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SPECIAL ARTICLE

Poliomyelitis: Eradication in sight

INTRODUCTION

Great strides have been made towards the control of poliomyelitis since the introduction of the two poliovaccines – inactivated poliovirus vaccine (IPV), which was licensed in the United States in 1954, and live attenuated oral poliovaccine (OPV), in 1961. Today a large majority of physicians and other health-care workers in industrialized countries never see a patient with paralytic poliomyelitis. Unfortunately, this is far from the situation in many developing countries, particularly in tropical and subtropical climates, where hundreds of thousands of children still become paralysed victims, year in and year out.

It is rare for a serious disease to be controlled so quickly and dramatically as was poliomyelitis in many of the developed countries. In 1955 a total of more than 76000 cases of poliomyelitis were reported from the United States, Canada, Australia, New Zealand and 23 European countries plus the Soviet Union. By 1967 the number recorded in these same countries fell to 1013 cases – a reduction of 99%. Numbers of poliomyelitis cases have continued to fall; in industrialized countries, poliomyelitis is now a rare disease.

In the United States, before the inactivated virus vaccine became available, there were 10000–21000 paralytic cases per year, and the annual rates were between 5 and 10 per 100000 population [1]. Cases were far fewer after the inactivated vaccine came into use. In some years incidence rates fell tenfold, to as low as 0·5 per 100000 population. Nevertheless, this meant that significant numbers of cases were still occurring; in 1960 there were more than 2500 paralytic patients, and some of these cases were in fully vaccinated individuals. In a study of several thousand paralytic cases, 17% were in children who had received three injections of the inactivated vaccine. Some of the disappointing results were due to potency problems which have since been corrected, particularly in the few small countries that have used inactivated virus vaccines solely through most of the vaccine era.

After live attenuated vaccine was introduced and came into widespread use in the United States, the numbers of cases were reduced precipitously. In the 1980s the annual number of cases was less than 10 per year. This translates into case rates as low as 0·001 per 100000 population [1, 2].

For many years the United States has relied almost completely on live poliovirus vaccine. It appears that there is no longer any endogenous reservoir of wild polioviruses within the country, and that a true break in the chain of infection has been achieved. Wild strains may continue to be introduced, but even such imported cases are sporadic and almost never result in secondary cases. The use of live poliovirus vaccine has achieved this result by establishing widespread intestinal resistance to the wild virus, thus reducing the pool of susceptible

individuals to a level below that required for perpetuation of the virus in nature. Many other countries with extensive and continuing live vaccine programmes are also reporting virtually no cases and few if any poliovirus isolates other than vaccine-like strains [3–5].

In Sweden, Finland and the Netherlands, where the inactivated poliovaccines have been used almost exclusively, good results also have been obtained [1]. These are countries with relatively small populations (a total of 28 million persons), culturally homogeneous and socially advanced. They have excellent public health services, and inactivated virus vaccine has been administered in intensive and regularly maintained immunization programmes, achieving vaccine coverage and boosting among children that has approached 100%.

However, there can be important deficiencies in protection, even in well-vaccinated countries. This vulnerability was demonstrated in 1978 and 1979 by outbreaks of poliomyelitis among members of closely knit interconnected religious groups who refused vaccine on religious grounds. Imported into the Netherlands from the Middle East, a virulent type 1 strain spread to related religious groups in Canada and the United States. In none of the countries involved did paralytic cases occur beyond the unvaccinated members of these interconnected religious communities. However, subclinical infections with the epidemic virus did occur in significant numbers of children who had been vaccinated with IPV. In nursery and primary schools in some of the affected Netherlands communities 71% of the unvaccinated children excreted the poliovirus and 24% of those vaccinated with IPV were also observed to be excreting the epidemic virus [6].

In Finland, where the use of standard IPV had produced 20 years of freedom from poliomyelitis, 10 cases occurred between August 1984 and January 1985. On the basis of virus isolations from healthy individuals and from sewage, it was estimated that at least 100000 persons in the general population were infected. The 1984 epidemic strain was a wild-type-3 variant that differed in both immunological and molecular properties from the type-3 vaccine strains [7]. Analysis of sera collected before the outbreak indicated that neutralizing antibodies against new-type-3 isolates were much less prevalent in the population than antibodies to the type-3 strain (Saukett) used in the killed vaccine.

The precipitating factor in the outbreak was judged to be the appearance of a wild strain of poliovirus type 3 that was sufficiently aberrant to break through the type-3 immunity of the population. However, immunization with the new enhanced IPV or with standard OPV induced high titres of serum antibody against all known type-3 strains, including the Finnish epidemic type-3 strain. Thus, although intratypic differences among strains from various parts of the world have indeed been demonstrated for many years, the major neutralizing antigen of each poliovirus serotype has proved to be remarkably stable.

The study of the 1988 outbreak in Israel has also yielded pertinent information [8]. Most cases occurred in young adults who had been given OPV during the first year of life but who had not received any booster doses. This suggested an age-related deficit in immunity against the 1988 wild virus.

