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Vaccination against poliomyelitis in economically underdeveloped countries

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Poliomyelitis lameness surveys in children of school age recently reported from Burma, Egypt, Ghana, and the Philippines have indicated an estimated, average annual endemic incidence of paralytic poliomyelitis similar to or higher than the overall average annual rate in the USA during the peak years in the prevaccine era. Contrary to oft-expressed dogma, high rates of paralytic poliomyelitis are occurring annually in regions with high infant mortality rates, continuing undernutrition, and absence of basic sanitary facilities. Recent data indicate that prolonged breast feeding does not impede the effectiveness of oral poliovirus vaccine (OPV). A high prevalence of nonpoliovirus enteric infections can modify, delay, and lower the frequency of seroconversion after OPV, but these effects are overcome by multiple doses. The problem of eliminating paralytic poliomyelitis from economically underdeveloped countries depends on administrative rather than immunological or epidemiological factors, although a specially concentrated effort is needed in countries where most of the cases occur during the first two years of life and where paralytic polioviruses are propagating throughout the year in a large proportion of the infant population. Under such circumstances, expanded routine infant immunization programmes, which include OPV but reach at best only 20–40% of the total infant population, who receive only one or a few doses of vaccines requiring multiple doses, cannot be expected to eliminate paralytic poliomyelitis as an important public health problem. Injections of multiple doses of quadruple vaccine (DPT + inactivated poliomyelitis vaccine) would not only greatly increase the cost of routine immunizations but would not achieve more or as much as feeding OPV at the time of the DPT injections. Mass administration of OPV each year *on 2 days of the year 2 months apart, to all children under 2, 3, or 4 years of age (depending on the epidemiological situation), without reference to the number of OPV doses they may have had before, can be expected to yield optimum results in countries with small numbers of professional health personnel and many other year-round problems.*

One of the aims of the WHO Expanded Programme on Immunization is the prevention of paralytic poliomyelitis in the developing countries. The purposes of this article are to:

1. Evaluate recent information on the current magnitude of the problem in different developing countries.

2. Review the special epidemiological and other problems connected with the prevention of paralytic poliomyelitis by vaccination in these countries and indicate why the highly effective vaccination schedules of the developed countries can at best have only a limited effectiveness in the developing countries.

3. Describe an optimum strategy involving the

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annual mass administration of oral poliomyelitis vaccine (OPV) to all children under 2, 3, or 4 years of age (depending on the epidemiological conditions in the region), without reference to previous history of vaccination.

All countries are in a sense developing countries, but my special concern here is with over 100 *economically underdeveloped* countries in Africa, Asia, and Latin America inhabited by more than 50% of the total world population with average *per capita* incomes under US $200 per annum. Hundreds of millions of these people exist on annual incomes of less than US $75 compared with incomes of over US $3000 for most of the 15% of the world's population living in Europe and North America (*1*). In these economically underdeveloped countries, shortage of food and lack of basic sanitary facilities, such as adequate water supplies, sewage disposal, and suitable housing, which are direct results of poverty, are the main causes of debility and poor health.

The association between high infant mortality rates and low *reported* incidences of poliomyelitis (*2*) led to the dogma that paralytic poliomyelitis was an important public health problem chiefly in economically developed countries, and that it could be expected to increase in various countries when their living conditions improved as reflected by infant mortality rates below 75 per 1000 live births (*3*). The economically underdeveloped countries we are considering here are predominantly in the subtropical and tropical regions of the world where polioviruses spread extensively throughout the year. In 1962, I called attention to the increasingly higher *reported* endemic and epidemic rates of paralytic poliomyelitis, limited to children under 3 years of age, during the preceding 10 years in many tropical countries in America, Africa, and Asia without improved living standards and with continuing high infant mortality rates (*4*).

CURRENT INCIDENCE OF PARALYTIC POLIOMYELITIS IN DIFFERENT ECONOMICALLY UNDERDEVELOPED COUNTRIES

Although it is well known that official reporting of paralytic poliomyelitis varies in different countries with underdeveloped health services and is at best incomplete, the *Weekly epidemiological record* periodically publishes accumulated data that provide an important insight into the problem. The total impact of paralytic poliomyelitis in a country is best measured by the average annual incidence of the disease during 5-year periods, because prior to the introduction of effective vaccination programmes years of high incidence were followed by years of low incidence and *vice versa*. Thus, during the prevaccine period of 1951–55, when poliomyelitis had its peak incidence in the USA, the average annual incidence of the *paralytic* disease was in the range of 100 per million total population (*5*); by 1971–75 this had been reduced to 3 questionable indigenous cases per 100 million total population (*6*).

The 1971–75 data for reported cases of poliomyelitis and infant mortality rates for 17 African countries (Table 1), 17 Asian countries or areas (Table 2), and 15 Middle and South American countries (Table 3) show high and low *reported* rates of poliomyelitis in the presence of very high rates of infant mortality. Some of the poliomyelitis rates were similar or close to those that were obtained in the USA during the prevaccine era of 1951–55. Although all these countries or territories have used OPV in different ways and to a varying extent, it is evident that the remarkable control achieved by Japan and tropical Hong Kong and Singapore in Asia as well as by subtropical Cuba and Puerto Rico in Middle America is

Table 1. Africa: Cases of poliomyelitis reported by some countries or areas, 1971–75. Average annual incidence per million total population for mid-1975 in relation to infant mortality[a]

Country or area	Population (millions)	Poliomyelitis (No./million)	Infant mortality[b] (No./1000)
Gabon	0.5	110	229
Sudan	18	86	141
Mali	6	72	188
Libya	2	57	130
Senegal	4	40	159
Niger	5	36	200
Malawi	5	32	148
Egypt	38	23	103
Kenya	13	22	135
Upper Volta	6	22	182
Zaire	25	22	160
Ghana	10	19	156
Zambia	5	13	157
Algeria	17	10	128
Morocco	18	9	149
Tunisia	6	8	128
Nigeria	63	6	180

[a] *Sources of data:* Mid-1975 population (rounded to nearest million) and infant mortality rates from Hansen, R. D. *The U.S. and world development*. New York, Praeger Publishers, 1976, pp. 132–141. The numbers of cases per million total population were calculated from the average annual number of cases reported for 1971–75 in the *Weekly epidemiological record* of 23 December 1977 and the mid-1975 population data.

[b] Live-born infants who died during the first year of life.

Table 2. Asia: Cases of poliomyelitis reported by some countries or areas, 1971–75. Average annual incidence per million total population in relation to infant mortality rate for mid-1975

Country or area	Population (millions)	Poliomyelitis (No./million)	Infant mortality[a] (No./1000)
Kuwait	1	83	44
Iraq	11	48	99
Malaysia	12	29	75
Sri Lanka	14	25	45
Philippines	44	20	78
Pakistan	71	15	132
Thailand	42	14	65
Iran	33	12	139
India	613	12	139
Turkey	40	11	119
Burma	31	10	126
Bangladesh	74	4	132
Afghanistan	19	3	182
Indonesia	136	0.4	125
Hong Kong	4	0.5	17
Singapore	2	0.5	20
Japan	111	0.05	26

[a] Live-born infants who died during the first year of life.

Table 3. Middle and South America: Cases of poliomyelitis reported by some countries or areas, 1971–75. Average annual incidence per million total population for mid-1975 in relation to infant mortality rate

Country or area	Population (millions)	Poliomyelitis (No./million)	Infant mortality[a] (No./1000)
Brazil	110	78	94
Nicaragua	2	34	123
El Salvador	4	21	58
Guatemala	6	20	79
Colombia	26	15	76
Ecuador	7	14	78
Honduras	3	12	115
Venezuela	12	10	50
Peru	15	9	110
Mexico	59	7	61
Argentina	25	4	60
Chile	10	1.5	71
Uruguay	3	0.3	40
Puerto Rico	3	0.3	24
Cuba	10	0.1	25

[a] Live-born infants who died during the first year of life.

related to their highly developed health services as reflected by their very low infant mortality rates. The actual incidence of paralytic poliomyelitis in most of the other countries shown in these tables remains unknown, but could be estimated by the type of clinical surveys for residual paralysis in young children that were recently reported from Burma, Egypt, Ghana, and the Philippines (*7–11*).

