminated. The most important finding was that, in Madras, virus on such objects was rapidly inactivated, even when they were heavily contaminated; he concluded that fomites were of little importance in the transmission of smallpox in India. In temperate climates virus in scabs could survive on fomites such as cotton for long periods of time (MacCallum & McDonald, 1957); however, virus in scabs rarely appears to have been a source of infection.

As might be expected, the corpse of a fatal case of smallpox and the associated clothing remained heavily contaminated, and smallpox sometimes occurred as an occupational disease among pathologists and mortuary attendants, particularly from unrecognized cases of haemorrhagic smallpox (Dixon, 1962). In endemic countries cases were sometimes associated with funerals (Hopkins et al., 1971c), but these could have been due to exposure by contact with unrecognized cases as often as to infection from the corpse or clothing. From time to time other fomites, such as letters, have been suspected, but incriminating evidence was hard to obtain and the subject is of historical interest only; Dixon (1962) provides a summary.

Another purported association of smallpox with infection from inanimate objects is mentioned only to be dismissed. This relates to folklore in several parts of Africa and India which held that European missionaries who occupied a house in which smallpox had occurred months or years before sometimes contracted the disease, supposedly because of residence in that house. However, in such endemic areas there were always opportunities for infection by contact with active cases of smallpox. During the Intensified Smallpox Eradication Programme repeated efforts were made to investigate such stories, but no instances were found in which infection appeared to have been caused by residence in a "contaminated" house.



c. 1970

Plate 4.3. Cyril W. Dixon (b. 1912). Worked in the Department of Preventive Medicine at the University of Leeds, England, in 1947–1959, and was Professor of Preventive and Social Medicine at the University of Otago, New Zealand, from 1959 to 1977. He was the author of the standard textbook on smallpox in the English language, which was published in 1962.

FACTORS AFFECTING THE SPREAD OF SMALLPOX

Individual Susceptibility

In the absence of immunity due to vaccination or other prior infection with an orthopoxvirus, human beings appeared to be uni-

versally susceptible to infection with variola virus. By far the most important factor affecting individual susceptibility was the immunity provided by vaccination. Individual susceptibility to the effects of infection in unvaccinated subjects was influenced by genetic factors and physiological factors such as age and pregnancy. The risk and severity of exposure was influenced by certain occupational factors.

Genetic factors

Although racial differences in susceptibility probably did exist, they were never convincingly demonstrated. Inhabitants of India, a country subject to endemic variola major for some two thousand years, remained highly susceptible to the effects of the virus, case-fatality rates of over 20% among unvaccinated individuals being common right up to the time of eradication. However, it is impossible to read the accounts of smallpox among the indigenous inhabitants of the Americas (North America: Stearn & Stearn, 1945; Mexico: Crosby, 1967; Peru: Hemming, 1970; Brazil: Hemming, 1978) without suspecting that the Amerindians, an unexposed population when smallpox was first introduced into the Americas, were more susceptible than unvaccinated whites or Negroes. When variola minor was introduced into New Zealand in 1913 from the USA, there were 114 reported cases among Europeans, with no deaths, and 1778 reported cases among the local Polynesians (Maoris), with 55 deaths (Dixon, 1962). People of the Maori race had never before been exposed to smallpox.

It seems likely that a disease as lethal as smallpox must have exerted some selection for more resistant genotypes within populations in which it had been endemic for centuries. Such selection was readily demonstrated among European rabbits exposed to the poxvirus disease myxomatosis in as short a period as 10 years (Fenner & Ratcliffe, 1965), but this was initially a much more lethal disease and it was possible to test rabbits experimentally to determine their genetic resistance. As noted in Chapter 3, the only tests of genetic susceptibility that were conducted in man related to the possibility that deaths due to smallpox had some effect on the present-day distribution of genes of the ABO blood group system. The results reported were unconvincing but do not exclude the possibility that the selection of more resistant genotypes had indeed occurred in countries such as India. The linkage between cytotoxic T-cell activity, which is important in the process of recovery from orthopoxvirus infections, and the major histocompatibility antigens (HLA in man) suggests that the latter may have been important in influencing resistance to smallpox (Chapter 3). However, very few relevant studies were carried out and no definitive data were ever obtained.

Age

The age incidence of smallpox depended mainly on the acquired immunity of the exposed population, whether due to vaccination, variolation or prior natural infection. In the absence of protective immunization, the age incidence reflected the level of endemicity. Thus, when populations were first exposed to smallpox, persons of all ages and both sexes were affected. However, if smallpox was endemic, as in the larger cities of Europe in the 17th and 18th centuries and in modern India, it was mainly a disease of childhood. On the other hand it was less explicitly a children's disease than measles or even chickenpox. In the Intensified Smallpox Eradication Programme it was found that more than one-quarter of the cases occurred among the adult population, even in India (see Table 4.2) and Bangladesh (Chapter 16, Table 16.17).

Rural areas and small villages often escaped infection for several years, and when the disease was introduced it usually affected most of the large proportion of susceptible persons that had accumulated, thus causing much greater devastation in terms of economic disruption than was the case in places in which the disease was always present.

Apart from special physiological factors such as pregnancy (see below), and in the absence of immunizing infections with either variola virus or a related orthopoxvirus (e.g., vaccinia or cowpox), the severity of smallpox, as indicated by the case-fatality rate, was greatest in the very young and the elderly (see Tables 4.2–4.5). The great susceptibility of the very young is shown in all series of figures; it was more difficult to obtain clear-cut evidence of the level of resistance in elderly persons because of the opportunity that they had of being vaccinated or of becoming infected with variola virus earlier in life. What is clear from all data is that case-fatality

rates in the age group 5–14 years were much lower than in any other age group.

Physiological factors

Apart from severe immunological deficiency states (see Chapter 3, Fig. 3.8), which, for most of history everywhere and in the countries in which smallpox had been endemic after 1967, would usually have led to death from infection during infancy or early childhood, pregnancy was the physiological state associated with the highest susceptibility to severe disease and death. Rao's data (Rao, 1972), summarized in Chapter 1, illustrate well the severity of smallpox in pregnant women; other investigators report similar findings (e.g., Dixon, 1948).