Neutralizing antibody assays on sera collected from healthy persons under 30 years of age in Israel prior to the outbreak indicated high antibody levels against the Sabin strains in OPV, but very low levels against the wild virus. A booster dose

of OPV given in 1988 brought the antibodies to high levels against both the Sabin and the wild strains [8]. Non-vaccinated adults over 30 years of age who had lived through the prevaccine period and who had been exposed to wild viruses as children were found to have high levels of antibody to both Sabin strains and wild virus in their pre-epidemic sera. After receiving a single dose of OPV in 1988 they also responded with an increase in antibody titre. These findings indicate that a gap in immunity against a wild polio may occur in persons who are vaccinated with OPV in the first months of life and who are not given booster vaccine or who are not exposed to wild virus in the early years after vaccination when antibody levels are highest. This gap in immunity against wild poliovirus strains can be overcome by a booster dose of OPV later in life.

While cases have almost vanished from the industrialized world, polio continues to be an urgent problem, particularly in developing nations in tropical and subtropical zones. The WHO estimates that well over 200000 cases of paralytic poliomyelitis occur each year. In India alone, more than 100000 cases were reported annually throughout the 1980s. Of these cases, 98% were in children under 5 years of age; 42% of the patients were infants in the first year of life. As has been shown by surveys of lameness indicative of past paralytic poliomyelitis, in many developing countries the reported cases may represent no more than 10% of the actual number of cases that occurred [9, 10].

WORLD TRENDS IN THE CONTROL OF POLIOMYELITIS

The worldwide magnitude of the problems that remain unresolved, as well as some encouraging trends, are illustrated in Fig. 1 and in Tables 1 and 2. The figure depicts on a world map the incidence of paralytic poliomyelitis reported to the WHO for 1985 from various areas. The tables give examples of the reported numbers of poliomyelitis cases since 1951 in two regions of the world, and compares countries which had controlled the disease by 1985 with countries in which control of poliomyelitis was incomplete at that time [9–11].

Table 1 is based on data from representative countries of the Western Pacific Region [9–11]. The top line of the table shows data from countries that experienced a very high incidence in the years 1951–5, during which they were in transition from the insidious endemic phase of poliomyelitis to the epidemic phase. With the availability and widespread use of OPV, these countries succeeded in controlling polio by 1980. For this entire 'polio-controlled' group, which in 1985 had a total population of 162 million, there were only 10 cases in 1980, and only 5–7 cases each year since then – an incidence of 0·003–0·004 per 100000 population. The countries selected for this example are Australia, Japan, New Zealand, Singapore, Hong Kong and Malaysia. The first four of these countries accomplished control of polio very quickly, have had relatively few cases since 1966 and virtually none has been seen for many recent years. Hong Kong and Malaysia had a longer struggle, but have now succeeded in establishing control [9–11].

The data in the lower line of Table 1 illustrate a contrasting trend; these countries were reporting relatively few cases in 1951–5, at a time when wild-type