Estimate of average annual incidence of paralytic poliomyelitis by clinical surveys

Residual paralysis attributable to poliomyelitis early in life is sufficiently distinctive (flaccid paralysis with atrophy of affected muscles and diminished or absent deep tendon reflexes, one leg shorter or smaller than the other, no sensory loss, asymmetrical involvement, history of acute onset without progression in subsequent months or years) to permit a diagnosis with a high degree of probability. Although the methods used in the clinical surveys recently reported from Burma, Egypt, Ghana, and the Philippines were different, they all revealed an unexpectedly high prevalence of residual poliomyelitic paralysis. In each of these countries, about 90% of the paralytic episodes occurred during the first 2 or 3 years of life. The estimated average annual endemic incidence of paralytic poliomyelitis based on these surveys was, with the exception of Egypt, higher than that in the prevaccine era in the USA with its frequent epidemics, despite the fact that no corrections were made for the expected mortality specifically attributable to poliomyelitis or the relatively high mortality from other causes during the first 5 years of life (Table 4).

Ghana. The excellent studies that were carried out in Ghana will be briefly summarized because they provide a good model for comparable clinical surveys for the actual incidence of paralytic poliomyelitis in other economically underdeveloped countries. The initial report by Nicholas et al. (*7*) was based on a 1974 survey of lameness attributable to poliomyelitis in children of school age in a rural district of the country with no history of epidemics, where it was assumed that paralytic poliomyelitis was relatively rare. The total population in this 518-km² district (32–80 km north of Accra) was 60 000, the majority living in villages with a mean population of 600, each with either a primary or middle school. Prior to 1970 there was no piped water supply and only 22% had access to such water at the time of the survey in 1974. An annual census in this district provided accurate denominators

Table 4. Relationship between estimated average annual number of poliomyelitis cases based on clinical surveys for residual poliomyelitic paralysis and the number of reported cases for 1971–75

Country	Date surveyed	No. of children surveyed	Poliomyelitis cases per million per annum based on: Clinical survey: 0–4 years age group	Clinical survey: Total population	Reported cases (total population)
Ghana (Danfa rural)	1974	19 430	1400	280	
Ghana (national)	1975	74 609	1160	232	19
Burma (Rangoon)	1975	?	3800	589	10
Egypt (Alexandria)	1976	264 513 (219 082) [a]	233 (439) [a]	37 (70) [b]	23 (51) [c]
Philippines (Davao)	1976	3 000	867	145	20

[a] Number of children aged 5–9 years surveyed in 1976 and number with paralysis acquired at 0–4 years of age.

[b] Estimate for poliomyelitic residual paralysis per million total population per annum during the period of 1966–70.

[c] Average annual number of reported cases per million total population for 1966 to 1970 based on 30 million population in 1970.

for calculating epidemiological rates and the infant mortality rate was 100 per 1000 live births. School started at age 6 years and 60% of the 6–15-year old children attended school. The survey began with a questionnaire that was sent to the head teachers of 59 primary and 29 middle schools asking them to list children with lameness, defined as "not being able to walk properly or having one leg shorter or smaller than the other", in their school or village. The investigators then visited each school to check whether all lame children had been reported and also to perform muscle and neurological examinations of the lame children. These examinations revealed that in 81 (63%) of 128 lame schoolchildren lameness was attributable to poliomyelitis, the remaining cases being due to a variety of conditions, including cerebral palsy, acute hemiplegia, encephalitis, chronic osteomyelitis or arthritis, congenital defects, such as club foot or genu valgum, trauma, etc. Based on a study of 11 294 children who attended school and of 8181 children (0–15 years) who were not attending school, the prevalence of poliomyelitic lameness was found to be 7 per 1000 children of school age and the average annual incidence was estimated to be at least 280 per million total population. The "at least" is justified because the survey obviously did not include the children who died during the acute phase of poliomyelitis or of other causes during the first 5 years of life, nor did it include those without lameness but with residual paralysis not involving the lower extremities. The accumulated data also showed that about 91% of the children with poliomyelitic lameness had their acute episode during the first 2 years of life, and 96% under 5 years of age. This study also established the manner in which a teacher questionnaire could be used in postal surveys to provide a rapid means of estimating the prevalence of paralytic poliomyelitis in regions with enough primary schools.

The second study (*8*), involving a postal survey of schools throughout Ghana, showed an estimated prevalence of poliomyelitic lameness of 5.8 per 1000 children of school age and a mean annual incidence of 232 per million total population in the absence of epidemics. This incidence is only about 8% of the reported cases and more than twice as great as the 100 per million average annual rate of paralytic poliomyelitis in the USA in the prevaccine era (*5, 6*). Ofosu-Amaah et al. (*8*) drew the following justifiable and broadly relevant conclusions from their Ghana studies: "These [data] suggest that mean annual incidence rates in tropical endemic countries have always been as great, if not greater, than those experienced by temperate countries during epidemic periods in the twentieth century and that the total number of cases of paralytic poliomyelitis occurring in the world each year has been reduced by only 25% since the advent of polio vaccine. Immunisation against poliomyelitis must have a high priority in Ghana and other tropical countries where the disease is endemic."

Burma. In 1975, an *ad hoc* survey for "asymmetric flaccid paralysis without sensory loss" revealed a prevalence of residual paralysis of 19 per 1000 primary schoolchildren in the Rangoon area and an estimated "annual incidence of paralytic poliomyelitis of 5 per 1000 children in the 0–4 years of age" (*9*). Since the 0–4 age group constitutes about 15.5% of the total population, the average annual incidence of paralytic poliomyelitis can be estimated at 589 per million total population in the Rangoon area (if not for all of Burma), which is about 60 times the officially reported 10 per million total population of Burma (Tables 2 and 4) and about 6 times the rate in the USA in the prevaccine era (*5, 6*).

Egypt. "A survey of permanent paralysis due to poliomyelitis was conducted in Alexandria in July 1976, to obtain an estimate of poliomyelitis incidence, prior to conducting a national mass vaccination programme" (*10*). The procedure of this clinical survey was more elaborate than that in Ghana and Burma

since it involved a house-to-house survey of all children 10 years of age and under (a total of 524 654) by school health visitors and the staff of the Alexandria health offices. "Primary screening was performed by asking the children to walk to observe any limping, and by checking for paralysis of any of the limbs. The suspected cases detected by this method were visited by clinicians and well-trained nurses to confirm the occurrence of paralysis and to collect further information". A total of 897 children with residual paralytic poliomyelitis were found, i.e., 1710 per million children aged 10 years and under. The data on age at onset of paralysis show that 91.5% occurred during the first 3 years of life and 97.5% in the 0–4 age group. Further analysis of the data shows that among the 264 513 children in the 0–4 age group (i.e., those born in 1971–75) there was a total of 308 with residual paralysis (i.e., 1164 per million or an average annual rate of 233 per million), while among the 219 082 children in the 5–9 age group there was a total of 481 with residual paralysis (i.e., 2200 per million or an average annual rate of 439 per million), 97.5% of whom acquired the disease during the first 5 years of their life, i.e., from about 1966 to 1970. Since the 1960 census in Egypt showed that about 16% of the population was in the 0–4 age group, one can estimate on the basis of the clinical survey an average annual poliomyelitis rate of at least 37 per million total population during the 1971–75 period and 70 per million for the 1966–70 period for Alexandria, compared with reported rates of 23 and 51 per million total population in Egypt during the same two periods. These results show a smaller discrepancy between the number of reported cases and the number found by clinical survey than was seen in Ghana and Burma, and also a much lower estimated annual incidence. It is possible that the use of OPV in a proportion of the children in Alexandria and other Egyptian cities for at least 10 years prior to the 1976 survey may have decreased the actual incidence of paralytic poliomyelitis in Alexandria and other cities much more than in the rural areas, where a comparable survey might have revealed much more residual paralysis. The possible effect of vaccination in Egypt is reflected by the decline in the number of paralytic cases among those born during the period of 1971–75 compared with the number in those born in 1966–70 in the Alexandria survey as well as in the total number of officially reported cases during these two 5-year periods. Ofosu-Amaah et al. (*8*) also noted that the rates of residual paralysis in urban primary schoolchildren were lower than in rural primary schoolchildren, while the rates among children in the middle schools were the same in the urban and rural areas. They estimated that up to 20% of children in Accra may have received OPV and suggested that the more widespread use of vaccine in the urban areas could explain the observed differences. The efficiency of official reporting may also be much higher in Egypt than in Ghana and Burma.

