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Understanding the Scientific Basis of Preventing Polio by Immunization. Pioneering Contributions from India

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"All truth goes through three steps.
First it is ridiculed;
Second it is violently opposed;
Finally it is accepted as self-evident"
(Arthur Schopenhauer)

The Inactivated poliovirus vaccine (IPV) became available in 1954-55 and the oral polio vaccine (OPV) in 1961-62. The World Health Organization (WHO) mandated the use of OPV in all developing countries, under the Expanded Programme on Immunization (EPI), established in 1974. But already in 1972, children developing polio in spite of 'complete immunization' with the stipulated three doses of OPV (called vaccine failure) and its basis as unsatisfactorily low antibody response frequency (called seroconversion rate) in vaccinated children had been detected in India, documented, reported to WHO and published in peer-reviewed journals. By 1974 when EPI was formally launched and several years before 1978 when India adopted it, much work had been done in India, mostly in the author's laboratory in Vellore, and published, clearly showing the utter inadequacy of a 3-dose regimen using OPV to protect all children against polio. Both WHO and the Government of India ignored these results, the accompanying warning and the several alternate solutions that were designed and successfully tested both in the laboratory and in the field. Consequently, the magnitude of polio in India, already one of the highest in the world, did not decline for over a decade from the introduction of OPV in EPI. The solutions found to overcome the inadequate protective efficacy of 3 doses of OPV included a five-dose regimen with giving a dose at each contact with the infant for other vaccines, annual repetitive pulse immunization using 3 doses of OPV, or the use of three doses of IPV to be given in a combination product with diphtheria-tetanus-pertussis components, thus avoiding additional injections or even stock and store management of an additional vaccine.

This failure (to control polio) of a major Public Health programme (EPI), lasting over one decade, was ignored, until OPV doses were liberalized in 1995 for the purpose of polio eradication. The possible reasons why both WHO and Government of India did not use scientific data and rationale to design EPI or to make mid-course corrections when deficiencies were identified can only be speculated. That the 3-dose OPV schedule was defended even though indefensible, indicated a certain blind bias in favour of OPV and its reputation. During the last few years of 1990s and during 2000s India had to give repeated doses of OPV, particularly in annual pulses, to infants and preschool children to interrupt poliovirus transmission. Had the lessons of science been applied earlier, India could have controlled polio in a much shorter time and eliminated virus transmission at least one decade ago and thus become a world leader in this field. The failure to do so has resulted in India lagging behind in global polio eradication, and when it is finally achieved, India would be one of the last countries, if not the very last, in the world, to achieve interruption of virus transmission. Public Health programmes must be guided by good science.

Key Words: Animal model, Epidemiology, Herd effect, Immune response, Poliovirus, Poliovirus vaccines, Poliomyelitis, Pulse immunization, Vaccine efficacy, Vaccine failure

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Introduction

This review presents two themes, based essentially but not exclusively on scientific enquiries conducted in Vellore, spanning over 3 decades. The first theme is on the epidemiology of poliomyelitis (hereafter abbreviated as polio, the paralytic disease caused by poliovirus types 1, 2 or 3) and its prevention, control and elimination by the tactical use of immunization. Drawing heavily on my own research and field experiences on issues regarding polio and its prevention, this account will have an inevitable and obvious personal slant. In spite of establishing early leadership in understanding the nuances of epidemiology and intricacies of interventions, India lagged behind most other countries in the actual control of polio. Literally lakhs of children became paralysed due to a disease that could easily have been prevented if only we as a nation had the 'political will' to apply scientific knowledge in our Public Health programme of polio prevention. Today India is counted as one among the last countries in the world to progress towards its elimination. Indeed, currently (in 2003) India is one among only 6 countries in the world, and the only country in the South East Asian Region, with continued circulation of wild polioviruses (John et al. 2003). The second theme of this paper, therefore, is to explore why India was not able to use scientific information generated in India as the basis of its Public Health programme regarding polio prevention, over these 3 decades. Witnessing this phenomenon from the ringside has been hurting and frustrating and once again the personal viewpoint will become clear in this account.