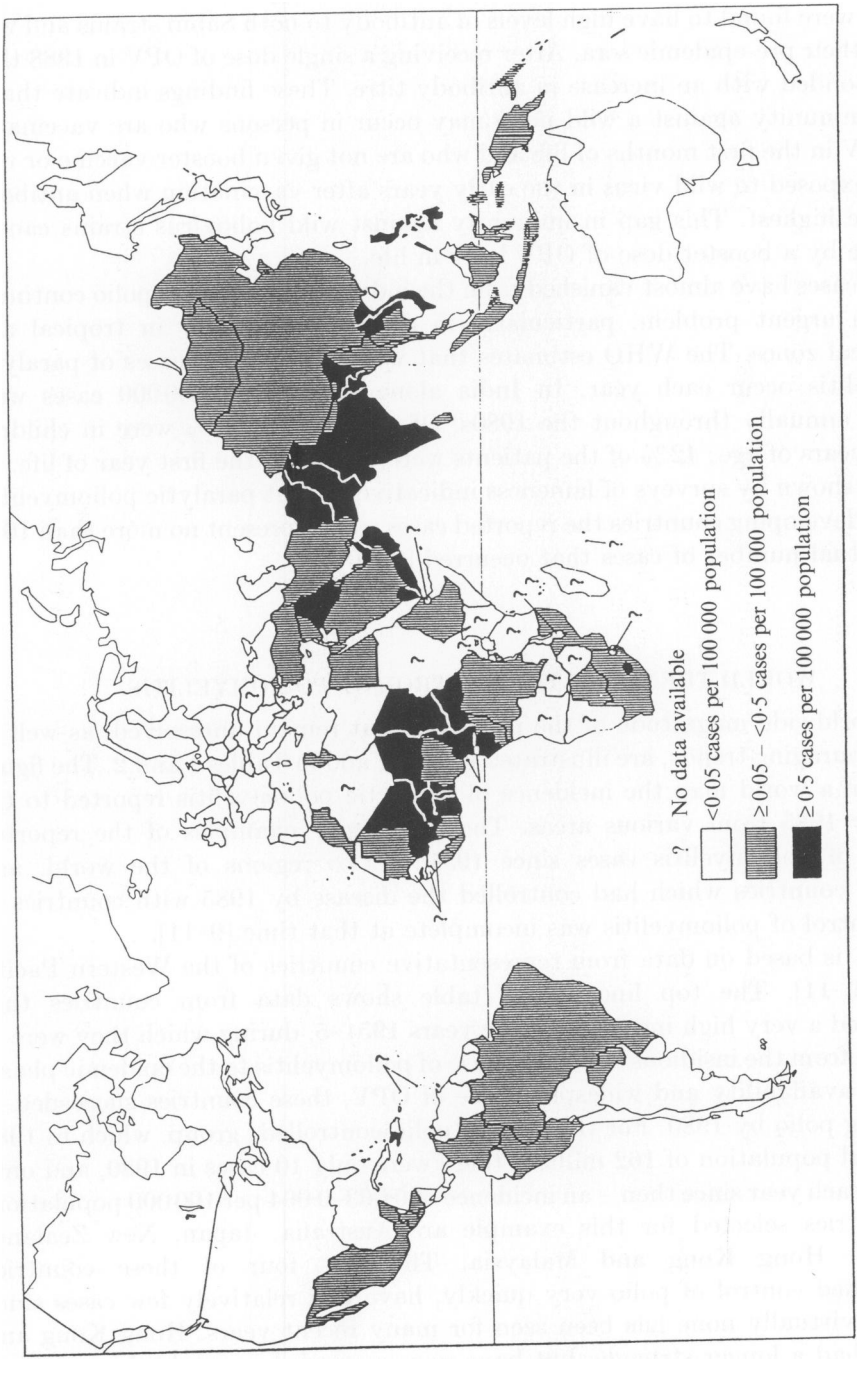

Fig. 1. Poliomyelitis incidence per 100000 population, as reported to the WHO for 1985 [10].

Table 1. *Paralytic poliomyelitis in the Western Pacific Region: comparison of countries in which the disease was brought under control and those in which it was incompletely controlled as of 1985*

	Population (millions) (est. 1985)	Average annual number of cases				Annual number of cases				
		1951–5	1966–70	1971–5	1976–80	1981	1982	1983	1984	1985
				Polio controlled*						
Totals	162	5233	142	359	37	7	7	5	6	6
				Polio incompletely controlled†						
Totals	1180	276	746	1092	9920	5640	8958	4792	3555	3729

* The 'Polio controlled' countries included above are: Australia, Hong Kong, Japan, Malaysia, New Zealand, Singapore.
† The 'Polio incompletely controlled' countries included above are: China, Laos, Papua New Guinea, Philippines, Viet Nam.

Table 2. *Paralytic polio in American Region through 1985: progress in countries in which the disease was brought under control, and those in which it was incompletely controlled as of 1985*

Population (millions) (est. 1985)	Average annual number of cases				Annual number of cases				
	1951–5	1966–70	1971–5	1976–80	1981	1982	1983	1984	1985
			Polio controlled*						
(317)	44391	470	221	34	9	79	39	9	10
			Polio incompletely controlled†						
(332)	2202	14453	10249	3837	1538	884	881	526	855

* 'Polio controlled' countries included above are: Argentina, Canada, Cuba, United States.
† 'Incompletely controlled' countries included above are: Brazil, Colombia, Mexico, Peru, and 10 others.

polioviruses were circulating widely but infections were inapparent or unrecognized. Greatly increased numbers were then reported, with control still not established by 1980, and only now beginning to be achieved. The totals shown are from China, Laos, Papua New Guinea, the Philippines, and Viet Nam. From an annual average of 221 cases reported during 1951–5, cases in the Philippines increased to an annual average of 894 during 1976–80; the annual average for the period 1981–5 remained high – almost 450 cases. The pattern in Viet Nam illustrates even more dramatically the shift from endemic to epidemic polio. After only 54 cases being reported annually during 1951–5, by 1980 the number had risen to more than 1700. In the next 5 years the numbers ranged from 644 in 1981 to 1600 in 1985. China, with more than 7700 cases reported in 1982, reduced this number to 1537 cases reported for 1985, chiefly from rural areas.

Table 2 summarizes the data for 41 countries or areas in the American region [9–11]. As in the Western Pacific, the 27 countries in the Americas that had controlled polio by 1980 were the same ones that reported huge numbers of cases in the prevaccine period: an annual average of more than 44000 in 1951–5. With widespread use of vaccine, the incidence in these populations was greatly reduced over the decade, 1966–75, and since 1971 a number of areas have had only a few cases or none at all [12].

In contrast, the lower part of Table 2 shows that during 1951–5 there was a relatively small number of cases reported from 14 countries where polio was endemic. By 1966–70 the average annual number of cases reported had increased more than six times as the disease entered its epidemic phase. The number of cases remained high through 1980, in spite of the use of OPV. A large share of those cases came from only five countries (Bolivia, Brazil, Colombia, Honduras and Mexico), several of which have had many of the problems that hinder adequate vaccination coverage – that is, a large geographical area, regions difficult to reach, and growing urban fringe populations. Since then, much progress has been made in the Western Hemisphere. However, in some regions, particularly in Africa and Southeast Asia, large numbers of paralytic cases continue to occur annually.

THE POLIO VACCINES

The merits and the problems associated with the use of inactivated and of live poliovirus vaccines are summarized in Tables 3 and 4 [13].

Inactivated poliovirus vaccine (IPV), if properly prepared and administered, can confer humoral immunity if sufficient doses of the new vaccine of enhanced potency are given. IPV can be incorporated into a regular paediatric immunization schedule along with other injectable vaccines (DPT). In certain tropical areas where live vaccine has failed to 'take' in some young infants, IPV has proved useful. Because living virus is not present, the use of IPV excludes the possibility that the vaccine virus can revert towards virulence. Also for this reason, it can be given safely to immunodeficient or immunosuppressed individuals and to the household contacts of these immunocompromised persons.