Philippines. In 1976 in the Davao Province "slightly more than 3000 schoolchildren, age 5–10 years, were surveyed and 13 of them exhibited lameness of either [one] or both upper or lower extremities, suggestive of poliomyelitis" (*11*). On the reasonable assumption that practically all of these 13 children were paralysed during the first 5 years of life, a prevalence rate of at least 4333 per million and an average annual incidence of 867 per million children in the 0–4 age group can be assumed. In 1972, it was estimated that children aged 0–4 years constituted 16.7% of the total population in the Philippines. Accordingly, one can assume a minimum average annual incidence of at least 145 paralytic poliomyelitis cases per million total population, which is 7 times the number of officially reported cases (Tables 2 and 4).

"Lameness" surveys for estimating the magnitude of the paralytic poliomyelitis problem in urban and rural areas of economically underdeveloped countries

Since decisions on whether or not to undertake *effective* immunization programmes for the prevention of paralytic poliomyelitis in economically underdeveloped countries with many other important health problems must depend on a proper evaluation of the magnitude of poliomyelitis as a public health problem, it is important to use the simplest and most reliable procedure.

Serological surveys that some have recommended (*5*) are useless for this purpose, because while they provide an indication of the extent of infection with the polioviruses they give no information regarding the incidence of the paralytic disease. In almost all economically underdeveloped nations of the world, official reporting is unable to provide a realistic evaluation of the magnitude of the paralytic poliomyelitis problem (Tables 1–4). Properly performed clinical surveys for poliomyelitic lameness in children of school age, such as were carried out in Ghana (*7, 8*), provide the simplest procedure for estimating the magnitude of the problem in different urban and rural areas, and should be carried out in any country contemplating an effective vaccination programme. The age at onset of the paralytic cases is an adequate guide to the age groups that must receive maximum vaccine coverage.

SPECIAL EPIDEMIOLOGICAL AND OTHER PROBLEMS INFLUENCING EFFECTIVENESS OF VACCINATION WITH OPV

Consideration of the epidemiology of poliomyelitis in the economically underdeveloped countries must

take into account the fact that they are located predominantly in tropical and subtropical regions where extensive dissemination of polioviruses and other enteric viruses occurs throughout the year, and where poor conditions of sanitation and hygiene contribute to a very high rate of infection with these viruses even during the first 6 months of life (*12*). It used to be assumed that under these conditions high rates of infection with polioviruses were usually associated with low paralytic rates, except for occasional epidemics related to mass movements of populations from widely scattered villages into crowded development areas (*4*), and that higher paralytic rates could be expected chiefly in crowded urban centres. These assumptions have now been challenged by the lameness surveys among school-age children, especially those carried out in rural and urban areas in Ghana (*7, 8*). It is doubtful that Ghana will turn out to be unique in this respect, but we shall not know if this is so until comparable rural and urban surveys have been carried out in other regions of Africa, Asia, and Latin America, where vaccination has been minimal or absent.

Impediments to optimum effectiveness of OPV

Both prolonged breast-feeding and the role of other enteric viruses in preventing adequate multiplication of the oral poliovirus vaccine strains in the intestinal tract have been studied as possible impediments to the optimum effectiveness of OPV.

Role of breast-feeding. While human breast milk contains specific poliovirus antibodies, the highest concentration is present in colostrum and much less is usually present in the regular milk. Tests on 52 breast-fed and 53 bottle-fed infants who received trivalent OPV at 2, 4, and 6 months of age in suburban Philadelphia (USA) showed that 100% had developed antibodies against all 3 types in tests carried out at 7–15 months of age (*13*). No antibody was found in the regular breast milk of 8 of 12 mothers in Nigeria, and the titre in the 4 positive milks was low (*14*). Studies in Uganda (*15*) and India (*16*) also showed no effect of breast-feeding on the antibody response in infants receiving OPV at 6 weeks of age or later during the first year of life.

Role of high prevalence of enteric viruses. The cause of the lower frequency of serological response to OPV in some tropical and subtropical countries, especially the role of the high prevalence of enteric viruses, has been studied by many investigators (*4, 12, 14–21*) with divergent results and conclusions, e.g., lower seroconversion rates in Nigeria (*19*) and India (*20*) were found to be not significantly different in subjects with and without demonstrable nonpolioviruses in their intestinal tract prior to administration of OPV. Some of the divergent results may be related to the following facts:

(*a*) some of the neutralization tests fail to detect as much as 15% of antibodies that are in low titre (*22*) but are nevertheless associated with intestinal resistance to infection indicative of acquired specific immunity (*23*);

(*b*) a proportion of infants and adults have no demonstrable antibody indicative of previous infection but are nevertheless immune and have enough intestinal resistance to prevent the amount of multiplication of the orally administered vaccine viruses required for stimulating an antibody response (*23, 24*);

(*c*) under conditions of high prevalence of infections with a variety of enteric viruses, the frequency and time of development of poliovirus antibodies is influenced by the opportunity to become infected by vaccine strains excreted by other recently vaccinated children, an opportunity that readily occurs in nurseries and day-care centres or even more extensively during mass campaigns (*12*);

(*d*) the frequency of antibody response to any one of the three types of poliovirus is higher after a single dose of monovalent vaccine than after a single dose of trivalent vaccine in persons who lack immunity to any two or all 3 polioviruses, because, of the three types in the oral vaccine, type 2 virus multiplies more extensively than types 3 and 1, and the type 3 virus more than type 1 (*17*).

The capacity of concurrent infections with certain echo, coxsackie, and adenoviruses to modify or suppress the intestinal multiplication of the poliovirus vaccine strains and the antibody response to them was clearly established in detailed studies in an institution of mentally retarded children in the USA where the prevalence of enteric virus infections throughout the year is as high as in the tropics (*17*). Before attempting to evaluate the different infections with enteric viruses, it is necessary to examine the factors that have been shown to affect the results obtained in different kinds of neutralization tests.

Influence of different kinds of neutralization tests on rates of seroconversion. The neutralization tests in general use have depended either on prevention of cytopathic effect (CPE) or on the detection of metabolic inhibition, i.e., absence of acid production indicated by a change in pH; both of these tests may be conducted in either macro or micro systems. Although the amount of virus in a serum–virus mixture is constant at about 50–100 $TCID_{50}$ regardless of the volume, the actual amount of antibody added has varied as much as 10-fold, i.e., from 0.025–0.05 ml of undiluted or diluted sera in the micro tests to 0.25 ml in the macro tests. The incubation of the serum–virus mixtures has varied from 1 hour at room temperature or 30–60 minutes at 37°C to as much as 6 hours at room temperature or 37°C followed by overnight at 4°C. The length of incubation is important because

different kinds of poliovirus neutralizing antibodies are produced at different times after infection with naturally occurring or OPV polioviruses (*23, 25*). During the first weeks after infection the antibody is entirely or predominantly IgM (low-avidity), which is gradually replaced by IgG (high-avidity). Low-avidity antibody requires more time for neutralization and the neutralization is more readily reversible on dilution. In the macro CPE tests, 0.2 ml or 0.4 ml of serum–virus mixture is added to 2 ml of medium in established monolayer tissue cultures, but no appreciable dilution occurs in the metabolic inhibition or micro CPE tests, since only a small volume of cells is added to the incubated serum–virus mixtures. Using a short-incubation CPE microtest for a serological survey of several age groups in Barbados, 25% of sera were negative compared with only 10% when overnight incubation of the serum–virus mixtures was used (personal communication from Dr Dorothy M. Horstmann).