It is difficult to obtain data on the effects of nutritional deficiencies on the severity of smallpox, apart from the suggestion (Dixon 1962) that blindness due to smallpox occurred most frequently in ill-nourished subjects. Epidemiologists working in India during the eradication campaign formed the impression that cases of smallpox were more severe and deaths more frequent among ill-nourished villagers and refugees than in better-nourished subjects, but no reports have been published which document a relationship between malnutrition and smallpox comparable to that claimed for measles (Gordon, 1976).

Occupational risk

Occupational risk was related directly to the possibility of unvaccinated or inadequately vaccinated persons coming into close contact with cases of smallpox. In Europe and the USA in the period since the Second World War, nurses in particular, and doctors to a lesser extent, were often inadequately vaccinated, although they could be exposed to massive doses of virus when treating imported cases, especially cases of unrecognized haemorrhagic smallpox. Perhaps because of the effects of large doses of virus, the case-fatality rate in nurses exposed to imported cases was sometimes very high.

Social Factors

The spread of smallpox in a community depended not only on the biological factors just elaborated, the excretion of virus and the infectiousness of cases, the mode of transmission and individual susceptibility, but also on a variety of social factors that affected the opportunities for susceptible persons to come into close contact with sources of infection, primarily overt cases of smallpox. These varied from one society to another. In many countries with well-marked dry and rainy seasons, the population was much less mobile during the rainy season, and smallpox was more confined. In the dry season, travel to markets, religious festivals, fairs and similar gatherings enhanced the opportunities for the widespread seeding of cases into previously unaffected communities. Another factor, prevalent in Indonesia, was the habit of exhibiting children infected with smallpox and taking them on visits to relatives (see Chapter 13).

In contrast to diseases such as leprosy, syphilis and gonorrhoea, no social stigma was attached to smallpox, which lessened the tendency to conceal cases. Nevertheless, in a number of communities in India and in parts of Africa, cases were hidden from the public health authorities because families distrusted the local infectious disease hospitals, or because religious beliefs generated opposition to vaccination, which would have been administered to family contacts if a case had been discovered. Such concealment caused some of the most persistent outbreaks in regions otherwise free of smallpox—e.g., the Faith Tabernacle outbreak in Nigeria (WHO/SE/68.3, Thompson & Foege), and the outbreak among the Mazezuru people in Botswana (WHO/SE/74.69, Presthus & Sibiya; see Chapter 20). During national eradication programmes, cases were sometimes concealed by both local and national health service staff, the former because they feared reprimands based on accusations of inadequate vaccination and the latter for reasons of national pride. The reward system did much to minimize concealment by local health staff.

Demographic Factors

The size and density of the population at risk affected the chances of contact between susceptible and infectious persons, and thereby the extent and rapidity of the spread of smallpox. These factors have been better analysed with measles than with smallpox, but the same principles hold for both diseases, although the transmission of measles is more

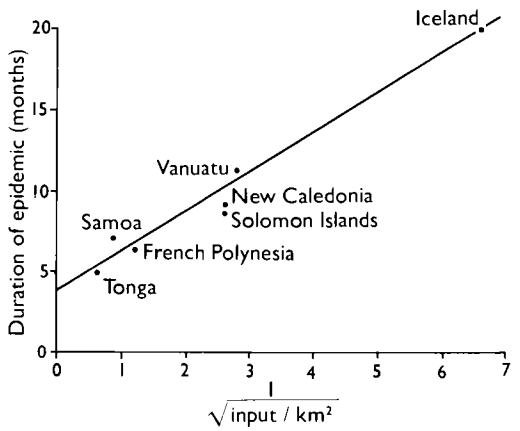


Fig. 4.10. Relationship between population density and the duration of epidemics of measles. The average distance, in kilometres, between newborn infants added to the respective populations each year is given in terms of the inverse square root of the number of new susceptible individuals added to the population per square kilometre. In island populations of roughly comparable size, the duration of epidemics was inversely proportional to the density of the population. (From Black, 1966.)

Table 4.11 Effects of population density on the numbers of unvaccinated persons remaining per unit area (km²), at various levels of vaccination coverage[a]

Persons per km²	Number of unvaccinated persons remaining when vaccination coverage is:				
	20%	40%	80%	90%	95%
500	400	300	100	50	25
300	240	180	60	30	15
100	80	60	20	10	5
25	20	15	5	3[a]	2[a]
10	8	6	2	1	1[a]

[a] Rounded to nearest integer.

efficient and rapid than was the spread of smallpox. Black (1966) has shown that in populations of about the same size, measles spread more rapidly and outbreaks terminated sooner in areas of greater population density (Fig. 4.10).

During the smallpox eradication campaigns WHO epidemiologists found that population density, when translated into the density of the susceptible population—i.e., the number of unvaccinated persons per square kilometre—was a useful concept for assessing the difficulty of controlling smallpox by mass vaccination in different endemic countries or different regions within a country (Arita et al., 1986). The effects of population density on the number and density of unvaccinated persons remaining after vaccination coverage at various levels is shown in Table 4.11. It is clear that a vaccination coverage of 80%, which was once recommended by WHO as being adequate to interrupt the transmission of smallpox, may leave a population density of 100 unvaccinated subjects per square kilometre or more in countries with a high population density, such as Bangladesh. This is very much higher than the overall country-wide population density of any African country. Arita et al. (1986) provide an example. In 1967 there was a vaccination coverage of 80.8% in the Matlab Thana, an area of about 194 square kilometres in Bangladesh. The population density was 582 per km², so that the density of unvaccinated persons was 112 per km². In that year 119 cases of smallpox were reported (and probably many more occurred). This is not surprising; it would be highly unlikely that smallpox could have been eradicated from Nigeria (population density 54 per km²) or the Philippines (population density 116 per km²), for example, with no vaccination at all. Clearly, mass vaccination alone was doomed to failure in countries with high population densities; control could only be achieved when it was supplemented by a vigorous campaign of surveillance and containment (see Chapter 10). Even in countries with low population densities, surveillance and containment greatly accelerated the achievement of eradication.