Problems with IPV are summarized in the lower part of Table 3. In the United States, the Soviet Union and other countries, the low potency of the original IPV

Table 3. *Inactivated poliovirus vaccine: advantages and problems**

Advantages
- Confers humoral immunity in vaccinees if sufficient doses of potent vaccine are given
- Can be incorporated into regular paediatric immunization, with other injectable vaccines
- Absence of living virus excludes potential for mutation and reversion to virulence
- Absence of living virus permits its use in immunodeficient or immunosuppressed individuals and their households
- Has greatly reduced the spread of polioviruses in small countries where it has been properly used (wide and frequent coverage)
- Beneficial in certain tropical areas where live vaccine has failed to 'take' in some young infants

Disadvantages
- Early studies indicated a disappointing record in percentage of vaccinees developing antibodies after three doses, but more immunopotent antigens are now produced
- Generally, with the vaccines that have been commercially available, repeated boosters have been required to maintain detectable antibody levels
- Does not induce sufficient local intestinal immunity in the vaccinee to block transmission of wild polioviruses by the faecal–oral route
- More expensive than live vaccine
- Growing scarcity of monkeys for kidney tissue substrate was a problem but has been overcome by use of continuous-passage monkey cells (Vero) for vaccine production
- Use of virulent polioviruses as vaccine seed creates potential for tragedy if a single failure in virus inactivation were to occur in a batch of released vaccine. This risk is somewhat increased since monkey neurovirulence tests are no longer required before release of inactivated vaccine. However, this problem is being overcome by use of attenuated strains for production

* Modified from Melnick [13].

Table 4. *Live poliovirus vaccine: advantages and problems**

Advantages
- Confers both humoral and intestinal immunity, like the natural infection
- Oral administration is more acceptable to vaccinees than injection and is easier to accomplish
- Induces antibody very quickly in a large proportion of vaccinees
- Under epidemic conditions it not only induces antibody quickly but also rapidly infects the alimentary tract, blocking spread of the epidemic virus
- Is relatively inexpensive, both to produce and to administer
- When properly stabilized, it can retain potency under difficult field conditions with less refrigeration and without freezing

Disadvantages
- Vaccine viruses may mutate, and in very rare instances (about 1 per million) have reverted towards neurovirulence sufficient to cause paralytic polio in recipients or their contacts
- Vaccine virus also spreads to household and community contacts. (Some people consider this spread to be an advantage, but the progeny virus excreted and spread by vaccinees often is a mutated virus, and obviously cannot be a safety-tested vaccine, licensed for use in the general population.)
- In certain tropical countries, induction of antibodies in a satisfactorily high proportion of vaccinees has been difficult to accomplish
- Contraindicated in those with immunodeficiency diseases, and in their household associates, as well as in persons undergoing immunosuppressive therapy, and their households
- Requires monkeys for safety testing. However, the new molecular techniques that monitor any change in the nucleotide sequence of the attenuated poliovirus genome may supplant the monkey test

* Modified from Melnick [13].

led to a disappointing record in the numbers of vaccinees who developed antibodies after a full course of three doses. With the inactivated vaccines that were commercially available, repeated boosters were necessary to maintain detectable antibody levels. The need for repeated booster injections added to higher costs, and in developing countries also presented logistic problems of injecting several doses of vaccine at intervals into large numbers of infants and pre-school children. The immunity conferred by IPV, although it impedes pharyngeal and faecal shedding of virus to some extent, does not provide a high degree of intestinal immunity; therefore, when wild poliovirus is introduced, IPV vaccinees become infected; they excrete the wild virus and thus become a source of infection to others. Even in countries with highly developed health-care systems and populations very well vaccinated with IPV, imported wild virus can circulate not only in unvaccinated sectors of the population but also through those who have been vaccinated.

The new, more concentrated and potent, inactivated poliovaccines prepared by the van Wezel procedure are proving to be more effective with fewer doses than the original Salk vaccine. Such vaccines are now being used in some West European countries, and selective field trials are being conducted elsewhere. Hopes have been high that newer, more potent IPV could provide long-lasting immunity after two doses [14, 15]. However, the results in terms of resistance to the development of paralytic poliomyelitis have been somewhat disappointing in at least one field study in Africa [16].

Live oral trivalent poliovirus vaccine (OPV) has been widely used because of its ease of administration, its ability to induce not only serum antibodies but also intestinal resistance, and its rapid induction of an enduring immunity, similar to that induced by the natural infection. OPV rapidly infects and colonizes the alimentary tract of suceptibles, thus blocking spread of wild virus. Lower cost is an important factor for many countries; not only is the vaccine itself less expensive, but its administration does not require use of highly trained personnel, thus further reducing programme costs, and continuing boosters are not required.

All living creatures undergo some degree of mutation, and polioviruses are no exception. The mutations that occur during replication of OPV have produced, in very rare instances, strains with neurovirulence sufficiently increased to cause paralysis in vaccine recipients or their susceptible contacts.