India began the attempt to control polio by immunization in 1978/79, but failed to achieve any reduction in its incidence during the next one decade, as will be elaborated later. All industrialized countries and most of the South East Asian countries had succeeded in either eliminating or drastically reducing indigenous transmission of natural (wild) polioviruses by immunization during the 1970s or 80s. In 1984 the Rotary International established a global programme called the 'PolioPlus' towards achieving a polio-free world by 2005, its centenary year. I was a founder member of PolioPlus. In 1985, utilizing fund support from the PolioPlus, the Pan American Health Organization initiated a plan to eliminate polio due to natural ('wild') polioviruses from all the nations in the North and South American Continents by 1990. Based on these developments, the 1988 World Health Assembly of the World Health Organization (WHO) resolved to 'eradicate' wild-virus polio globally by the year 2000, with 12 years of lead-time (World Health Assembly 1988). India was a signatory to this resolution. To be certified polio-free in 2000, we should have had no wild-virus polio beyond 1997, since a three-year interval without polio is the requirement for certification. While that target was missed, it was hoped that the last wild virus detection would be in the year 2000, thus staying within the definition of eradication by 2000. We have missed that target also. There were 265 wild poliovirus isolations in 2000 and 268 in 2001, mainly in Uttar Pradesh (UP) and Bihar. In 2002 there were 1600 wild-virus polio cases in India, mostly in UP and Bihar, with exportation of the virus to many other States (Francis. P, Deshpande JM Personal Communication 2003). This was a large outbreak of polio while intense eradication efforts were under way, acting as a spotlight on the weaknesses of the vaccine in use and the manner in which it is applied (John et al. 2003). The earliest we can hope for the interruption of wild virus transmission is in 2003 and to be certified polio-free by 2006.

Once the transmission of wild polioviruses is interrupted and the country is so certified, the next major goal of the eradication programme should be to discontinue polio immunization altogether, in order to reap the economic benefit from the colossal investment for eradication. Obviously, there will be a time interval from the point of certification of polio-free status till the day when we can safely discontinue vaccination. During this interval (which may be called the final phase of eradication) the continued use of the live oral polio vaccine (OPV) will raise serious scientific, operational and ethical questions (John 2000). The attenuation of vaccine viruses is genetically unstable and reversible and the vaccine itself may cause polio (known as vaccine-associated paralytic polio, VAPP) albeit rarely (Henderson et al. 1964, World Health Organization Consultative Group 1982, Minor 1992). Recent evidence shows that vaccine viruses may revert to

wild-like genotype and phenotype, in terms of both neurovirulence and efficiency of transmission from person to person. Such revertants have been called vaccine-derived polioviruses, but are really vaccine-derived wild-like (VDWL) polioviruses, since they are known to cause outbreaks of polio (Kew et al. 2002). Due to these issues, this review will also function as a background presentation for discussions among policy makers and Public Health leaders, on the tactics of managing the final phase of polio eradication in India.

As part of the first theme, this review will cover four broad areas, namely, the qualities of OPV and the inactivated polio vaccine (IPV), the epidemiology of polio and the intelligent use of vaccines for its control and elimination. Needless to say that they are closely interrelated, and they will be presented to understand their complexities. The second theme will be speculative, and more subjective, as it explores unwritten elements of motivations of the Indian Health Ministry and Public Health officials and WHO experts, which ultimately resulted in the unscientific and slipshod manner in which polio control was addressed in India in the past, making us the country that trailed in global polio eradication.

Two Vaccines Against Polio

The inactivated polio vaccine (IPV), developed by Jonas Salk, consists of formalin-inactivated whole virions of polioviruses, without adjuvant (Robbins 1994). It was licensed in the USA in 1954 after a massive field trial confirming its safety and efficacy (Robbins 1994). Its potency is expressed in 'D antigen' units (van Wezel et al. 1984). The original vaccine formulation had inexact potency, but later it was standardized to contain 20, 2 and 4 D antigen units of poliovirus types 1, 2 and 3, respectively (van Wezel et al. 1984). In 1982, the Dutch scientist Antony van Wezel improved the production and purification processes and developed IPV containing 40, 8 and 32 D antigen units of the three virus types (van Wezel et al. 1984). Originally we designated it as 'IPV of enhanced potency' (Simoes et al. 1985). Since all IPV manufactured currently is with enhanced potency, hereafter the name IPV will stand for this product. The original vaccine will be referred to as the 'old IPV'.