The age structure of the population affected the average severity (and case-fatality rate) of smallpox, since the very young, the elderly and pregnant women had particularly high case-fatality rates. Males aged between 5 and 20 years were important in extrafamilial spread, since they moved between family groups more frequently and readily than other segments of the population and often sustained relatively mild infections, so that they were important both as "exporters" and "importers" of the disease into previously unaffected family groups. The destruction of whole tribes that occurred when smallpox was first introduced into the populations of Amerindians in the Americas and Hottentots in South Africa (see Chapter 5) was due to a combination of the lethal effects of the disease itself in what were immunologically and genetically "naive" populations, and the

social disruption and famine that accompanied the simultaneous illness of many adults of active age, as well as persons in other age groups, in these subsistence societies.

Political and Economic Factors

The level of economic development of communities generally determines the level of health services (Fig. 4.11). The higher the level of economic development, the more effectively did surveillance and containment principles apply and the earlier was variola major, in particular, eliminated from the country (see Chapter 8).

Variola minor posed an unusual problem. Because of its low case-fatality rate compared with variola major and the lack of sequelae (facial pockmarks), it had long been tolerated as an endemic disease even in affluent countries such as the United Kingdom and the USA. In poor developing countries, such as Ethiopia, variola minor ranked very low as a national public health problem, and in the 1970s it was much more important for the rest of the world than for those countries to eliminate the disease. This justified the much larger input of international manpower and funds into the programmes in the poorer countries, in order to achieve global eradication.

Variolation and Laboratory-Associated Smallpox

Although close contact with overt cases was responsible for the vast majority of cases of smallpox, there were two other potential sources of infection: variolation and the smallpox laboratory. For many centuries and as recently as August 1976, some cases of smallpox originated from the practice of variolation (see Chapters 6, 14 and 21). Such cases of inoculation variola themselves constituted potential sources of infection for susceptible subjects in close contact with them.

Until the 1970s, laboratories in endemic countries and in countries liable to importations conducted studies in the diagnosis of smallpox and often held stocks of variola virus to assist them in this work. Laboratory procedures are associated with some risk of infection both for those working with viruses that are pathogenic for man (accidental injection, trauma) and for visitors to such laboratories, which may use procedures that generate aerosols. Of all the dangerous human pathogens, variola virus was regarded by virologists as among the safest with which to work in the laboratory, since regular vaccination and revaccination provided complete protection to the workers involved. However, administrative mistakes sometimes occurred and a few cases of laboratory-associated infection

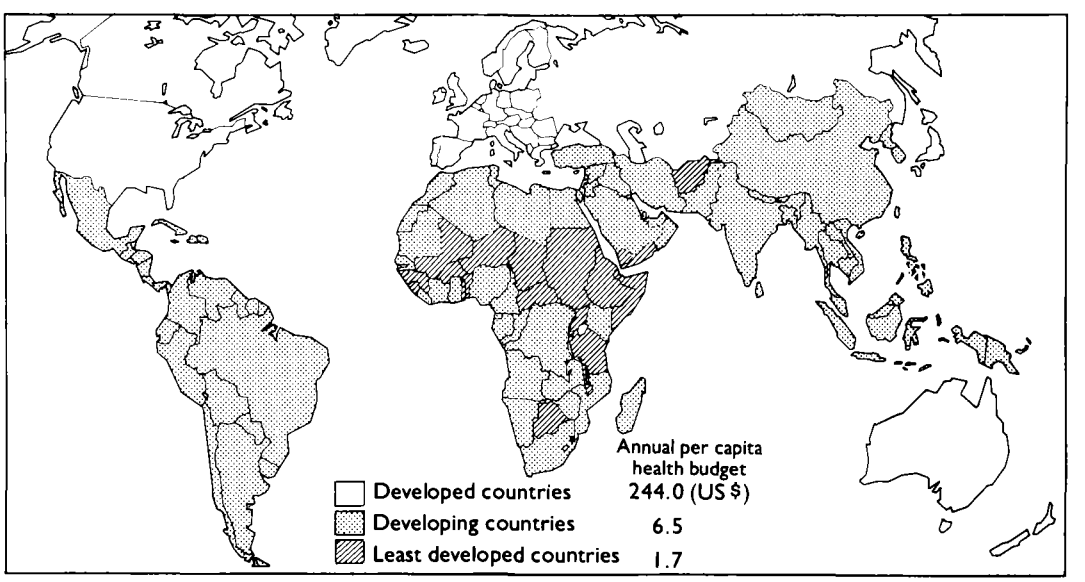


Fig. 4.11. National levels of economic development, as determined by the United Nations on the basis of average per capita income for the year 1982. Average per capita expenditures on health in US$ are also shown.

were documented in non-endemic countries. It seems likely that cases may occasionally have occurred in endemic countries also, but the source would have been more difficult to identify with certainty. The importance of the laboratory as a potential source of infection is discussed in Chapter 30.

PATTERNS OF SPREAD IN POPULATIONS

In the earlier sections of this chapter the infectivity of cases of smallpox and the susceptibility of individual human beings were discussed. The final section is concerned with various aspects of the spread of smallpox in populations, looking first at the situation in countries as a whole and then at small communities, including institutions. Several case studies are analysed which describe the epidemiology of smallpox in rural and urban settings.

Spatial Distribution

Secular trends in the occurrence of smallpox dealt with earlier in this chapter were drawn from the numbers of cases reported annually by different countries. The fact that cases were grossly and continually underreported almost everywhere meant that these figures greatly underestimated the incidence of the disease. Further, by ascribing cases to countries they fail to express the spatial distribution of smallpox. Even when smallpox was essentially uncontrolled it was never uniformly distributed within a country. An "epidemic year", for example, usually indicated a high incidence of the disease not throughout a country, but in a number of scattered villages and towns. Although smallpox remained endemic throughout the year in the large cities of endemic countries, it occurred as many small outbreaks in different suburbs and districts within the city. As the maps showing the falling incidence of smallpox in India from 1972 onwards illustrate (Basu et al., 1979), the distribution of the disease by district was patchy, and it was patchy even within affected districts.

Effective public health measures in non-endemic countries limited the spread of smallpox after importations, usually to the family and close contacts of the index case, but sometimes, as in Yugoslavia in 1972, unrecognized cases spread the disease more widely before its nature was recognized.