The proven risks of paralytic polio associated with OPV are exceedingly small, and by the 1980s such cases had decreased to an almost vanishing number. Three sequential 5-year studies of polio cases have been conducted collaboratively among 12–15 nations, under the auspices of the WHO. In these and other studies, live poliovirus vaccine has been judged repeatedly to be an extraordinarily safe vaccine [17, 18], with less than one reported case for every million babies vaccinated. These estimates were based on the maximum risk (the risk calculated as though every 'vaccine-associated' case were indeed vaccine-caused). In a recent evaluation of cases in the United States, covering the period 1973–84 [2], it has been estimated that the overall frequency of vaccine-associated poliomyelitis was one case per 2·6 million vaccine doses distributed. However, the associated frequency of paralysis was one case per 520000 first doses, versus one case per 12·3 million subsequent doses. These rates include recipients with immune deficiencies.

Increasing the percentage of type 3 in OPV

In some tropical countries live vaccines have not induced antibody production in a satisfactorily high percentage of vaccinees. This lower rate of vaccine 'take' has been ascribed to various factors, such as interference from other enteroviruses already present in the intestinal tract, the presence of antibody in breast milk, the presence of cellular resistance in the intestinal tract due to previous exposure to wild polioviruses or perhaps to related viruses, and the presence of an inhibitor in the saliva (alimentary tract) of infants that blocks multiplication of the vaccine virus. Some feel that this low response, especially to type 3, can be overcome by proper and repeated use of live vaccine. In addition, a significant improvement in the rate of seroconversion to type 3 has been obtained in a field trial in Brazil with a trivalent OPV containing a twofold increase in concentration of the type-3 vaccine strain [19]. The increased effectiveness of the latter, more expensive vaccine might be due to an increased ratio of type 3 to the other types, rather than to the doubled concentration of type 3, from $10^{5.5}$ to $10^{5.8}$ $TCID_{50}$. The ratio of types 1, 2, 3 in the vaccine ordinarily used is 10:1:3, based on standard doses of 10^6, 10^5, $10^{5.5}$. In the Brazilian trial mentioned it was 10:1:6. An increase of type 3 in the ratio could also be achieved by lowering the concentration of the first two types, especially of the highly dominant type 2. The vaccine might consist of $10^{5.8}$, $10^{4.5}$, and $10^{5.5}$ $TCID_{50}$, for the three serotypes, or a ratio of 20:1:10. This increase in ratio can be attained, whilst simultaneously lessening the cost of the vaccine.

Immunization at the time of birth

The problems of controlling paralytic polio by the use of vaccine are often exacerbated by the fact that in some areas the newborn infant has only a short time in which to acquire protective immunity because exposure to wild viruses comes so early, in their first months of life [20]. Various plans have been proposed [21–23] and some are now being pursued in different developing and tropical countries.

The Global Advisory Group of the WHO's Expanded Programme on Immunization (EPI) [24] has concluded that immunization of the newborn with OPV vaccine is a safe and effective means of improving protection and that OPV may be administered simultaneously with BCG vaccine. Although the serological response to OPV in the first week is less than that observed after immunization of older infants, 70% or more of neonates benefit by developing local immunity in the intestinal tract. In addition, 30–50% of the infants develop serum antibodies to one or more poliovirus types. Many of the remaining infants have been immunologically primed and they respond promptly to additional doses later in life.

The EPI Advisory Group emphasizes that for those infants in many countries whose only encounter with preventive services is at the time of birth, this single dose of vaccine will offer some protection and they will be less likely to be a source of transmission of wild polioviruses during infancy and childhood. For the infants who receive only one or two additional doses of poliovirus vaccine, the initial dose at birth will help ensure higher levels of immunity. The EPI schedule designed to provide protection at the earliest possible age is: at birth, and then at 6, 10 and

14 weeks of age. If the vaccine is not given at those ages, it should be given as soon as possible afterwards. Intervals between doses greater than those listed do not require restarting the series.

Incorporation of polio vaccine into routine immunization schedules

OPV has been included in the regular childhood immunization programmes without necessarily being preceded by mass vaccination campaigns. This has led to a gradual increase in vaccine coverage and an associated gradual decrease in polio incidence. In a number of countries using this approach, reported polio cases have significantly declined since the early 1970s.

An example of recent progress can be seen in special programmes conducted in three areas in tropical Africa that were experiencing incidence rates (as estimated from lameness surveys) ranging from 25 to 62 per 100000 population in the mid- to late 1970s. The programme emphasized intensive and carefully targeted schedules of routine vaccination. Programmes were instituted in Yaounde, Cameroon, in The Gambia, and in Abidjan, Ivory Coast [25]. They included administration of three doses of OPV during the first year of life, 1 month apart starting at 2–3 months of age. The vaccine coverage achieved was evaluated [26], and surveillance of poliomyelitis was conducted both before and after the vaccination programme [27–30]. Within a few years the proportion of the children who received three doses of the vaccine (which had been virtually zero except for low coverage in Abidjan) was increased up to 50–70%. Even with this less-than-optimal vaccine coverage, the incidence of poliomyelitis decreased significantly. In Yaounde [31], among the children 12–23 months of age, only 35% had received three doses of OPV, but the incidence of paralytic polio decreased by 85%.

