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Impact of population density on immunization programmes

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SUMMARY

The eradication of smallpox was achieved by surveillance and containment vaccination after the failure of mass immunization campaigns. The reasons for this failure are considered in this paper. Comparison of population densities in the Indian subcontinent and Africa show that in highly populated areas even an 80% vaccine coverage will still leave a density of susceptibles high enough to maintain the disease, a finding with important implications for other vaccine campaigns.

INTRODUCTION

The achievement of global eradication of smallpox in 1977 (World Health Organization, 1980) has had several consequences in terms of other global immunization programmes. The early successes of the smallpox programme led directly to the establishment of the Expanded Programme on Immunization of the World Health Organization, which has the goal of reducing the morbidity and mortality from six cosmopolitan diseases by providing immunization for all the world's children by 1990. International conferences have been held on the possibilities of global eradication of other infectious diseases (Stuart-Harris, Western & Chamberlayne, 1982; Katz, Krugman & Quinn, 1983; Horstmann, Quinn & Robbins, 1984). For these and many other infectious diseases, immunization provides the most effective method of control and a possible way to achieve eradication. Recognition of this fact and the explosion of knowledge in molecular biology has led to a widespread interest in new vaccines (Bell & Torrigiani, 1984; Lerner, Chanock & Brown, 1985).

Given the facts that variola virus had no animal reservoir, that recurrent infectivity did not occur after an attack of smallpox, and that the delay in the onset of infectivity until the rash appeared made surveillance and containment a successful strategy, the quality of the vaccine available was the most important feature of the smallpox eradication campaign. It was provided as freeze-dried vaccinia virus and subjected to effective international quality control (Arita, 1985).

and was efficacious, extremely heat-stable, and could be administered without the need for a syringe and needle. The last two features account for the current interest in the potential use of vaccinia virus as a vector for genes specifying other immunogens (Quinnan, 1985).

One aspect about which there has been little comment, however, is the extent of vaccination coverage of the population needed to control and then eradicate smallpox. Prior to 1967, the goal in smallpox control programmes had been defined in terms of the number of vaccinations performed, and in 1959 the Executive Board of the World Health Organization, in a preamble to recommendations on the global eradication of smallpox, stated: '. . . it has been demonstrated that eradication of smallpox from an endemic area can be accomplished by vaccinating or revaccinating 80 per cent of the population within a period of four to five years' (World Health Organization, 1959). As well as influencing operational procedures in most endemic countries, this premise was incorporated into the strategy of the national smallpox eradication programme of India. For the vaccination campaign of 1961–4 it was decided that when the vaccinations in each district were equivalent to 80% or more of the population census, the programme would revert from an attack phase, involving mass vaccination, to a maintenance phase, in which basic health workers would vaccinate infants and others not vaccinated in the mass campaign (Government of India, 1966). However, subsequent experience showed that outbreaks of smallpox still occurred in districts in which the goal of 80% had been reached, both in India (Gelfand, 1966) and elsewhere (Emmet, 1971).

One consequence of these observations was that a group of experts meeting in Geneva in 1967 commented that 'in general, when 80% of each village, social, sex and age group are immunized, smallpox transmission should cease. In densely populated areas, however, higher proportions may be required' (World Health Organization, 1968). Of greater importance was the discovery that case-finding and containment by isolation and vaccination (surveillance-containment) was effective in controlling transmission even when vaccination coverage was much less than 80%. This led to a markedly diminished emphasis being given to mass vaccination in favour of surveillance and containment. However, no adequate analysis appears to have been made why mass vaccination was effective in some countries but not in others. This paper provides a rationale for such observations and may be valuable in planning vaccination programmes for the control of other diseases.

RESULTS

Although vaccinial immunity wanes with time, and where smallpox is endemic, some persons will be immune because they have recovered from an attack of smallpox, in the analysis which follows it has been assumed that susceptibility to smallpox can be equated with absence of vaccination (Table 1).

The significance of these figures will be demonstrated by comparing the history of smallpox control in two parts of the world: the Indian subcontinent and several countries in western and central Africa. Although the population density within every country differs regionally, we will show that useful conclusions can be drawn from the overall country-wide data.

Table 1. *Population density (persons/km²) of susceptibles at various levels of vaccination coverage*

Population density (persons/km²)	Proportion vaccinated				
	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	2·5	1·25
10	8	6	2	1	0·05

Bangladesh (then East Pakistan) initiated a mass vaccination programme in 1961. The country had a relatively well developed health infrastructure and carried out 71 million vaccinations between 1961 and 1963 and 68 million more during the succeeding 3 years (1964–6) – in all, more than twice the population of the country. Despite this, smallpox remained endemic, the reported number of cases being 316 in 1965, 3207 in 1966 and 6848 in 1967, figures which we believe represent only 1–2% of the real incidence. In 1967 the Cholera Research Institute in Dhaka investigated the smallpox vaccination coverage in Matlab Thana, an area of 194 km² inhabited by 113000 persons (population density, 582 persons/km²). Of 103539 persons investigated, 83695 (80·8%) had been vaccinated. Although the coverage recommended at that time by WHO had been achieved, 119 cases of smallpox were discovered in this area during 1967 (Thomas *et al.* 1971*a*,*b*). The population density in Bangladesh as a whole in 1967 was 444/km². If we assume that Matlab Thana was representative, and that the overall vaccination coverage in Bangladesh was 80%, the overall density of susceptibles in Bangladesh would have been 89/km².