The Rate of Spread within Small Groups

The devastating effects of smallpox in non-immune populations in the Americas, southern Africa and the islands of the Pacific Ocean (see Chapter 5) gave rise to the view that it was one of the most infectious of all diseases. It is true that very brief exposures of susceptible persons to a case did occasionally lead to infection. For example, one case in the outbreak at Meschede, described above, was a person who had never been in face-to-face contact with a case of smallpox and had been exposed to possible airborne infection for a period of 15 minutes or less. The last person to contract endemic smallpox in the world—the unvaccinated hospital cook Ali Maow Maalin—was exposed to the disease for a few minutes only, while he directed a vehicle carrying two active cases of smallpox from the hospital in Merca, Somalia, to the home of the local smallpox surveillance team leader (Deria et al., 1980). Sometimes one index case infected a dozen or more people, as in the outbreak in Yugoslavia in 1972 (see Chapter 23). These episodes, however, were exceptional. Epidemiologists engaged in the global smallpox eradication campaign in Africa, South America and Asia agree with Dixon (1962) that smallpox usually spread rather slowly.

Attempts have been made to express quantitatively the infectiousness (or contagiousness) of different human diseases by calculating in various ways the proportion of cases among exposed contacts. The most widely used figure is the secondary attack rate—i.e., the proportion of susceptible individuals exposed to an index case within a household who became infected within the expected transmission interval of the disease. It is surprisingly difficult to obtain suitable series of data to make this calculation; often the term "secondary attack rate" has been used to include all subsequent attacks (first, second and third generation cases). Hope Simpson (1952) developed a measure that makes use of results of second and later generation attacks to provide a figure comparable to the first generation secondary attack rate—what he called the susceptible-exposure attack rate.

Some figures for measles, chickenpox and smallpox are set out in Table 4.12. The numbers available for the calculation of the

Table 4.12 First generation secondary attack rates (or the equivalent) in measles, chickenpox and smallpox

Disease and locality (for smallpox)	Vaccination scar[a]	Total number of household contacts	Contacts who developed disease		Reference
			Number	%	
Measles	..	266	201	75.6	Hope Simpson (1952)
Chickenpox	..	282	172	61.0	Hope Simpson (1952)
Chickenpox	..	888	771	86.8	Ross (1962)
Variola minor					
Brazil	–	38	20	52.6	Angulo et al. (1967)
Brazil	+	56	8	14.3	
Brazil	–	674	466	69.1	Suzart de Carvalho Filho et al. (1970)
Brazil	+	204	7	3.4	
Variola major					
Nigeria	–	27	12	44.4	Foege et al. (1975)
Nigeria	+	45	12	26.2	
Benin	–	17	8	47.0	Henderson & Yekpe (1969)
Benin	+	13	2	15.4	
Madras	–	103	38	36.9	Rao et al. (1968a)
Madras	+	1 146	14	1.2	
Pakistan	–	45	33	73.3	Heiner et al. (1971a)
Pakistan	+	190	6	3.2	
Pakistan	–	22	10	45.5	Heiner et al. (1971b)
Pakistan	+	338	3	1.3	
Pakistan	–	43	38	88.4	Mack et al. (1972a)
Pakistan	+	180	13	7.2	
Calcutta	–	80	61	76.3	Mukherjee et al. (1974)
Calcutta	+	661	47	7.1	
Bangladesh	–	21	9	42.9	Thomas et al. (1971b)
Bangladesh	+	57	4	7.0	
Average (variola major)	–			58.4	
	+			3.8	

[a] .. = not applicable; + = scar present; – = scar absent.

secondary attack rate were often quite small and the reported secondary attack rates varied widely. For variola major, the overall average secondary attack rate was 58.4% in unvaccinated family contacts, and 3.8% in vaccinated contacts. Vaccination protected most close family contacts from overt disease (but not necessarily from subclinical infection—see Heiner et al., 1971a). The highest secondary attack rates were those reported for Pakistan by Heiner et al. (1971a) and Mack et al. (1972a). These workers suggested that one of the causes of this phenomenon might have been the dry meteorological conditions prevailing for most of the year in the Punjab, compared with other parts of the Indian subcontinent. On the basis of secondary attack rates in susceptible subjects, smallpox appears to have been somewhat less infectious than either measles or chickenpox, since the figures for chickenpox exclude subclinical infections, which occur in at least 5% of varicella virus infections but are extremely rare in unvaccinated persons infected with variola virus.

This comparison of the secondary attack rates of smallpox and other common infectious diseases fails to take cognizance of an important feature of variola major, which substantially decreased the rate at which it spread outside the household. Patients in the prodromal stage of variola major, before the rash had appeared and before they could transmit infection, were usually quite ill, with toxaemia, headache and backache. Most took to bed, so segregating themselves from the general community, although not from their household contacts. In contrast, patients in the early and highly infectious stages of chickenpox and measles have few symptoms and are usually mobile, and thus spread these diseases to school and street contacts as well as to members of the household. Although its inherent transmissibility was probably lower than that of variola major, because less virus was excreted in the oropharyngeal secretions, variola minor resembled chickenpox in the mobility of infectious patients, which partly accounts for its persistence in many countries after variola major had been eliminated.

Another measure of infectiousness is the duration of outbreaks in particular community units. There are many records in the

literature of the slow spread of smallpox—for example, the outbreak of variola minor in New South Wales (Australia) in 1913–1917 (Cumpston & MacCallum, 1925; see Chapter 8) and among nomads (see below). Smallpox sometimes took several generations of infection to spread through quite small populations.

Spread in Institutions

Because of the importance of face-to-face contact in the transmission of smallpox, the household or family unit was by far the most frequently affected group. Nevertheless, some institutions, especially hospitals and schools, and public events, such as fairs and religious festivals, played an important part in the dissemination of smallpox.

Hospitals

The role of hospitals was particularly significant in amplifying outbreaks of imported smallpox, for undiagnosed and misdiagnosed cases were often admitted into general wards, and the proportion of unvaccinated or poorly vaccinated hospital personnel and patients was usually high (Millar, 1965). Over half the cases that occurred after importations of variola major into Europe between 1950 and 1971, and all the large outbreaks, were to be found among persons associated with hospitals, either occupationally or as patients or visitors (Mack, 1972). An outbreak in Glasgow in 1950 (Laidlaw & Horne, 1950) was characteristic. An Asian seaman with 4 vaccination scars and a history of revaccination 3 years earlier was admitted to hospital with what was regarded by an experienced consultant as chickenpox, but was in fact modified-type smallpox. Thirteen of the 18 cases which ensued were infected in hospital, including 10 members of the hospital staff. Six died, all of whom were unvaccinated or had failed to respond to vaccination after exposure.