Maintaining a routine immunization schedule that reaches virtually all of the target population requires the maintenance of supply of viable vaccine constantly at the point of contact. This can be difficult in warm climates with limited cold-chain facilities, particularly if the vaccine has not been treated with a stabilizer equal or superior to molar $MgCl_2$ [32–35].

Mass vaccination campaigns

Sabin [21, 22] advocated that paralytic poliomyelitis in tropical countries might best be eliminated by repeated mass administration of OPV. Annual campaigns should include all age groups in which cases are occurring. All children from birth to 3, 4 or 5 years of age (depending on the epidemiological situation in a given country) should be given two doses of OPV each year regardless of how many doses of live vaccine they may have received previously. This mass administration would reach those missed in previous campaigns and would avoid the problems of record-keeping, which often has been a barrier to full coverage in administering the vaccine.

Mass campaigns with OPV have been conducted successfully in a number of countries, not only bypassing the need for constantly maintaining refrigeration as well as other logistic problems, but also providing a high level of coverage. The introduction of massive quantities of live vaccine virus colonizes the alimentary tracts of susceptible hosts, thus blocking circulation of wild virus. In Cuba since 1962, all children from birth to 3 or 5 years (depending on concurrent serosurvey

findings), regardless of individual immunization history, have been given OPV on two Sundays, two months apart, each year [22]. Serosurveys show almost universal immunity by the age of three, and since the end of the first campaign year, over a quarter of a century ago, only six cases have been reported. Czechoslovakia, using the same strategy, has had similar success, with the total disappearance of paralytic poliomyelitis [22]. High levels of public co-operation, discipline and dedication seem to be vital factors in these successes – levels that may not necessarily be present in all situations.

This strategy of periodic mass campaigns, sometimes alone, sometimes combined with a regularly maintained schedule for immunizing infants, has been highly successful in some areas. Brazil in 1980 instituted such a programme, entailing a huge national effort in which, regardless of any vaccine history, each child in the selected age groups is given a dose of live vaccine twice each year, with a two-month interval between doses. Some 90000 vaccination stations (10 times the number of regular health stations) were established and 400000 volunteers were mobilized. From several thousand cases annually in the late 1970s, paralytic cases of poliomyelitis in Brazil have been reduced dramatically, to an annual average of 80 during 1981–4 [36, 37]. However, there was an increase to 461 cases in 1985 [10] and to 612 in 1986. This seems to have been a temporary setback due to low potency of the type-3 component of the vaccine [12]. This problem is being rectified by increasing the ratio of type-3 to the other types [19].

Such a programme poses important questions: Would developing nations be able and willing to make such an annual commitment of two days for each of two doses, with a 2-month interval between them? Would these nations have the resources to conduct such an annual repetitive mass vaccination programme? There also had been some misgivings as to whether the absence of record-keeping could be detrimental to the programme and whether concentration on OPV could detract from other needed health services. In practice in Brazil and elsewhere, the annual polio programme has led to an increased awareness and activity for other immunizations.

Mexico likewise has had a long struggle to control polio through routine vaccinations, and still had an annual average of almost 700 cases during 1976–80. In 1981, mass national immunization campaigns were instituted [38]. Monovalent type-1 vaccine – the type that has long predominated in their paralytic cases – was used for the first dose, followed by trivalent vaccine two months later. Much fuller vaccination coverage is being achieved (about 80% in 1982), and polio has been drastically reduced, to 186 cases in 1981, 80 cases in 1987, 25 in 1989, and almost to extinction in 1990 [4, 12].

The effectiveness of OPV has been particularly striking in the Western Hemisphere as a result of the Expanded Programme on Immunization and the continuing surveillance for specific virus and antibody. Not only has the number of paralytic cases caused by wild polioviruses decreased, but also there has been a precipitous decrease in the circulation of wild polioviruses. Only 11 of the 2456 cases of acute flaccid paralysis (AFP) reported in 1990 have been confirmed as polio. In addition, 57 of the AFP cases were regarded as compatible, 477 were still under investigation, and 1911 were categorized as non-polio [39]. In the few areas of the Americas where cases due to wild polioviruses occur, the EPI activities are

focusing on mopping-up operations consisting of intensive use of OPV in these localities. It seems that circulation of type-2 poliovirus no longer occurs in the Western Hemisphere, and that the entire region will soon be declared free of all indigenously transmitted paralytic polio [39]. In 1991, as of this writing, only two cases of paralytic polio have been identified in the Americas, both in Colombia. The last case was reported in February (Ciro de Quadros, personal communication).

In India, despite many efforts at controlling poliomyelitis, thousands of cases still occur, the highest incidence being in infants 6–18 months old [40]. It is estimated that in the 1980s more than 200000 cases occurred annually in that country alone [40, 41]. To increase the level of immunity, a 'pulse' mass-vaccination programme has been proposed [41], i.e. OPV is given to all the target children in each community at the same time, rather than following individual routine immunization schedules. This proposal recommends three doses of OPV before the first birthday, and three more between the 1st and 2nd birthdays; a village would be visited three times in the course of a year at intervals of 4–6 weeks, and then no more vaccine would be given over a 9-month period.