A smallpox eradication and measles control programme was organized in 20 countries of western and central Africa in 1966, under bilateral aid arrangements with the USA. In keeping with policies at that time, the initial approach was to try to vaccinate the entire population, using jet injectors. When the vaccination level reached about 80%, in 1969, smallpox ceased to occur in many of these countries and it was eradicated from all countries in the region by the end of 1970 (Foege, Millar & Henderson, 1975). The numbers of susceptibles per km² in these countries after the vaccination campaign and the reported cases of smallpox, 1966–70, are shown in Table 2.

Before 1966, such vaccination programmes as took place in the countries listed in Table 2 utilized vaccine of dubious quality and covered only the major cities, although most of the population lived in rural areas, so that it can be assumed that in 1966 vaccination coverage was probably extremely poor. Within 3 years, vaccination programmes, which in ten different countries covered between 77% and 95% of the population, reduced the average number of susceptibles in those countries from 3·0/km² (80·9% coverage), and to 1·9/km² in the 20 countries which had an overall vaccination coverage of 84%. The last cases of smallpox in all these countries were recorded in 1969 or earlier, except in Nigeria – much the most densely populated country in the region, where the last case occurred in 1970.

Table 2. *Estimate of density of susceptibles (persons per km²) in twenty countries in western and central Africa and reported cases of smallpox 1966–1970*

Country	Area (km²)	1966 Population (000's)	1966 No. of persons per km²	1969 Population (000's)	1969 Vaccination coverage* (%)	1969 No. of susceptibles per km²	Smallpox cases 1966	1967	1968	1969	1970
Benin	112622	2440	22	2650	80	4·7	490	815	367	58	—
Central African Rep.	622984	1470	2·4	1580	—		—	—	—	—	—
Chad	1284000	3370	2·6	3570	78	0·6	—	86†	5†	—	—
Congo	342000	1090	3·2	1170	—		—	—	—	—	—
Equatorial Guinea	28051	270	9·6	290	—		—	—	—	—	—
Gabon	267667	470	1·8	490	—		—	—	—	—	—
Gambia	11295	430	38	450	—		3	—	—	—	—
Ghana	238537	7190	33	8440	93	2·5	13	114†‡§	24‡	—	—
Guinea	245857	3610	15	3840	90	1·6	56	1530	330	16	—
Ivory Coast	322463	3930	12	4210	—		10	2§	—	—	—
Liberia	111369	1400	13	1490	83	2·3	32	6	5	—	—
Mali	1240000	4650	3·8	4930	95	0·2	281	293	134	1†	—
Mauretania	1030700	1060	1·0	1130	—		76	—	—	—	—
Niger	1267000	3610	2·8	3910	79	0·6	1023	1187	678†	28†	—
Nigeria	923768	49890	54	53730	77	13·4	4953	4753	1832	203	66
Senegal	196192	3570	18	3780	—		—	—	—	—	—
Sierra Leone	71740	2400	33	2510	84	5·6	293	1697	1143	80	—
Togo	56000	1750	31	1900	88	4·1	201	332	784	83	—
Un. Rep. Cameroon	475442	5420	11	5730	—	—	2	119†	37†	3†	—
Upper Volta	274200	4960	18	5280	—	—	69	195	100	—	—
	9121887	102980	11	111080	84	1·9	—	—	—	—	—

* Based on Henderson *et al.* (1973) and Millar & Foege (1969).
† Cases resulting from importations from Nigeria, either all or in part.
‡ Cases resulting from importations from Togo, either all or in part.
§ Cases resulting from importations from Upper Volta, either all or in part.

Table 3. *Estimates of density of susceptible persons in three Asian countries in which the vaccination coverage in 1973 was about 80%*

Country	Area (km^2)	Population in 1973 (000's)	Population density (per km^2)	Vaccination* coverage (%)	No. of susceptible persons (per km^2)	Reported cases of smallpox, 1973
Pakistan	303943	66749	83	80	17	9258
India	3280483	574216	175	80	35	88114
Bangladesh	142776	71614	502	79·2	100	32711
Total	4227202	712579	169	80	34	

* Estimates based on unpublished programme records for Pakistan, India and Bangladesh.