The experience in the epidemic in Yugoslavia in 1972 (Stojkovic et al., 1974) was particularly dramatic: an undiagnosed case of haemorrhagic-type smallpox infected 2 contacts in a bus and then a total of 36 persons in 3 hospitals to which he was admitted.

Hospitals sometimes played a role as amplifiers in countries with endemic smallpox. Almost everywhere, they were important

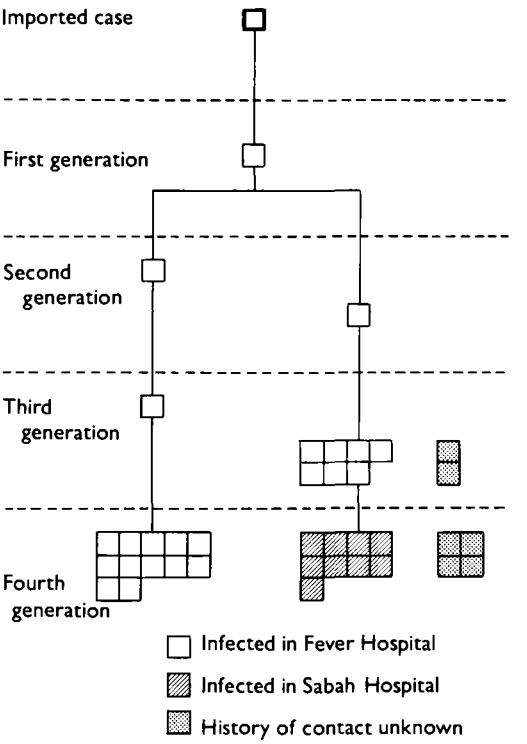


Fig. 4.12. The pattern of transmission of smallpox in an outbreak in Kuwait in which two hospitals were the principal foci of infection. (From Arita et al., 1970.)

disseminators of smallpox. Obviously, if all staff were regularly vaccinated and patients and visitors vaccinated on entry—as ideally they should have been—the risk of spread would have been very low. However, with a few exceptions, such as the Infectious Diseases Hospital in Madras (Rao, 1972), this did not occur. Two outbreaks exemplify the risk.

Kuwait is a small country which in 1967 had been free of endemic smallpox for the previous 10 years, but which was constantly exposed to the risk of importations from nearby endemic countries. Smallpox misdiagnosed as chickenpox spread in the Fever Hospital over a period of 2 months before a second generation fatal case was correctly diagnosed, after it had caused 9 third generation cases. One of these, unrecognized, was transferred to another hospital (Sabah), where it produced several more cases (Fig. 4.12). Twenty-one of the 39 cases were in children under 4 years of age; only 8 patients, 6 of them aged 15 years or more, had ever been vaccinated. In contrast to the usual situation in Europe, all cases, except one vaccine-modified attack, occurred among patients rather

than nurses or other hospital personnel, whose immune status had been maintained by regular revaccination (Arita et al., 1970).

An outbreak in a children's hospital in Brazil described by Morris et al. (1970a) demonstrates clearly the importance of the hospital as a potential focus for transmission in countries in which variola minor was endemic. The epidemic had been smouldering in the community and the hospital for at least 10 months before it was extinguished and 40 of the 51 cases that occurred in the hospital during 1967 were certainly or possibly (4 cases) hospital-associated. Over the period, there were at least 11 and possibly 15 separate introductions of smallpox into the hospital, which formed a continuous source of infection because visiting was not restricted and smallpox cases were treated in the outpatient clinic. Only one hospital employee was infected—a kitchen worker who had never been successfully vaccinated.

Schools

Because of their accessibility, schoolchildren in endemic countries were usually well vaccinated. Unvaccinated children in the infectious stages of variola major were usually too ill to attend school. Even with variola minor, contacts between children in the household or, to a lesser extent, in playgrounds appeared to have been more important than their contacts at school (Angulo et al., 1968). Space–time cluster analysis of variola minor within two schools suggested that transmission was most likely to occur from infected children to susceptible children sitting next to them (Klauber & Angulo, 1974a); studies in schools when two or three shifts of pupils occupied the same classroom each day revealed that contaminated desks or other fomites played no part in spread (Klauber & Angulo, 1974b).

In a study in Mali, Imperato (1970) found that smallpox spread much more rapidly and extensively among schoolchildren than among equally inadequately vaccinated children of the same age who did not attend school. The epidemic was confined to a group of straw buildings in which there was severe overcrowding and did not spread to children in less crowded cement-block buildings in the same school compound. However, even in the straw buildings transmission, mostly between susceptible and infected persons in close contact, was slow and went on for a long time because of the absence of an effective response by the local health personnel.

Markets, fairs and religious festivals

Markets are regular institutions at which households mingle; fairs and religious festivals, although held less frequently, draw attendance from much wider areas. Both are important as mechanisms for the wide dissemination of infectious diseases, because of the dispersion of participants during the incubation period. Great international religious festivals, such as the pilgrimage to Mecca, are kept under strict medical surveillance and appeared to have played only a minor role in the international spread of smallpox during the latter part of the 20th century, although it seems likely that some outbreaks did occur but were concealed. The national religious festivals in India were always important for the dissemination of smallpox, and in the later stages of the eradication campaign they served as convenient observation posts for sampling the vaccination status and awareness of smallpox in village populations (see Chapter 15).

On rare occasions funeral ceremonies provided an opportunity for the spread of smallpox. When death due to unrecognized smallpox occurred, relatives, friends and other associates who were obliged to attend the funeral could be exposed to a variety of sources of virus (Hopkins et al., 1971c). Like markets or fairs, funerals were important because the participants subsequently dispersed and could then produce secondary cases among widely separated family groups.