Insurance against polio through vaccination

An innovative approach to obtain better delivery of vaccine – not only of OPV but also of other paediatric immunizations – has proven productive in one area of China (Gaoyi County, Shijiazhuang Prefecture, Hebei Province), a county with a total population of 140000 in 107 villages. To increase family co-operation in immunization programmes and to encourage health-staff members to enhance their preventive health efforts, the new plan, introduced in 1984, was expanded by early 1986 to include more than 12000 children (62% of children under 7 years of age in the county) [42].

The average annual family income in Gaoyi is 438 yuan (about $220). The parents pay 10 yuan to the health centre in the first year of their child's life, with a contract that 'guarantees' that their child will not contract measles, pertussis, poliomyelitis, tetanus or diphtheria if he or she received the full recommended course of immunization. If the insured child suffers from measles or whooping cough, the parents receive an indemnity of 50 yuan; if poliomyelitis, diphtheria or tetanus, 300 yuan.

The insurance premiums received (nearly 100000 yuan as of 1985) are distributed among the village doctor, county health centres, and the county epidemic station, which uses them for immunization equipment and education, reserving funds to compensate parents when an enlisted child contracts any of the designated diseases. In turn, the village doctor and the county agencies share the costs of compensation. Up to the end of January 1986 a total of only 750 yuan had been paid in compensation, covering 15 cases of measles or whooping cough. There were no cases of poliomyelitis.

The advantages of this system have been described as follows [42].

1. It stimulates staff of health centres and village doctors to implement immunization activities.
2. Parents are enthusiastic to have their children immunized because they feel that they have paid a lot of money.
3. The primary health care setting has been strengthened because the staff can earn one-quarter to one-half more than their regular income.

4. Under-reporting of cases has been reduced because parents are motivated to report a suspected case in order to receive compensation.

5. Wastage of vaccine has been minimized because the activities have been carried out strictly according to the schedule due to the enthusiasm of staff and parents.

Combined schedules using both live and killed poliovaccines

In some localities it has been found advantageous to establish immunization schedules using both killed and live poliovirus vaccines. One type of situation in which this strategy has been successfully carried out has been the relatively recent addition of killed poliovaccine to supplement live poliovaccine immunization schedules in some high-risk localities where there is very early and repeated exposure of infants to challenge by importations of wild virulent viruses [20, 43, 44]. In such high-risk areas, IPV alone has been inadequate, as in Israel in 1988 [45]. The lessons of the 1988 outbreak in Israel are (i) that IPV alone does not interrupt the circulation of wild virus, which singles out susceptible contacts as targets; (ii) that OPV alone, administered in infancy, is not completely effective for life. A combined schedule [43, 46, 47] offers substantial benefit, with the optimal times of vaccination yet to be determined for different regions. For ease of administration, giving parenteral IPV and oral OPV simultaneously offers advantages. This procedure has been used regularly, starting in 1978, in the West Bank and Gaza, where some cases had been occurring, particularly in infants, despite extensive campaigns of immunization with OPV. The combined schedule included administration of OPV (type-1 monovalent) during the first month of an infant's life; then at 2·5 months and again at 4 months of age trivalent OPV is given together with a quadruple vaccine consisting of DTP plus IPV; trivalent OPV is given at 5·5 months, and again at 12 months. The rationale for the combined schedule was that, under conditions of regular and heavy importation of virus resulting in frequent challenge from virulent wild polioviruses early in infancy, features of both types of vaccine are needed. OPV acts by inducing protective immunity both in the form of circulating humoral antibodies and in the form of intestinal immunity. Furthermore, the immunity that ensues is long-lasting, like that which follows the natural infection. IPV, on the other hand, provides an immediate immunogenic stimulus that is not subject to the interfering or inhibiting factors described above, that may prevent live vaccine 'takes' in some young infants. By administering both vaccines in a combined schedule, immediate protection can be provided in the critical first weeks or months of life, and long-lasting protection, both humoral and intestinal, also is provided. A combined immunization schedule compatible with that of EPI is shown in Table 5.

Studies of the combined vaccine programme described above indicate: (i) protection provided by OPV alone was about 90% effective; that is, the case rate in those who received OPV alone was one-tenth the rate in those who were not vaccinated or who were incompletely vaccinated (receiving only part of the series of live vaccine feedings). (ii) The children who were fully vaccinated with OPV and had IPV in addition were even more effectively protected; virtually 100% protection was seen in those who received both vaccines. Two serum surveys in children aged 9–36 months revealed high antibody levels, substantiating their protection [46]. Another type of combined programme has been the addition of live poliovaccine in 1968 to supplement inactivated poliovirus vaccine (IPV) in

Table 5. *A combined vaccination schedule proposed for EPI*

Age	Vaccine doses*
At birth	BCG/OPV
6 weeks	DPT1/OPV1
10 weeks	DTP2·IPV1/OPV2
14 weeks	DTP3·IPV2/OPV3
6–12 months	Measles

* The first, second and third doses are indicated by the numbers. A non-scheduled dose is also recommended at birth when the infant is readily available. After the circulation of wild poliovirus in the community is sharply reduced by the above schedule, progress toward eradication can be achieved by use of OPV alone.

Denmark, where, despite extensive coverage with IPV alone, epidemics still occurred, and antibody prevalence was less than desired [48]. The combined IPV/OPV programme has resulted in the elimination of poliomyelitis from Denmark, as well as from Israel, Gaza and the West Bank. In earlier years the incidence of polio in the latter region had been one of the highest in the world, and today paralytic polio continues to be reported in the neighbouring countries of the Middle East.