Another factor influencing antibody status or seroconversion data is the initial serum dilution tested because infection-induced immunity measured by partial or complete resistance to reinfection can be associated with very low titres of antibody (*23*). The extent to which neutralization tests using 1:8 or 1:10 initial dilutions of sera can lower the percentage of positive results is strikingly demonstrated by recent serological survey data in Italy (*22*). Using a CPE microtest (0.05-ml quantities of serum and virus incubated for 1 hour at 37°C plus 0.1 ml of cells) with initial serum dilutions of 1:2, antibody titres of 1:2 or 1:4 but <1:8 were found in 12% for type 1 poliovirus, 10% for type 2, and 15% for type 3. Moreover, even in well-nourished immune persons, the antibody level can occasionally be so low that it is demonstrable only in undiluted serum tested by CPE (*13*) or only by the pH metabolic inhibition test, more often for type 3 (*23, 26*). Evidence that antibody demonstrable only by the pH method occurs not infrequently many months after documented primary infection and is associated with documented resistance to reinfection was obtained in studies on young adult volunteers who were fed attenuated type 1 or type 3 polioviruses (*23*).

Another manifestation of intestinal resistance without serological evidence of previous infection became evident in OPV field tests in the USA in which seroconversions for all 3 types occurred in 99–100% of children aged 1 month to 9 years but in progressively lower percentages of older children and adults, the figures being as low as 71%, 87%, and 61% for types 1, 2, and 3 in persons aged 40 years and older (*27, 28*). In economically underdeveloped countries in which natural infection with polioviruses has been demonstrated in 1-month old infants (*12*), and where 30–40% of paralytic cases occur during the first year of life, it is obvious that many infants experience poliovirus infections very early in life and a proportion of them have undetectable, delayed, or poor antibody responses and yet may have sufficient intestinal resistance (*24*) to prevent the occurrence of seroconversion after feeding OPV, especially when neutralization tests are used that fail to detect different kinds of antibody or low levels of antibody.

The above observations may have a bearing on the interpretation of the low seroconversion data reported after the feeding of 10^5 $TCID_{50}$ of type 1 vaccine virus to infants aged 2–11 months living with their families in Nigeria (*14*). Antibodies were tested by the more sensitive macro pH test, beginning with a 1:4 dilution of serum. The data for all 43 infants originally negative at 1:4 showed seroconversion of 42% at 6 weeks after feeding, but the rate was much higher in the younger than in the older infants; thus it was 73% for the 11 infants aged 2–4 months, 33% for the 21 aged 5–6 months, and 27% for the 11 aged 7–11 months. An additional 8 children under 6 months of age who were counted as not converting because their titres were 1:4 both before and after vaccination possibly represented infections with delayed or low antibody responses. If this were so, at least 72% (23/32) of the infants under 6 months of age may have responded to the one dose of monovalent vaccine. A similar study with a 10 times larger dose (10^6 $TCID_{50}$) of type 1 virus was carried out in Cleveland (USA) on 60 predominantly black 3-month-old infants living with their families, who were in the lower socioeconomic group. This study showed that 93% excreted virus and 95% had developed antibody by 7 months of age using the same kind of macro pH neutralization test (*29*). Since the dose of virus and the time after vaccination when the serum was tested were different, a direct comparison is not possible, but the frequency of antibody response of the non-immune infants, especially those under 6 months of age, in Nigeria was probably higher than was actually observed 6 weeks after feeding the vaccine virus.

In a study performed in Uganda, a 10^6 $TCID_{50}$ dose of type 1 virus (comparable to that used in Cleveland), contained in a teaspoonful of tea with sugar, was given in a rural child welfare clinic to 87 infants aged 3–30 months, who were regarded as non-immune because no antibody was detected in 0.025 ml of a 1:8 dilution of serum in a micro pH test (*15*). There is reason for doubting the sensitivity of this test because only 34% of 103 children aged 24–35 months attending this clinic had antibody, compared with 73% of 30 Nigerian children aged 12–35 months whose sera were tested in a dilution of 1:4 in a macro pH test (*14*). However, by means of this probably less sensitive test 53% of the 87 non-immune Uganda infants, bled 5–6 weeks after vaccination developed antibody at 1:8 or more and 62% excreted virus. Here again, there is reason for considering the possibility

that some of the non-immune infants were actually immune with low or undetected levels of antibody, and thus excreted little or no virus, and that some of the vaccinated infants had a low, undetectable, or delayed antibody response that was not detected by the neutralization test performed at 5–6 weeks after vaccination.

For all of these reasons, the seroconversion rates reported from some tropical countries do not fully reflect the total seroconversion rates that probably occur after administration of OPV and cannot be compared with reports of 100% seroconversion rates in infants after 3 doses of trivalent vaccine in the USA, where sera that were negative at 1:4 were retested and found to be positive at 1:2 or undiluted (*13*). Thus, in the lower seroconversion results reported from India (*15, 20*) a microtitre CPE test was used, with incubation of the serum–virus mixtures for only 30 minutes at 37°C, and a starting dilution of 1:8 (*16*) or 1:10 (*20*), sera without neutralization at these dilutions being regarded as negative; and yet, after 3 doses of trivalent OPV given to 6–51 week-old infants, the seroconversion rates at 4 weeks after the last dose were 72%, 88%, and 79% for types 1, 2, and 3, respectively (*16*). I doubt whether the 100% seroconversion reported from the USA (*13*) would have been found if the sera had been tested only at beginning dilutions of 1:8 by the same procedure at 4 weeks after vaccination rather than at 7–15 months of age when delayed antibody responses are more readily detected. Delayed antibody responses in suburban Philadelphia (USA) cannot be attributed to spontaneous supervening infections as they could in tropical areas. A good example of delayed antibody response in infants in the USA is found in the observation that after feeding a large dose of virus within hours after birth only 35% of 26 infants who excreted virus had detectable antibody by the sensitive macro pH test at 3 months of age compared with 98% of 43 infants who excreted virus and were tested at one year of age (*29, 30*).

Documented influence of high prevalence of enteric viruses and their role in impeding effective use of OPV. Results of tests for the presence or absence of potentially interfering enteric viruses in children receiving OPV in different studies can be compared only when the factors influencing the frequency of positive results are taken into consideration. Thus, more enteric viruses can be found when (*a*) 10% stool suspensions rather than rectal swabs are used and (*b*) human cell lines (e.g., HEp-2, human kidney), which can detect some coxsackie A viruses, or monkey kidney cells plus suckling mice are used (*12, 15*). It is noteworthy, therefore, that even a single rectal-swab survey of over 1500 children in August 1959, just before the mass immunization campaign in Toluca, Mexico (latitude 19°N), revealed 50–70% of carriers of polioviruses together with other enteric viruses among children aged 2 months to 6 years; the tests for the viruses were made using monkey kidney cells, HEp-2 cells, and newborn mice (*12*). It is possible that a peak carrier rate approaching 100% might have been detected if 10% stool suspensions had been tested. A comparable rectal-swab survey of 397 children aged 5 months to 3 years carried out in August, 1964, just before a mass immunization campaign in Ibadan, Nigeria (latitude 7°N), revealed 44–58% of carriers when only HEp-2 cells were used for the tests (*19*). On the other hand, tests carried out on 10% stool suspensions obtained just before administration of OPV to children aged 5 months to 4 years in child welfare clinics during the period of February to May 1972 near Kampala, Uganda (latitude 1°N), yielded only 21.5% positives of 302 tested only in monkey kidney tissue cultures and 45.5% positives of 200 tested in newborn mice as well as in monkey kidney cultures treated with human erythrocyte extract (*15*).

It appears, therefore, that subtropical Toluca, Mexico (*12*) had the highest documented incidence of potentially interfering viruses just before the mass administration of a single dose of trivalent vaccine (about $10^{5.4}$ $TCID_{50}$ of each type)—at least as high an incidence as in tropical Nigeria (*19*). And yet in a specially followed group of children without detectable antibodies for one or more types of viruses (at a 1:2 dilution of serum) just before receiving vaccine, the seroconversion rates 10 weeks after vaccination were 68% for type 1, 82% for type 2, and 43% for type 3 using a macro CPE neutralization test (serum–virus mixtures incubated 4 hours at 37°C and overnight at 4°C), which may still occasionally miss antibody detectable by the macro pH test, especially for type 3. Since some of the children who failed to develop antibody excreted poliovirus during the first weeks after the vaccine, the estimated infection rate after the single dose of mass administered trivalent vaccine was 80% for type 1, 87% for type 2, and 47% for type 3. Evidence for competition among the 3 types, and for dominance of the type 2 virus over types 1 and 3, was found in the seroconversion rates in "single-negative", "double-negative", and "triple-negative" children; for type 1, seroconversion was 100% in "single-negatives", 88% in "double-negatives", and 55% in "triple-negatives"; for type 3 it was 59%, 42%, and 37%, respectively, for "single-", "double-", and "triple-negatives"; for type 2, seroconversion was in the range 80–82% in all 3 categories. It is not surprising, therefore, that a second dose of trivalent vaccine brought the total seroconversion rate up to 96% for types 1 and 2 and 72% for type 3, despite the documented high prevalence of other enteric viruses.