Dispersal by Travellers

Because of the long incubation period of smallpox, travellers of various kinds—migrant workers, nomads, tramps, bus and train passengers, and air travellers—could cover long distances while apparently healthy and introduce the disease into areas far removed from the place in which they had acquired the infection. The situation was dramatically illustrated by importations into European countries by air travellers (Hagelsten & Jessen, 1973; see Chapter 23), but the movement of train and bus travellers in endemic countries was no less important. Fellow-travellers

were sometimes infected when ambulant patients, perhaps with vaccine-modified smallpox, travelled in buses or trains (see, for example, WHO/SE/72.41, Suleimanov & Mandokhel). Usually the travellers became infectious after arriving at their destination, where they initiated new outbreaks. Perhaps the most dramatic of such instances of dispersal of smallpox to distant areas were those from the Jamshedpur industrial complex in Bihar, India, in 1974 (see Chapter 15, Fig. 15.20). During a 6-week period, between the end of February and mid-April 1974, travellers from Jamshedpur caused nearly 300 outbreaks in other Indian states, dispersal occurring mainly through train passengers travelling from the Tatanagar railway station. During 1974 there were many exportations from India to Nepal and in 1975 smallpox was reintroduced into India from Bangladesh on 32 occasions (see Chapter 15).

Because of their greater mobility, adult men were much more likely than women or children to acquire smallpox outside the home; the movement of sick peasants or workers from the city back to their villages appeared to be important in the maintenance of smallpox in some rural areas in the Indian subcontinent (Thomas et al., 1971a; Thomas et al., 1972; Sommer & Foster, 1974). Indeed, it was suggested that in Pakistan the cities were the reservoir of smallpox during the monsoons, the disease being carried back to the rural areas after the rains. However, when effective active surveillance was introduced, a number of affected localities were found in rural areas immediately after the monsoons, in spite of reports of "no transmission" during the rains (see Chapter 14). Not surprisingly, in countries such as India, in which 80% of the population was rural, the predominant travel pattern (74%) was from one rural area to another, and smallpox transmission followed the pattern of population movement.

Dispersal by refugees

Although they constituted a special type of traveller, refugees were of particular importance in the spread of smallpox, because of the vast numbers involved in the flight from war- and famine-stricken areas. Such dispersal was directly responsible for the re-establishment of endemic variola major in Bangladesh in 1972 (see Chapter 16). Many other instances occurred, both between and especially within countries. Movement of refugees provided almost ideal conditions for the promotion of spread—large numbers of persons of all ages living in close proximity under very unsatisfactory conditions, often suffering from malnutrition and often poorly vaccinated. The isolation of cases was difficult or impossible.

Illustrative Case Studies in Rural Areas

In the developing countries in which smallpox was most recently endemic the vast bulk of the population lives in villages in the rural areas. In India, for example, the 1971 census figures showed that 80% of the population of 548 million lived in 580 000 villages, of which 318 000 had a population of less than 500. There were only 148 towns and cities with a population of more than 100 000. In Bangladesh and in most countries of Africa the proportion of population in the rural areas was even higher. In some countries, such as Afghanistan and Somalia, some of the rural population lived a nomadic life; these nomads presented special problems in smallpox eradication programmes.

Studies in Africa

Henderson & Yekpe (1969) described the spread of smallpox in a village in southern Benin, in which about half the population of 300, as well as about half the members of the infected households, had old vaccination scars. The chronology of the epidemic and the probable chains of transmission which started with the movement of an infected woman and her children back to the village are shown in Fig. 4.13. The 3 cases infected outside the village lived in house A and the disease spread to 5 contiguous houses (B–F) by moving from one infected household to the uninfected household nearest to it. Seventeen of the 28 persons living in that cluster of houses (A–F) became ill. A 17-year-old boy living in house G, who carried food to persons in the infected cluster of households, became ill but produced no secondary cases; both his parents had vaccination scars. Infection was brought to house H by the "*grand fêticheur*" (Case No. 22), whose occupation involved frequent contacts with all cases of smallpox, and he was probably responsible for the other 6 cases in the village, in houses H and I. The 2 patients in household I joined the *grand fêticheur* in the funeral ceremonies of smallpox victims. Frequent casual contact occurred between the

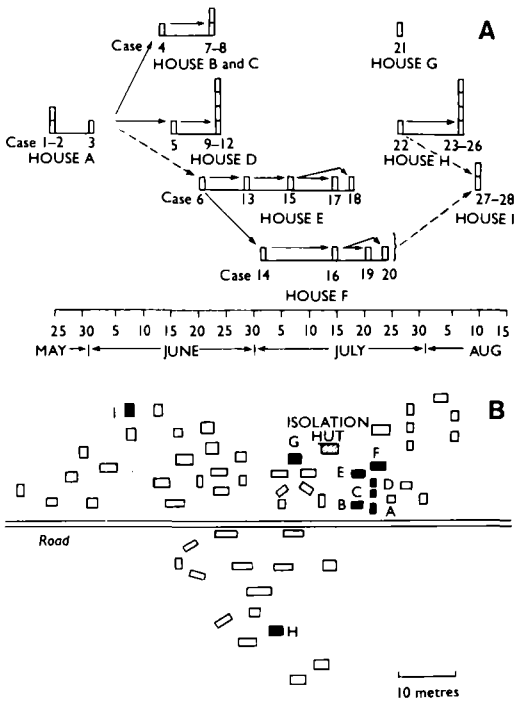


Fig. 4.13. The spread of smallpox in a village in Benin of 300 inhabitants, living in 59 houses, extending from May to the end of August 1967. **A**: Chronology and spread. Solid lines = routes of transmission; broken lines = probable routes of transmission. **B**: Location of households. (Based on Henderson & Yekpe, 1969.)

villagers in general and the smallpox sufferers, although once the rash had developed the patients were generally avoided.

The striking feature of this epidemic was the spatial localization of the disease, which reflected intimate social contact between at least some members of the affected households. Once smallpox had been introduced into a household, secondary cases occurred within it. The transmission of smallpox appeared to stop when the number of susceptible individuals in the village who were in casual contact with cases was still large but the supply of such persons in prolonged and intimate contact with cases was virtually exhausted. Even among the household contacts smallpox was not highly contagious; prolonged or intimate exposure was usually necessary. Because of this pattern of spread, it is not surprising that smallpox was eliminated from many African countries much more rapidly than had originally been anticipated (see Chapter 17).

Studies in Brazil

Similar observations emerged from a study of the spread of variola minor in a semi-rural school district in São Paulo, Brazil, in which there were two types of social agglomerates: school classes (Angulo et al., 1964) and households (Angulo et al., 1967). All the secondary cases in the 12 infected households resulted from a single introduction by a known primary case of smallpox, who was usually a child infected in the school. Infection occurred only among persons in intimate and face-to-face contact, either in the household, in the school, or in shared household facilities (Angulo et al., 1968).