Thus vaccination coverage of about 80% was achieved in both Bangladesh and these African countries. Despite the fact that the health-service infrastructure was better developed and the personnel better trained in Bangladesh than in the African countries, transmission continued in Bangladesh but was interrupted in Africa. In spite of the gross oversimplification involved in assuming an even distribution of population throughout each country, we suggest the difference between the density of susceptibles after immunization in Bangladesh (89/km^2) and in western and central Africa (average, 1·9/km^2) is sufficiently large to explain this difference, at least in part.

The implications of this assumption can be examined by considering the situation in the three largest countries of the Indian subcontinent (Table 3). With 80% vaccination rates in these three countries, even the lowest population density of susceptibles in 1973 (17 in Pakistan) was higher than that of the most densely populated country in western Africa in 1969 (13 in Nigeria). Even with 80% vaccination coverage, India had a higher population density of susceptibles than the total population density of any country in western or central Africa except Nigeria and Gambia, and in Bangladesh the population density of susceptibles was about three times higher than in India. It is therefore not surprising that mass vaccination failed to interrupt transmission in the Asian countries, but succeeded in Africa with the exception of Nigeria.

This impasse was overcome by replacement of the strategy of mass vaccination by a strategy of surveillance and containment. This required locating all smallpox foci in an area, vaccinating primarily susceptibles who could have been in contact with the case, and ensuring that every such person was vaccinated (Henderson, 1974). Since cases of smallpox were not infectious until the rash appeared, and were by then usually too sick to be mobile, and since endemic foci were not distributed evenly throughout a given area, this method worked very effectively. At first those in charge of national smallpox eradication programmes in some of the endemic countries did not appreciate the importance of this strategy, and mass vaccination programmes were not replaced by surveillance and containment until 1973. The results then achieved were remarkable. After energetic adoption of a policy of active searching for cases of smallpox, isolating patients and vaccinating contacts, Pakistan recorded its last case of smallpox in October 1974, India in May 1975 and Bangladesh in October 1975. The overall levels of vaccination coverage and density of susceptibles had not changed from those obtained 3 years earlier, when smallpox was still out of control.

In western and central Africa surveillance and containment measures were introduced late in 1968, at a time when the density of susceptibles in all countries except Nigeria had already been reduced to fewer than 6 persons/km^2 (Table 2). At that time many cases of smallpox in neighbouring countries were due to importations from Nigeria, where the density of susceptibles was 13/km^2. Transmission in all the countries was interrupted within a year, except in Nigeria where surveillance and containment had to be energetically pursued through 1970 before transmission was interrupted. In all countries except Nigeria, the reduction of the density of susceptibles to a low level by mass vaccination appears to have been sufficient on its own to interrupt the chains of transmission of smallpox.

DISCUSSION

Smallpox was usually transmitted by close (face-to-face) contact between a case with rash and a susceptible person. It did not spread rapidly and in endemic countries only a few villages and sections of urban areas were affected at any particular time. Observations over several years showed that the disease moved through populations in a cyclic pattern, both geographically and in time (Foege *et al.* 1975). A survey in Bolivia in 1958 demonstrated that, given the same percentage vaccination coverage, there was a higher density of people with pockmarks in densely populated than in sparsely populated regions, provided that all age groups were included to compensate for the cyclic variation (Frederiksen, 1962). In Pakistan, Thomas *et al.* (1972) showed that persistence of smallpox in rural areas depended on introductions from outside, most of which could ultimately be traced to towns. The analysis presented here shows that continuing transmission associated with areas of high population density and is also found at country-wide and regional level.

Needless to say, important factors other than the population density of a country affect the success of immunization programmes. These include the level of acceptance of immunization by the population, and population movements for religious or social reasons or because of wars or natural calamity. Within all except very small countries, there are large regional differences in population and, as Fox *et al.* (1971) have pointed out, all populations consist of subgroups with different frequencies of contact and the proportions of susceptibles within different subgroups may differ substantially. Nevertheless, the concept of the density of susceptibles at a country-wide and regional level may be a useful index in global immunization programmes for other diseases transmitted from person to person via the respiratory route.

Eradication of diseases like pertussis, poliomyelitis and measles would be much more difficult than was the case with smallpox. The frequent occurrence of subclinical or atypical infections in pertussis and poliomyelitis makes the surveillance and containment strategy less effective. In measles, the high infectivity during the prodromal stage also makes application of this strategy difficult. Thus Anderson & May (1982) suggest that an overall vaccination coverage of about 94 % (higher in densely populated cities, somewhat lower in rural communities) would be necessary to eliminate measles from Britain. Nevertheless, endemic measles has been virtually eliminated from Czechoslovakia and the USA, where health administrators have undertaken vigorous vaccination programmes. Our analysis suggests that even higher, and probably unattainable, coverage would be required in densely populated Asian countries, especially where there is great population mobility. In contrast, lower and potentially attainable vaccination coverage might suffice in sparsely populated countries. However, the risk of importation would remain, and measles vaccination would have to be maintained.

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