It seemed at the time that the postulated interfering

effect of the other enteric viruses was largely overcome by subsequent infection with circulating polioviruses, since a marked increase in the circulation of polioviruses in the community was demonstrated during the first 3 weeks after OPV administration (86% of all the children under 11 years of age in Toluca received one dose of trivalent OPV within 4 days). A subsequent study in Toluca by Ramos-Alvarez (*18*) indicated the actual relation between the presence or absence of enteric virus infections in individual children and the development of antibody after the feeding of monovalent vaccines (3 drops of vaccine dropped directly into the mouth) at 4–5-week intervals (type 1, followed by type 3, and then type 2) and 7–8 weeks after a single dose of trivalent OPV. The data, summarized in Table 5, are of special interest in several respects:

1. In the absence of detectable enteric virus infection the seroconversion rate was 95% for types 1 and 2 and 96% for type 3 when undiluted serum was tested both before and 4–5 weeks after each monovalent dose of vaccine using a long-incubation macro CPE neutralization procedure.

2. The presence of enteric virus infection at the time the monovalent doses were given reduced seroconversion by 36% for types 1 and 2 and by 46% for type 3.

3. In the group receiving the single dose of trivalent vaccine, there was a lower reduction of seroconversion by enteric virus infections—14% for type 1, 28% for type 2, and none for type 3, perhaps because the multiplication of more than one type of poliovirus in "double-" and "triple-seronegatives" more readily overpowered the interfering enteric virus.

4. The total seroconversion (i.e., without reference to enteric virus infections) was about the same after the single dose of trivalent vaccine as after the 3 doses of monovalent vaccine given seriatim. Especially surprising was the seroconversion for type 1—73% after monovalent and 77% after trivalent.

5. The total seroconversion of 77%, 84% and 50% for types 1, 2, and 3 in the absence of a mass campaign was strikingly similar to the 68%, 82%, and 43% for types 1, 2, and 3 during the mass campaign in Toluca in 1959. This raises doubts as to whether the temporary extensive circulation of the vaccine strains of

Table 5. Seroconversion in children mostly 7 months to 2 years of age without detectable antibody in undiluted serum showing its relation to the presence or absence of detectable enteric viruses prior to feeding of monovalent or single dose of trivalent oral poliomyelitis vaccine (Toluca, Mexico)[a]

Vaccine fed (1962)	Test for nonpolio enteric viruses[b]	Antibody[c] in undiluted serum after vaccination[d]					
		Type 1		Type 2		Type 3	
		No. tested	% converted	No. tested	% converted	No. tested	% converted
Monovalent $10^{5.5}$ $TCID_{50}$	Negative	39	95	43	95	29	96
	Positive	64	59	44	59	62	50
	Total	103	73[e]	87	77[e]	91	65[e]
Trivalent 1 dose Type 1 — $10^{5.7}$ $TCID_{50}$ Type 2 — $10^{5.0}$ $TCID_{50}$ Type 3 — $10^{5.4}$ $TCID_{50}$	Negative	69	83	64	97	87	49
	Positive	45	69	52	69	40	50
	Total	114	77	116	84	127	50

[a] The data in this table are derived from report of Ramos-Alvarez (*18*) and from information he transmitted by personal communication.

[b] Rectal swabs tested in human kidney cultures.

[c] Neutralization tests done by macro CPE procedure in tubes with incubation of the serum–virus mixtures for 1.5 hours at room temperature and overnight at 4 °C.

[d] 7–8 weeks after the single dose of trivalent vaccine; 4–5 weeks after each dose of monovalent vaccine.

[e] In earlier studies by Ramos-Alvarez et al. (*Boletín médico del Hospital infantil,* 1: 170, 1960) the monovalent vaccines yielded 100% seroconversion rates for each of the 3 types in children without enteric virus infections, whereas during the large-scale vaccination programmes in three Mexican cities (*32*) the total seroconversion rates varied from 72% to 89% for type 1, 74% to 87% for type 2, and 52% to 80% for type 3, indicating the variations in extent of interference in different places at different times.

Table 6. Seroconversion in 2-month-old infants receiving trivalent oral poliomyelitis vaccine[a] at 6-week intervals at well-baby clinics during winter or summer in Tel Aviv or Ashdod regions of Israel in relation to incidence of nonpoliomyelitis enteric viruses (NPV)[b]

Social group	Season	NPV[c] before 1st dose		% seroconversion[d] from < 1:10 to ⩾ 1:10 for type					
					1			2	3
		No. tested	% positive	No. tested	1 dose	2 doses	3 doses	3 doses	3 doses
Mothers had 12 or more years of school	Winter	51	2	28	81	86	100	100	100
	Summer	51	23	27	78	86	96	100	93
Mothers had < 12 years of school	Winter	66	9	38	67	92	100	100	100
	Summer	58	33	28	64	81	86	95	82

[a] Type 1: 10^6 $TCID_{50}$; type 2: 10^5 $TCID_{50}$; type 3: $10^{5.5}$ $TCID_{50}$.

[b] The data in this table are derived from the report of Swartz et al. (*21*).

[c] 10% suspension of stools, not rectal swabs, inoculated into 3 monkey kidney tissue culture tubes.

[d] Blood obtained on paper discs 6 weeks after the first and second doses and 8 weeks after the third dose. A macro CPE neutralization test was used in which the serum–virus mixtures were incubated for 4 hours at 37°C and overnight at 4°C before 0.2-ml amounts were added to the tissue culture tubes.

poliovirus in the community played a significant, if any, role in overcoming the high prevalence of enteric virus infections.

Several years later a WHO collaborative study in subtropical Israel (latitude 32°N) tested the impact of the higher rate of enteric virus infections during the summer, especially in lower socioeconomic groups, on the antibody response of 2-month-old infants to the routine administration of trivalent OPV at 6-week intervals (*21*). The pertinent data, summarized in Table 6, reveal the following findings of special interest:

1. When the same procedure of testing 10% stool suspensions only in monkey kidney tissue cultures was used, the isolation rate of nonpolioviruses from infants living at home in the higher socioeconomic group in Israel during the summer was as high (23%) as in tropical rural Uganda (*15*). In this higher socioeconomic group in Israel there was the same high rate of seroconversion for type 1 virus 6 weeks after the first dose of trivalent OPV during the summer (78%) as during the winter (81%), when the enteric virus infection rate was only 2%. This high type 1 conversion rate was remarkably similar to the 77% after one dose of trivalent OPV obtained by Ramos-Alvarez in Toluca (*18*), despite the fact that the initial dilution of serum tested was 1:10 in Israel and undiluted in Mexico. It is possible that this higher seroconversion at serum dilutions of 1:10 in the higher—but not in the lower—socioeconomic group in Israel was due in part (*a*) to the fact that the serum–virus mixtures in Israel were incubated for 4 hours at 37°C compared with only 1.5 hours at room temperature in Mexico prior to overnight incubation at 4°C, and (*b*) to the fact that very few, if any, of the 2-month-old infants in the higher socioeconomic group in Israel with antibody titres of <10 prior to vaccination had experienced poliovirus infections.

2. The type 1 antibody response after the first dose of trivalent OPV in the infants from families in the lower socioeconomic group was somewhat lower both in winter and summer, without reference to the difference in the prevalence of enteric virus infections. This lack of significant relationship to enteric virus infections is particularly striking when the 67% winter seroconversion rate in the lower socioeconomic group infants with 9% of enteric virus infections is compared with the 78% summer seroconversion rate in the higher socioeconomic group infants with 23% of enteric virus infections.