Studies in the Indian subcontinent

Thomas and his colleagues have reported detailed studies of smallpox in rural areas of Pakistan and Bangladesh (see Chapters 14 and 16). Their investigations in Bangladesh (Thomas et al., 1971a, b) showed that smallpox did not remain indefinitely endemic in a rural district in which 113 000 inhabitants resided in 132 villages scattered over an area of about 200 square kilometres. During a period of 12 months, 119 cases of smallpox occurred in 30 outbreaks in 27 widely dispersed villages. Inter-village spread occurred in only one case; in the other 21 outbreaks whose source could be determined, smallpox was introduced by a landless peasant from the village in question who had contracted smallpox during a visit to a city to obtain employment. The probability of an introduction was correlated with the population size of the village, and thus with the probable numbers of landless peasants from each village seeking employment in the cities. With the introduction of smallpox into a village, secondary cases appear to have occurred more frequently outside than inside families. Nevertheless, the secondary attack rates among unvaccinated persons were highest within families.

A further, substantially larger study was carried out in Pakistan (Mack et al., 1972a, b; Thomas et al., 1972). The most striking differences between the two studies were the very high secondary attack rate (88%) among unvaccinated contacts within compounds and the high proportion of cases (78%) resulting from spread between rather than within compounds. The explanation for

the very high secondary attack rate in Pakistan is not clear; possibly it was due to the low humidity prevailing in the Punjab for most of the year. As in Bangladesh, smallpox was not maintained as an endemic disease within the rural areas, even in one as large as 6000 square kilometres with 1.2 million inhabitants. Over half the outbreaks occurring in the study area were ultimately traced to cities, emphasizing the significance in Pakistan of these large aggregations of population for the maintenance of the disease.

Investigation in Pakistan by Heiner et al. (1971b) confirmed the high secondary attack rate in the Punjab, which reached 77% in unvaccinated compound contacts and 4.8% in previously vaccinated contacts, all of the latter having been exposed to severe or fatal index cases. Further, vaccinated persons generated many fewer cases among their contacts (4%) than did unvaccinated index cases (11.5%) (see Table 4.10), reflecting the greater severity of the disease in unvaccinated subjects.

Another investigation in rural villages in Pakistan, which was mainly concerned with inapparent infections (Heiner et al., 1971a), has been discussed at length in Chapter 1. Here we would note that in this study, village residents who were not household or compound contacts of cases were taken as one of the control groups. In contrast to vaccinated compound contacts, over half of whom had had overt or inapparent smallpox, only 6.5% of these other vaccinated villagers in this control group had sustained inapparent infections (none had overt smallpox), again showing the importance of intimate face-to-face contact in the transmission of smallpox.

Prolonged transmission among nomads

Nomads constituted a special problem in the Horn of Africa, sub-Sahelian western Africa and Afghanistan. On general principles, it could be predicted that smallpox would rarely persist for long in such small isolated populations, even in the absence of control measures. This was indeed usually the case. Outbreaks among nomads constituted 68% of 843 outbreaks in Somalia in 1977, but in only 10 of them did prolonged transmission occur (Table 4.13). The best documented of these outbreaks, in Mandeelo village (Foster et al., 1978), is described in Chapter 22. As indicated in Table 4.13, transmission was interrupted very soon after outbreaks in nomads were detected, and in some instances the last case had occurred before the outbreak was detected. Similar prolonged persistence of smallpox in nomadic groups of less than 15 persons have been described in both Cameroon and Niger (Henderson & Yekpe, 1969).

This slow and prolonged transmission was due to the balance between the supply of susceptible persons and the transmission rate. Nomads were usually poorly vaccinated and patients with variola minor were often ambulant throughout their illness. The transmission rate was low because most of the activities of nomads occurred in the open, where opportunities for face-to-face transmission by large-particle aerosols were greatly reduced. As noted above, these circumstances usually led to the spontaneous termination of outbreaks (in 98.2% of outbreaks), but if transmission was maintained it continued for many weeks, even in these very small populations.

Table 4.13 Prolonged transmission of smallpox in several nomadic encampments in Somalia in 1977[a]

Locality	Population	Number of cases	Number of days from first to last case	Date of:		
				First case	Last case	Detection
Darta	55	14	163	17 Feb.	1 Aug.	20 Aug.
Oridan	35	24	152	21 Jan.	23 June	28 June
Loala	98	20	106	22 March	6 July	22 June
Bilahey	75	23	95	14 March	8 June	19 June
Madhare	35	9	80	6 March	24 May	18 May
Berdebiole	65	9	74	20 April	4 July	5 July
Boldwene	50	6	73	26 March	8 June	17 May
Abdijelib	11	6	70	25 Feb.	7 May	24 April
Mandeelo	46	21	68	23 April	1 July	23 June
Shafa	60	12	65	28 June	1 Sept.	12 Aug.

[a] The great majority of outbreaks in such groups were rapidly detected and controlled, or the chain of transmission was interrupted spontaneously. (Based on Ježek et al., 1981.)

Illustrative Case Studies in Urban Areas

Outbreaks of smallpox in non-endemic countries since 1950, most of which occurred in urban settings, are discussed in Chapter 23. Of more significance than these episodes, in relation to the global smallpox eradication programme, was the pattern of spread in urban areas in countries in which smallpox was still endemic. Only a few reports of such situations have been published, mainly referring to cities in the Indian subcontinent (Madras: Pandit et al., 1959; Rao et al., 1968a; Rao, 1972; Calcutta: Mukherjee et al., 1974; Lahore and surroundings: Ali & Heiner, 1971; Thomas et al., 1972; Bangladesh: Sommer & Foster, 1974; Brazil (variola minor): Rodrigues-da-Silva et al., 1963; Azeredo Costa & Morris, 1975).