The OPV, developed by Albert Sabin, consists of a mixture of live attenuated polioviruses 1, 2 and 3, selected through repeated passages in cell cultures and laboratory manipulations of the growth conditions of neurovirulent (wild) polioviruses (Robbins 1994). It was licensed in the USA in 1963, even without a field trial, under the belief that it lacked neurovirulence based on the experience with its mass application in the USSR and some East European countries (Robbins 1994). It is given by mouth, usually as drops. The development of OPV was considered a breakthrough in vaccinology, it being the first successful mucosally given vaccine against a mucosally acquired infection. In the USSR, USA, European countries, Japan and Australia it was found to be highly efficacious, without any individual who had taken 3 or even 2 doses of OPV subsequently developing polio. In parallel, the seroconversion (antibody response) rate after three doses was over 98% against each of the 3 virus types (see below). The vaccinated children shed large numbers of viruses in their stool, and non-immune contacts in and around the household are at some risk for getting infected by the vaccine-derived viruses. Usually, transmissibility of vaccine virus from the vaccinated to the unvaccinated is considered to be an unwanted attribute in any live vaccine. However, in the case of OPV, the WHO experts considered this property as an advantage in developing countries with poor hygiene and sanitation, where faecal-oral transmission of vaccine viruses would occur more frequently (Wright et al. 1991). According to this viewpoint, even unvaccinated children in the neighbourhood of vaccinated children would get infected and immunized through 'contact immunisation'. Thus they expected to control polio with 80% coverage of infants with 3 doses of OPV, through the 'herd effect' of immunization (Basu 1980, Wright et al. 1991, John 2000). They had weighed the low cost and ease of administration of OPV, the expected high vaccine efficacy to protect the individual, 'contact immunization' of unvaccinated children in the neighbourhood, and the potential of mucosal immunity to retard wild virus transmission in the community (herd effect), as the reasons in favour of OPV (Wright et al. 1991). Any evidence already available against its efficacy or safety was ignored

(Wright et al. 1991). Thus, OPV coverage level of 80 % was made the target to be achieved by all developing countries by 2000, under the Expanded Programme on Immunization (EPI), which was established by WHO in 1974 and adopted by India in 1978 (Basu 1980).

Clinical 'Vaccine failure' of OPV in India: The Consequences

Professor John Webb, a British Paediatrician working in the Vellore Christian Medical College, had introduced OPV in the Immunization Clinic of our hospital in 1964. Between 1967 and 1972, we observed 6 children, who developed acute flaccid paralysis (AFP), clinically typical of polio, in spite of vaccination with the standard primary course of 3 doses of OPV (John 1972, Ratnaswamy et al. 1973). They were investigated virologically and polio viruses were detected in their stool samples, thus confirming the diagnosis of polio (John 1972, Ratnaswamy et al. 1973). We did not have the laboratory facilities to distinguish between wild and vaccine viruses at that time. In immuno-competent children VAPP occurs usually within about one month of taking the vaccine (Henderson et al. 1964). Since paralysis occurred 3 to 6 months after the last dose of OPV, the disease was most probably due to wild virus. The 3 doses of OPV had not protected these children. Such a phenomenon is usually called 'primary vaccine failure', defined as lack of immune protection in spite of the recommended doses of vaccine. Our source of OPV was the Wellcome Laboratories in UK and vaccine transportation and storage were under ideal conditions. Therefore, vaccine failure could not be attributed simply to loss of potency.

During those years OPV was available in this region only in our institution and only limited number of children were being vaccinated against polio, using imported vaccine. Therefore we felt that these children with polio could not have been infected with vaccine viruses by contact with other vaccinated children. We had no ready explanation for the vaccine failure, which had not been reported anywhere else in the world. There was no clinical reason to consider immune deficiency as a predisposing factor for VAPP in these children. Therefore we suspected (and subsequently proved as shown below) that vaccine failure was indicative of a previously unrecognized low vaccine efficacy (VE) in our communities. For want of evidence for its root cause, we have named this phenomenon simply as 'geographic variation' in VE (John 1989).