The unusually low type 1 antibody responses of 22% and 30% in tropical Nigeria without reference to detectable enteric virus infections may, in part at least, be related to the manner in which the different types of OPV were administered and to the time after administration when the blood was tested for antibody (*19*). The pertinent data, summarized in Table 7, show that type 2 monovalent vaccine was given first in a brief mass immunization campaign to a large proportion of the children under 3 years of age followed by a mixture of type 1 and 3 vaccines 4 weeks later. While the 66% type 2 seroconversion rate in the children with demon-

Table 7. Seroconversion in children under 3 years of age receiving first $10^{5.3}$ $TCID_{50}$ of type 2 OPV and 4 weeks later a mixture of types 1 and 3, $10^{5.3}$ $TCID_{50}$ of each, during a mass vaccination campaign in Ibadan, Nigeria, in relation to the presence or absence of detectable nonpoliomyelitis enteric viruses (NPV) prior to feeding of each dose[a]

		Seroconversion[b] from < 1:4 to ⩾ 1:4 for indicated type					
		NPV test[c] negative		NPV test positive		Total	
Vaccine fed	Type	No. tested	% converted	No. tested	% converted	No. tested	% converted
Type 2 ($10^{5.3}$ $TCID_{50}$)	2	110	63	135	66	245	64
Types 1 + 3 ($10^{5.3}$ $TCID_{50}$ of each)	1	115	30	67	22	182	27
	3	93	46	66	47	159	47

[a] The data in this table are derived from report of Poliomyelitis Commission of the Western Region Ministry of Health, Nigeria (*19*).

[b] Blood was obtained before the first dose and 4 weeks after the second dose. Neutralization tests done by macro pH method.

[c] Rectal swabs were obtained before the first and second doses of vaccine and were tested in HEp-2 cell cultures in roller tubes.

strable enteric virus infections is comparable to the 59% seroconversion rate after monovalent type 2 vaccine in the Mexican (Toluca) children with demonstrable enteric virus infections, the 63% type 2 seroconversion rate in the Nigerian children without demonstrable enteric virus infections is very much lower than the 95% in the comparable group of Mexican children (see Table 5). The exceptionally low type 1 seroconversion rate is probably largely related to the fact that feeding of this type 1 vaccine strain in a mixture with type 3, as well as its administration only 4 weeks after the dominant type 2 virus (which in many children still multiplies extensively at 4 weeks) are two factors that have been shown to diminish the implantation of the type 1 virus (*17*). Moreover, under these conditions the antibody response is more likely to be delayed beyond 4 weeks, especially in very young children whose immune response may be diminished by protein undernutrition. It is noteworthy that there were indications of a good epidemiological effect in terminating the predominantly type 1 epidemic that was in progress in Ibadan, Nigeria, at the time the mass vaccination was begun (*19*).

Other factors impeding elimination of paralytic poliomyelitis from economically underdeveloped countries by OPV. The preceding analysis has shown that a high prevalence of enteric virus infections by itself accounts for only a partial reduction, and in some studies no demonstrable reduction (*19, 20*), in the antibody response to OPV. Even when one takes into account the methodological and other factors that may account for lower seroconversion rates, such as were encountered in seronegative older children and adults in the USA (*27, 28*) or in older infants in Nigeria after feeding monovalent vaccine (*14, 19*), there is still a somewhat lower seroconversion rate in infants among economically underdeveloped populations that remains unaccounted for.

In any case, whatever may be the actual extent of somewhat lower seroconversion rates in economically underdeveloped populations it is overcome by the administration of multiple doses of OPV, and when used with regularity on a sufficiently large scale this regime has proved highly effective in eliminating paralytic poliomyelitis from subtropical and tropical countries and areas (e.g., Cuba, Puerto Rico, Panama, Singapore, Hong Kong). It may be concluded, therefore, that the most important factor impeding the elimination of paralytic poliomyelitis from economically underdeveloped countries is programme administration.

MASS VACCINATION CAMPAIGNS IN ECONOMICALLY DEVELOPED AND UNDERDEVELOPED COUNTRIES

In economically developed countries in temperate climates, a single mass OPV campaign covering 70% or more of the most susceptible population, followed by immunization of a majority of the newborn children during the first months of life, has brought about an immediate and lasting elimination of all or almost all paralytic poliomyelitis caused by the polioviruses, not only in the vaccinated but also in the unvaccinated (*6, 31*). Czechoslovakia, among the first countries to carry out such a programme in 1960, has had no indigenous cases of poliovirus-caused paralytic poliomyelitis since then. Moreover, a 1976 serological survey on 3022 persons in the Czech Socialist Republic showed almost 100% immunity in all persons aged 2 years and over, indicating a persistence of antibodies for at least 14 years without booster doses of vaccine beyond the first 18 months of life (personal communi-

cation from Professor Vilém Skovránek, Chief Epidemiologist, Ministry of Health, Czech Socialist Republic). In the USA comparable results have been achieved somewhat more slowly, despite extensive importation of paralytic polioviruses and a much lower percentage of preschool children with multiple doses of OPV (*6*). In temperate climates, during periods of low dissemination of polioviruses, initial mass campaigns carried out within a very short time quickly break the chain of transmission of the paralytic polioviruses, provided the percentage of the susceptible population receiving the vaccine is at least 70%. In subtropical countries, vaccination of 50% of the susceptible children has failed to prevent the continuing occurrence of paralytic poliomyelitis in the unvaccinated (*32*). Although there have been dramatic decreases in numbers of paralytic cases following well-executed mass campaigns in subtropical and tropical countries, it was found in Rio de Janeiro and São Paulo, Brazil, that even when about 90% of the susceptible children received two doses of trivalent vaccine the effect was temporary. Failure to vaccinate more than a small proportion of the children born after the mass campaigns and the continuous immigration of unvaccinated children from other areas with high prevalence of polioviruses contributed to the continued subsequent occurrence of large numbers of paralytic cases, predominantly in the unvaccinated.

Although many subtropical and tropical countries have had sporadic, regional well-executed mass campaigns, to my knowledge Cuba is the only country that has had an annual, national, mass programme since 1962 (*33*) and has had no indigenous poliovirus-caused paralytic poliomyelitis during the subsequent 16 years. Through the courtesy of the Ministry of Public Health, I visited Cuba in December 1967, and learned at first hand about the excellent and unusual organization of the programme and could survey the various childhood neurological conditions that had been admitted to the hospitals since 1962. In the Cuban programme, one dose of trivalent OPV has been given nationwide on each of two Sundays in January and March. The overall planning was centralized in the Ministry of Public Health while the organization responsible for the actual administration of the vaccine was decentralized in progressively smaller regional units, in which maximum use was made of unpaid non-professional personnel, an arrangement that is possible with an orally but not a parenterally administered vaccine.

PROPOSED PROCEDURE FOR THE ELIMINATION OF PARALYTIC POLIOMYELITIS IN ECONOMICALLY UNDERDEVELOPED COUNTRIES

Expanded programmes of immunization in which OPV is used concurrently with DPT and other immunizations can have only a limited impact on the elimination of poliomyelitis in economically underdeveloped countries because only a small proportion of infants are brought to well-baby clinics or are visited by mobile teams. No vaccine, live or killed, even if it were 100% effective in a single dose, could be expected to have more than a limited effect in communities in which almost 40% of the paralytic cases occur during the first year of life and only a small proportion of infants receive routine immunizations during that period.

The decision as to whether or not to undertake a special programme for the maximum possible elimination of paralytic poliomyelitis must be taken by individual countries, after the real magnitude of the problem in relation to the many other urgent health problems has been determined by lameness surveys of the type discussed earlier in this article. If the decision is reached that a special poliomyelitis elimination programme is warranted, optimum results can be expected only when poliomyelitis vaccination is organized as a public health activity that is separate from or additional to the year-round routine immunizations. In my judgement, the programme of choice is based on an annual OPV mass campaign for all children under 2, 3, or 4 years of age (depending on the epidemiological findings in the region) *regardless of the number of OPV doses they may have had before,* the vaccine being administered on 2 days of the year, 2 months apart.

The vaccine effectiveness and public health advantages of a national, well-planned, highly decentralized annual mass immunization programme of this kind are as follows:

1. The simultaneous feeding of the vaccine viruses to the largest possible number of children in the shortest possible time gives rise to a more extensive natural dissemination of excreted vaccine polioviruses (*12*) than occurs during an epidemic of naturally occurring virulent polioviruses. The vaccine strains thus have an opportunity rapidly to displace the large number of naturally occurring virulent polioviruses in a community, a result that cannot be achieved by the year-round administration of OPV to only small numbers of children at any one time. Moreover, the large number of partly or completely resistant intestinal tracts that are thus rapidly created provides an increased barrier to the subsequent spread of naturally occurring virulent polioviruses that may remain or be reintroduced in the community.