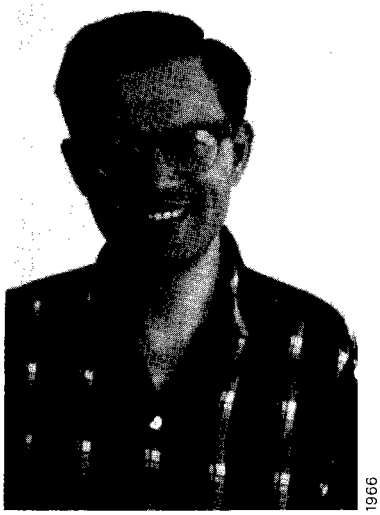
Transmission to household contacts in some cities, e.g., Madras (Rao, 1972), showed much the same pattern as that in rural areas; transmission was usually more common among intrafamilial than extrafamilial contacts, even when all those studied lived in compounds in which families shared an entrance, toilet facilities and a bath. The importance of the local social arrangements is shown by the fact that in Calcutta Mukherjee et al. (1974) found that the attack rates among household and compound contacts were very similar; in this situation the mixing of the inhabitants was so intimate that each compound could be regarded as a single large family.

In many endemic countries the larger towns and cities constituted the major reservoir of smallpox during the wet season. Sarkar et al. (1970) studied the epidemiology of off-season cases in Calcutta in 1967 and 1968. Most of the few cases that occurred during the months June–November of each year were in beggars and footpath dwellers or in manual labourers who did not work in fixed places and lived in the bustees (slum areas). Successive cases were sometimes widely dispersed, but the majority of cases could be grouped into 6 outbreaks in the bustees, different groups being involved in 1967 and 1968. Several cases were probably associated with introductions from villages outside Calcutta, and in one instance there was evidence that infection was introduced from Calcutta into a village 30 kilometres away in May 1968, maintained there by serial transmission, and reintroduced into another part of Calcutta in September 1968.

Several reports refer to the maintenance of smallpox in small pockets of unvaccinated individuals in otherwise well-vaccinated populations. In Lahore, for example, Ali & Heiner (1971) found that in a situation in which 93% of the population had vaccination scars or a history of smallpox, the disease could persist for most of the year, mainly because of the high concentration of unvaccinated children under 3 years of age and of older persons in whom the immunity conferred by primary vaccination many years before had waned.

Experience in Indonesia (see Chapter 13) provided one of the earliest and clearest demonstrations of the ineffectiveness of mass vaccination alone as a means of eliminating smallpox from populous countries. It used to be held that a vaccination level of 80% would suffice to raise the herd immunity to such an extent that transmission would cease (see Chapter 9). However, in Indonesia in 1969 and 1970 chains of transmission of variola major were maintained in communities in which the overall vaccination rate was about 90%. This happened because of the high population density (see Table 4.11), and because a large proportion of the unvaccinated were in the age group 0–4 years. The Indonesian practice, mentioned earlier in this chapter, of taking children with smallpox on social visits to their neighbours and relatives maintained a chain of transmission in this section of the population.

Thompson & Foege (WHO/SE/68.3) demonstrated that the existence of special groups who, for social or religious reasons, refused vaccination was of significance in maintaining endemic smallpox within an otherwise well-vaccinated urban community in Nigeria. The concealment of cases played an important role in the development of the epidemic, but the disease spread quite slowly (32 recognized cases over a period of 11 weeks), even in a compound where nobody had been vaccinated. In spite of frequent social mixing on religious occasions, transmission occurred most frequently as a result of family and compound contacts. Such situations were not restricted to urban areas, for the last outbreak of smallpox in southern Africa occurred among a religious sect in Botswana, who lived in closed communities in 9 small towns and likewise refused to be vaccinated (Presthus, 1974; WHO/SE/74.69, Presthus & Sibiya).



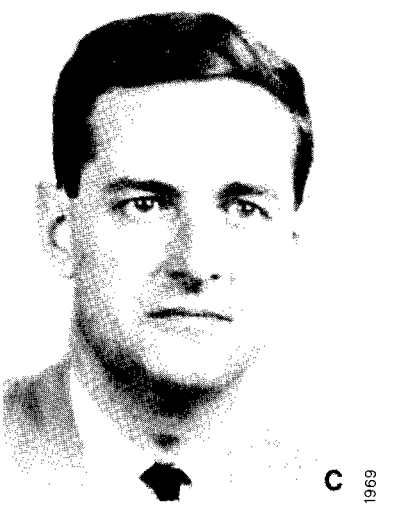


Plate 4.4. **A**: Thomas M. Mack (b. 1936), **B**: David B. Thomas (b. 1937) and **C**: Gordon G. Heiner (b. 1924), with Pakistani colleagues, conducted some of the most important and certainly the most comprehensive studies of the epidemiology of smallpox to be undertaken during the Intensified Programme. Working in what was then East and West Pakistan between 1965 and 1968, they demonstrated how surveillance and containment measures could be highly effective even in some of the most heavily infected areas.

SUMMARY

The basic facts of the epidemiology of smallpox may be summarized as follows:

(1) Smallpox was a specifically human disease; there was and is no known animal reservoir of variola virus (see Chapter 30).

(2) Compared with the infectious agents of many other human viral diseases, variola virions are relatively resistant to inactivation by physical and chemical agents; nevertheless, infection almost always involved the face-to-face contact of a susceptible subject with a person suffering from clinical smallpox.

(3) The detection and recognition of cases were relatively simple, since the rash was usually quite distinctive and occurred mainly on uncovered parts of the body.

(4) Subclinical infections with variola virus seldom occurred, except in vaccinated close contacts of cases. These individuals rarely, if ever, transmitted smallpox to others and were of little or no importance epidemiologically; almost all new cases could be traced to contacts with overt cases.

(5) An attack of smallpox was followed by death or recovery; persistent, latent or recurrent infection did not occur and cases were never infectious after the rash had gone.

(6) Different strains of variola virus differed in their virulence. Strains from outbreaks with case-fatality rates of about 1% in unvaccinated persons are designated variola minor virus. Most strains, for most of history, were associated with much higher case-fatality rates (5%–15%, and more commonly about 25%); these strains are designated variola major virus.

(7) All strains of variola virus are indistinguishable antigenically. In the vast majority of cases, immunity to reinfection was absolute. Similar protection could be reproduced, for a period of several years, by immunization with a live virus vaccine prepared from a related orthopoxvirus, such as cowpox or vaccinia virus.

(8) There was a pronounced seasonal incidence: smallpox was essentially a winter–spring disease.

(9) Smallpox spread rather slowly. There was an interval of 2–3 weeks between each generation of cases, and even during the transmission season an index case rarely infected as many as 5 other persons.