As events unfolded themselves over the years, paralytic polio consequent to primary vaccine failure became widely recognized in the academic circles as a serious problem in India (Maiya et al. 1981, Sundaravalli et al. 1981, John 1984, Sharma et al. 1990, Ahuja et al. 1996, Singh et al. 1999). In Vellore, the proportion of children with polio, who had earlier received 3 or more doses of OPV (hence qualified as fully vaccinated), increased from 5% in 1967 to 22% in 1981 (John 1984a). In Mumbai, vaccine-failure polio cases increased from about 5 % in 1972, to about 14% in 1981 (Unpublished Annual Reports of the Indian Council of Medical Research Enterovirus Unit, 1972-1981). Since then, the proportion had increased to about 30% in many places in India. As late as in 1997, among 53 children with laboratory proven wild-virus-caused polio in Delhi, 18 (34%) had earlier received 3 or more doses of OPV (Singh et al. 1999). Of all children with acute flaccid paralysis (AFP) syndrome typical of polio (n=158), 35% (n=55) had been fully vaccinated (Singh et al. 1999). Other studies had shown that the proportion of polio cases among fully vaccinated children rose from 2% (157/6503) in 1980-83, to 16% (798/5084) in 1988-91 and 22% (739/3416) in 1992-94 in places where the vaccination coverage improved relatively slowly over time (Sharma et al. 1990, Ahuja et al. 1996). Vellore and surroundings have maintained very high immunization coverage since the early 1980s. The proportions of fully vaccinated children with poliomyelitis admitted to our hospital increased from 10% in 1979 to consistently over 50% since 1988 (John 1996).

India had adopted the Expanded Program on Immunization (EPI) in 1978, 4 years after the WHO launched it globally (Basu & Sokhey 1982). OPV was introduced at first only in urban communities under the erroneous assumption that polio was prevalent only in towns and not in villages. From about 1981-1982, polio vaccination was introduced into rural communities also. In 1985 the EPI was modified into a Universal Immunization Program (UIP), under which the ceiling of coverage of 80 % was removed.

By 1990, when UIP covered all Districts in India, the national average of OPV coverage in infancy was 80% or more, thus enabling India to participate in the World Summit for Children in New York in September 1990, and to celebrate the achievement of 80% coverage, which had been set by EPI as the global target.

The reported numbers of cases of polio annually from mid-1970s to mid-1990s in India are presented in figure 1. For many decades the system of disease-reporting was through a few selected major hospitals, a form of 'sentinel surveillance' (Basu 1981). India established a nation-wide AFP surveillance system only in 1996. Until then, it had been estimated that only some 10% of the total cases were actually reported in the sentinel reporting, during the decades of 1970s and 1980s (Basu 1981, John 1984a). Therefore figure 1 presents an incomplete picture of the burden of polio in the country during the 20 years represented therein. But what is astonishing is the fact that the introduction of OPV in EPI did not reduce the numbers of reported for at least ten years. In reality the numbers increased during 1981, and remained

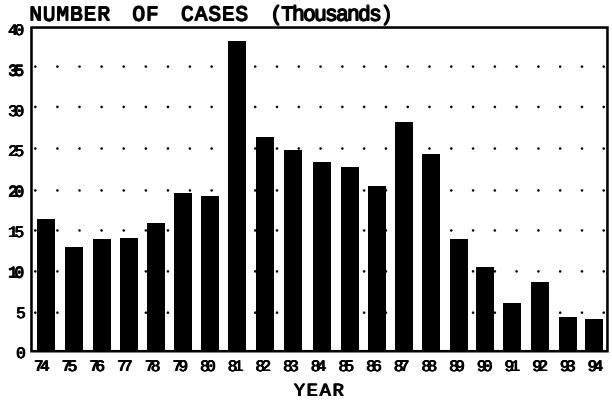

Figure 1 The reported annual numbers of cases of polio in India, through the sentinel reporting system, during two decades, 1974 to 1994. Note that EPI was introduced in 1978 and OPV was introduced in the immunization schedule in 1979, but the reported cases increased to an all-time record peak in 1981, indicating a nation wide epidemic. From 1982 there was a trend of gradual decline broken by another nation wide epidemic in 1987-88. From 1989 the declining trend continued, broken by the next outbreak year in 1992. Thus, polio had been occurring as endemic disease with superimposed outbreaks at intervals of 5-7 years. The pre-EPI level was crossed only in 1989, one decade after introducing polio vaccination. The trend of decline starting from 1982 continued up to 1994, obviously on account of sustained vaccination efforts with increasing coverage. (Reproduced with permission from John 1998a)