2. The massive dissemination of vaccine strains excreted by the vaccinated children also serves to infect and immunize children who for one reason or another are missed during the programme or who may have had an interfering non-poliomyelitis enteric virus

infection at the time they received the vaccine.

3. The interval of at least 2 months before the second dose of vaccine allows more time for prolonged multiplication of the vaccine viruses. This is essential for maximum intestinal resistance to reinfection by a poliovirus of the same type, and, when trivalent vaccine is the first dose, also for the ultimate cessation of multiplication of the dominant type 2 vaccine virus, which can interfere with subsequent implantation of type 1 or 3.

4. The annual vaccination of *all* children in the most susceptible age group, without reference to previous vaccination history, serves a dual purpose: (*a*) to reach the previously unvaccinated, i.e., those born since the previous annual campaign and those who for one reason or another were missed in previous campaigns or may have been refractory to the vaccine, and (*b*) to reinforce the intestinal resistance in those in whom the vaccine strains may have multiplied for too short a time on previous occasions.

5. The extensive public information programme immediately before each mass vaccination day makes it possible to reach larger numbers of children.

6. Limiting each public vaccination campaign to a single day helps to overcome the all too prevalent tendency to postpone until "tomorrow" actions that require some extra effort.

7. The public health responsibility for poliomyelitis vaccination is discharged during a brief period of time each year with the help of large numbers of unskilled and unpaid volunteers, leaving more time for the unavoidably limited number of professional personnel to attend to other urgent public health activities during the remainder of the year.

The question of which age groups should be included in such annual campaigns and the question of whether to include rural areas can best be answered either by determining the age at which 90% of the total reported cases during the preceding 5 years have occurred and where the cases have been occurring, or better by determining the age of onset in 90% of the cases of poliomyelitic paralysis discovered in lameness surveys of school-age children in urban and rural areas. I believe that the former custom of recommending that the starting age for vaccination should be about 2 months because younger infants may respond less well—owing to the immaturity of their immune mechanisms or other reasons—is not relevant for annual mass campaigns in which all children continue to receive vaccine twice a year as long as they remain in the most susceptible age group. For the same reason, it is unnecessary to encumber the annual mass campaigns with time-consuming bookkeeping or vaccination records of individual children. A report on the design of various immunization programmes in the developing countries (*34*) contained the following pertinent statement: "Experience has shown that most immunization programs, at their inception, have endeavored to keep far too complex and elaborate records, which almost inevitably have had to be abandoned as serving no useful purpose." A simple count of the total number vaccinated in each age group to match against the estimated or actual total number in the age group in the region can suffice to provide a needed index of the effectiveness of the campaign. Except for the basic principle of centralized national planning and decentralized regional and local implementation, most of the organizational details, such as the location and staffing of the maximum possible number of vaccination centres within walking distance of the parents, the training and supervision of the large numbers of unpaid, unskilled volunteers, the nature of the information programme, etc. must necessarily be different, not only in different countries but also in different regions of the same country.

Although trivalent OPV has previously been recommended for both the first and the second doses in such mass campaigns, it may be advisable to use only type 1 vaccine for the first dose because over the years type 1 poliovirus is responsible for 85% or more of the paralytic cases. In type 1 antibody-negative children without concurrent non-poliomyelitis enteric virus infections, this procedure is known to provide the maximum opportunity for intestinal multiplication of the most important type 1 strain without interference from the type 2 and type 3 poliovirus vaccine strains. Where the cost of the vaccine is an important factor, it is obvious that monovalent vaccine would cost less than trivalent vaccine and $10^{5.3}$ $TCID_{50}$ (which could be adequate for annual mass campaigns) would cost only one-fifth of 10^{6} $TCID_{50}$, the dose that is customarily included in trivalent vaccines prepared for the developing countries.

Until poliomyelitis is largely eliminated by annual mass immunization programmes, it would, in my judgement, be desirable to vaccinate newborn children whenever and wherever they can be reached, with the understanding that they must nevertheless also participate in the annual mass campaigns. The immediate newborn period, when enteric viral infections are rare, is a particularly opportune time for feeding OPV because infants delivered in hospitals could receive the vaccine shortly before discharge and midwives could give the vaccine to infants that they deliver. The practice of giving OPV to the newborn has been in use in some countries for many years, e.g., in Mexico (personal communication from Dr M. Ramos-Alvarez, Hospital Infantil de México, México, D.F.) and in the Republic of Panama (personal communication from Dr Carlos Brandariz Zuñiga, Dirección de Epidemiologia del Ministerio de Salud, Panamá 1, Panamá). In my judgement, the use of

10^6 $TCID_{50}$ of monovalent type 1 OPV can be expected to give good results in the newborn. Another place where newborn children can be reached, usually during the first two weeks of life, is in the offices where they must be brought for registration, and in some regions of Mexico, OPV has been administered also at this time. The practice of giving OPV to infants along with their routine immunizations should likewise be continued, with the provision that parents should be informed that the children must nevertheless also participate in the annual mass vaccination campaigns against poliomyelitis. The suggestion that inactivated poliomyelitis vaccine be combined with diphtheria-pertussis-tetanus vaccine and given as a single injection of "quadruple" vaccine (*35*) would not only markedly increase the cost of routine immunizations but would also not achieve more than, or as much as, the separate, simultaneous feeding of the much less expensive OPV.

ANTIEPIDEMIC MEASURES

Countries that for one reason or another will continue to have inadequate poliomyelitis immunization programmes, or none at all, can expect occasional epidemics. The best antiepidemic results have been obtained when homotypic rather than trivalent vaccine was administered in mass campaigns of brief duration (*4, 27, 36, 37*).

In 1967, I suggested (*31*) that the WHO regional offices could assist needy countries with the following poliomyelitis antiepidemic measures:

1. Develop a system for prompt notification of an unusual increase in cases.
2. Provide facilities for rapid isolation and typing of viruses in the nearest WHO Regional Virus Laboratory, so that whenever possible the appropriate monovalent vaccine can be used. With proper planning this could be achieved by the time an outbreak is confirmed and an organization for rapid mass vaccination is developed and rehearsed.
3. A cadre of consultants familiar with the procedures for identifying an incipient poliomyelitis epidemic and with the tactics and logistics of organizing a rapid mass campaign should be available to WHO regional offices for emergency assistance to local health authorities.
4. WHO should have emergency stocks of monovalent and trivalent OPV that could be made available rapidly and without cost to needy countries.

OCCASIONAL PARALYTIC ILLNESS IN WELL-VACCINATED CHILDREN

Before the advent of OPV it was established that a small proportion of cases of paralytic poliomyelitis is not caused by any of the 3 types of poliovirus (*38*) and therefore cannot be expected to disappear after the most successful poliomyelitis immunization campaigns. The Guillain-Barré syndrome and other paralytic syndromes not caused by poliovirus appear to be more frequent in children in the subtropical and tropical regions than in temperate climates (*39*). In postmortem studies on 57 Mexican children with acute lower motor neuron paralytic disease, Ramos-Alvarez et al. (*40*) found the neuropathological changes of poliomyelitis in only 32. Among the remaining 25 without inflammatory changes in the central nervous system, 10 exhibited the neuropathological changes of the Guillain-Barré syndrome and 15 presented hitherto unrecognized neuropathological syndromes—8 showed widespread and extensive cytoplasmic neuronopathy and 7 nuclear neuronopathy. Although 7 of 9 patients with the Guillain-Barré syndrome showed albuminocytological dissociation during the first week after onset of paralysis, only 1 of the 14 patients with the other non-inflammatory neuropathological syndromes tested during the first week after onset of paralysis had a slightly elevated concentration of protein in the cerebrospinal fluid. It is noteworthy that while no virus was found in the spinal cords of 17 of the patients with the non-inflammatory lower motor neuron paralytic syndromes, in one of these patients (a 2-year old child with nuclear neuronopathy who died 3 days after onset of paralysis) type 1 poliovirus was recovered in repeated tests on suspensions of colon, jejunum, ileum, and mesenteric lymph nodes. This important finding, as well as the presence of various enteroviruses in the stools of 7 other paralysed children without neuropathological evidence of poliomyelitis, emphasizes the fact that the isolation of a poliovirus or other enterovirus from the intestinal tract cannot by itself prove an etiological role of the virus in the paralytic condition. It is also noteworthy that in 23 of the 25 children with non-inflammatory paralytic syndromes, there was no fever at onset of paralysis and none exhibited nuchal or spinal rigidity. The significance of this finding is further emphasized by the fact that among patients admitted to the Children's Hospital of Mexico City with acute onset of flaccid paralysis, polioviruses were isolated from 82% of 144 children with fever and from none of 74 children without fever at onset of paralysis (*41*). The case-fatality rate in 120 paralysed children from whom polioviruses were recovered was 12% and in 71 from whom no polioviruses were recovered it was 25%. Clinical follow-up of patients in the USA from whom no polioviruses were recovered showed complete recovery in 3 months to 1 year in most and slight to severe residual paralysis in some 2 years later (*38*). A critical evaluation of available data shows that a diagnosis of paralytic poliomyelitis cannot properly be made in the absence of pleocytosis during the first week after onset of paralysis, especially when there is