OPV is now in use in most countries, and wherever it has been used, polio cases have decreased, but persist to different degrees in different areas. From the results to date, public-health workers should take advantage of the assets of both IPV and OPV to bring the disease quickly under total control. The schedule shown in Table 5 is proposed as one which would be compatible with current EPI recommendations. This schedule should (i) introduce IPV into the current OPV immunization programme so that in the first year of life both IPV and OPV are given to all infants, and (ii) in subsequent years, continue with the current EPI programme, which uses OPV alone for polio immunization.

For countries adopting mass campaigns, there would also be benefits from incorporating both IPV and OPV into the programme for the first year. For subsequent years, the programme with OPV alone would be sufficient to prevent wild poliovirus from colonizing the vaccinated population.

A note of caution has been raised recently. In a limited study of a small number of children, combining IPV and OPV immunization was highly effective in inducing both humoral and secretory antibodies, but virus excreted by children immunized with an IPV/OPV combination was found to possess a somewhat higher degree of reversion than virus excreted by children immunized by OPV alone. However, only 9 isolates in the OPV group and 12 in the IPV/OPV group were available for study [49].

General comment

Resolutions of the questions of how and where eradication of poliomyelitis can be achieved will continue to be major objectives in the next few years. The World Health Organization Expanded Programme on Immunization was initiated with the aim of reducing morbidity and mortality rates from seven target diseases, including poliomyelitis, by providing immunization against them for every child in the world. The programme depends heavily upon technical co-operation with and among developing countries, particularly those in tropical regions. Results are

already being seen: increasing numbers of countries now participate in the EPI programme or are otherwise enhancing their polio vaccination efforts. Better and more complete surveillance programmes have been implemented to detect and assess cases [4, 39]. More information is being gathered on the epidemiology of poliomyelitis in specific regional and geographical settings, and better-informed and more determined national commitments to immunization are being made.

Eradication of polio is part of the EPI goal of universal immunization of children. There have been significant increases in recent years with regard to OPV – from the situation at the beginning of 1986, when 45% of all children in the world received the required three doses of OPV in the first year of life, to that at the start of 1990, when this percentage had increased to 67%. The range at the beginning of 1990 varied from a high of 90% in the Western Pacific Region to a low of 45% in the African Region. Based on an expected worldwide polio incidence of 5 per 1000 infants, the global OPV programme is currently preventing at least 400000 cases of paralytic disease per year. As mentioned earlier, the disease has almost been eliminated from the Western Hemisphere.

CONTINUING BASIC RESEARCH ON POLIOVIRUS

Other objectives of research in this area are leading to increased knowledge of the structure of the virus [50] and its molecular biology [51, 52]. It is noteworthy that poliovirus continues to serve as an endless frontier for scientists engaged in basic research.

One important outcome is the detection of an increase in neurovirulence of the vaccine virus propagated either in cell culture or in the human gut by monitoring a change in the nucleotide at position 472 from uridine (U), found in the genome of the type-3 vaccine strain, to cytosine (C), found in type-3 wild-type strains [53]. This finding may lead to the replacement of the burdensome monkey neurovirulence test required in OPV manufacture by a simple biochemical test [54].

A key determinant of poliovirus infection is the cell receptor, upon which the restricted tropism of the virus depends. Molecular clones of the poliovirus receptor have been isolated, and the encoded protein identified as a new member of the immunoglobulin family [55]. Modification of the receptor may lead to control of disease by a new avenue.

Transgenic mice have been developed in which the human gene encoding cellular receptors for poliovirus have been introduced into the mouse genome [55, 56]. The new mice have proven to be susceptible to all three poliovirus types, and are being investigated as models for testing OPV lots for neurovirulence, which currently require the monkey test.

The diagnosis of infections by poliovirus and other enteroviruses is beginning to shift from the cell-culture laboratory to the biochemical laboratory. Nucleic acid hybridization with specific probes offers quick and reproducible methods for detecting these viruses [57, 58].

Finally, in spite of many investigations over the past half-century, several aspects of the pathogenesis of poliomyelitis and other enterovirus diseases are not well understood. Pathogenesis is now being re-examined with the aid of the new tools of molecular biology [59, 60].

CONCLUSION

Based on current knowledge, eradication of poliomyelitis is now not only possible but also probable. In the Western Hemisphere, circulation of wild type 2 has ceased and only a handful of cases caused by wild type 1 or 3 occurred in 1990.

This spectacular success has been achieved by the almost exclusive use of OPV. In some regions of the world the combined use of IPV and OPV may be desirable for at least one year, in order to bring the number of cases down to the vanishing point. Subsequently, circulation of wild virus can be blocked and the disease eliminated by the use of OPV alone.

Striking advances have been achieved recently in understanding the molecular biology of poliovirus, leading to the preparation of modified live vaccine candidates of potentially greater genetic stability. However, it will be difficult to field-test such new vaccine candidates, as it will be necessary to prove that the vaccines produce fewer than one vaccine-associated case per million susceptible recipients. The global application of the present OPV is fast achieving an interruption of the circulation of wild poliovirus, closing the window during which any newly developed vaccine strains can be properly field-tested.

While it is too early to say that the goal of eradication has been reached, the coming years should bring significant progress.

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