neither fever nor nuchal or spinal rigidity at the first appearance of paralysis.

Paralytic conditions, associated with pleocytosis, that are occasionally confused with poliovirus-caused paralytic poliomyelitis include transverse myelitis and postinfectious myelitis when the lesions are predominantly in the grey matter. Atypical forms of encephalomyelitis caused by arboviruses, mumps, or herpesviruses are occasionally mistakenly diagnosed as bulbar poliomyelitis. Of interest in this respect is a recent report from Chile (*42*), where OPV has been used with considerable success for many years, concerning the results of an investigation of 10 suspected cases of poliomyelitis that were reported in children under 15 years of age in 1977. The final diagnosis was Guillain-Barré syndrome in 4 cases and encephalitis or meningoencephalitis in 5. In one case (an infant with paresis and paralysis of the legs, which developed 4 days after initial symptoms of fever, sore throat, and general discomfort) the laboratory investigations did not confirm the clinical diagnosis of poliomyelitis. No confirmed cases of poliomyelitis were reported in Chile in 1976 and 1977.

RÉSUMÉ

VACCINATION CONTRE LA POLIOMYÉLITE DANS LES PAYS OÙ PERSISTE LE SOUS-DÉVELOPPEMENT ÉCONOMIQUE

La poliomyélite pose, dans les pays où persiste le sous-développement économique, un problème de santé publique dont les statistiques ou rapports officiels ne reflètent pas l'ampleur réelle et qui justifierait l'application de mesures spéciales. Les enquêtes cliniques faites récemment en Birmanie, en Egypte, au Ghana et aux Philippines pour recenser les cas de paralysie chez les enfants d'âge scolaire ont montré que l'incidence moyenne annuelle peut être très élevée dans les zones rurales aussi bien qu'urbaines, même en l'absence d'épidémies. Il serait extrêmement souhaitable que des enquêtes de ce genre soient menées dans de nombreux autres pays. Une proportion de cas paralytiques plus élevée que les taux enregistrés aux Etats-Unis pendant l'époque de forte incidence antérieure à la vaccination a été constatée dans des pays à forte mortalité infantile, où la pauvreté chronique se traduit par la sous-nutrition ou la malnutrition et l'absence d'installations sanitaires élémentaires. L'examen des rapports faisant état d'une fréquence réduite de la réponse immunitaire à une ou deux doses de vaccin buccal chez les nourrissons des pays économiquement sous-développés des régions tropicales et sub-tropicales a révélé le rôle qu'ont joué, à cet égard, d'une part l'emploi d'épreuves de neutralisation peu sensibles et, d'autre part, un phénomène semblable à celui qui est à l'origine des faibles taux de séro-neutralisation obtenus au début des années 1960 chez des enfants plus âgés et des adultes aux Etats-Unis. Il semble que ce phénomène soit dû au fait que, chez certains individus, l'immunité consécutive à une infection par des poliovirus peut être liée à une résistance intestinale à la réinfection qui se manifeste en dépit d'un taux d'anticorps très faible, voire non décelable. Si l'épreuve de neutralisation est effectuée avec des sérums fortement dilués (1:8 ou 1:10) et qu'en outre le mélange sérum/virus n'est pas soumis à une incubation à 37°C pendant 4 heures puis à 4°C pendant une nuit, il n'est pas étonnant qu'un résultat négatif soit obtenu pour des personnes déjà capables de résister à l'infection avant l'administration du vaccin buccal ou chez qui la réponse en anticorps est faible.

Il est hors de doute qu'une forte prévalence d'infections intestinales concomitantes dues à d'autres virus que ceux de la poliomyélite peut modifier, retarder et abaisser la réponse en anticorps suscitée par une ou deux doses de vaccin buccal, même si, dans certaines enquêtes sur le terrain, le fait n'a pas été décelé. De toute façon, il a été établi que cet obstacle à une efficacité maximale de la vaccination pour certains nourrissons dans les régions tropicales disparaît dès lors qu'on recourt à l'administration de doses multiples. L'allaitement au sein prolongé, souvent incriminé comme autre facteur pouvant compromettre l'efficacité du vaccin, n'a pas eu d'effet de cet ordre aux Etats-Unis ou sous les tropiques pour autant qu'on ait procédé à la vaccination de routine des enfants.

Il apparaît donc que le problème de l'élimination de la poliomyélite dans les pays où tarde le décollage économique est essentiellement d'ordre administratif et que les difficultés ne proviennent pas de facteurs immunologiques ou épidémiologiques. Il est également évident qu'un effort très spécial doit être fait dans les pays où la majorité des cas se déclarent au cours des deux premières années de la vie et où les virus à l'origine de la poliomyélite paralysante se propagent à longueur d'année dans l'intestin d'une grande partie de la population infantile. Mais l'application, toute désirable qu'elle soit, de programmes élargis de vaccination incluant l'administration du vaccin buccal antipoliomyélite ne permet, dans le meilleur des cas, d'atteindre que 20–40% de l'ensemble de la population infantile, qui ne reçoivent qu'une ou deux doses de ce vaccin alors que l'immunisation efficace en requiert davantage. On ne peut donc s'attendre, dans ces conditions, à ce que les programmes protègent également les enfants non vaccinés ou mal vaccinés de la communauté. D'un autre côté, l'administration de doses multiples de vaccin "quadruple" (DTC + vaccin antipoliomyélite inactivé), qui entraînerait une forte augmentation du coût de la vaccination systématique, ne donnerait sans doute pas de résultats meilleurs ou même aussi satisfaisants que la prise de vaccin buccal antipoliomyélite à l'occasion des injections du vaccin triple DTC.

Dans les pays où l'on doit faire face en permanence à de nombreux problèmes avec des effectifs restreints de personnel de santé qualifié, la meilleure solution—et la plus efficace—serait donc d'organiser des campagnes de masse annuelles de vaccination qui se dérouleraient en deux temps (soit chaque année deux jours séparés par un intervalle de deux mois) et qui permettraient d'administrer le vaccin buccal à tous les enfants de moins de 2, 3 ou 4 ans—selon le tableau épidémiologique dans la région—sans se préoccuper

du nombre de doses qu'ils peuvent avoir reçu auparavant. A titre d'exemple, l'auteur décrit une campagne de masse organisée au niveau national et exécutée aux niveaux régional et local en faisant largement appel à des volontaires sans qualification mais bien préparés à la tâche qui devait leur échoir. L'auteur rappelle également les grandes lignes d'un programme OMS de lutte contre les épidémies qu'il avait précédemment suggéré: un tel programme permettrait à l'Organisation d'aider les pays où des poussées éclateraient encore pour une raison ou l'autre.

L'auteur évoque enfin certaines affections paralysantes pouvant survenir chez des enfants correctement vaccinés. Ces affections ressemblent à la poliomyélite mais ne sont pas causées par des poliovirus. Les constatations faites dans des cas de ce type (syndrome de Guillain-Barré notamment) sont brièvement décrites.

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