higher than in the pre-EPI years until 1988; it was only in 1989 that the number reached a figure lower than the reported number of cases in 1978 or 1979 (World Health Organization 1995, John 1998a).

During the 1980s, the actual annual numbers of cases of polio in India were estimated to be between 199,000 and 448,000, indicating that only less than 10% of the total cases were being reported through the sentinel reporting system (Basu 1981, John 1984a). If we take that the annual numbers of polio were 10 times higher than what were being reported (see figure 1), in other words an average of over 200,000 cases per annum, then during from 1980 through 1990, there would have been a total of over 2,200,000 cases of polio. This was a clear sign of failed polio control. In contrast, in most countries in the world the incidence of polio declined rapidly, often within one year of commencing immunization with either IPV or OPV. This information was already available when WHO established EPI (1974) and when India adopted it (1978). Vaccination coverage with 3 doses had improved gradually, until we reached 80% by 1989. Yet, if we assume only 50% coverage over the entire period and 30% vaccine failure only in the 'fully vaccinated' children, some 300,000 children would have developed polio in spite of taking 3 doses of OPV (World Health Organization 1995, John 1998a). During the 1990's OPV coverage had increased further in the first 5 years in most States and the number of reported cases declined further (see figure 1) most certainly on account of the sustained immunization efforts. In the second half of 1990s immunization coverage reached virtually 100% in most parts of the country, on account of repeated vaccination campaigns for the purpose of polio eradication (pulse immunization, see below). The systematic polio surveillance with virological investigations on every reported child with AFP was begun in 1996. The problem of continued high prevalence of polio was addressed for the first time only in 1995 (17 years after introducing the vaccine), through nation-wide mass vaccination campaigns (pulse immunisation, see below). Since 1995, as the disease burden dropped quite rapidly as vaccine doses and coverage increased, the proportion (not necessarily the numbers) of vaccine-failure cases would have increased, as illustrated in figure 2.

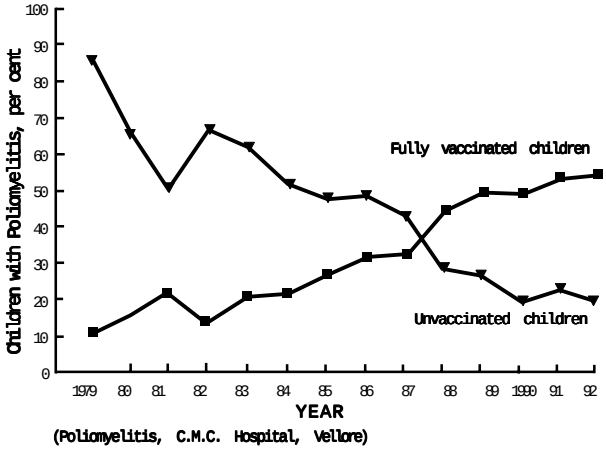

Figure 2 The proportions of children with polio, admitted to the Christian Medical College Hospital, Vellore, Tamil Nadu, according to whether they were unvaccinated or vaccinated with 3 or more doses. Incompletely vaccinated children are not included. When use of OPV was infrequent, like in 1979, only 10% cases were among fully vaccinated group. The frequency increased steadily since 1979. in parallel with increasing use of OPV in the community. Note that the lines crossed in 1987-88 and that in 1988 and thereafter 50% or more cases were in fully vaccinated children. *Reproduced with permission from John T J 1996*

While examining figure 1, the question why the Government of India (GoI) and the WHO ignored the failure of polio prevention for so many years, and remained mute witnesses to the massive numbers of children developing paralysis, demands attention. That India allowed over a quarter of million children develop polio in spite of the official policy of only 3 doses of OPV, without taking measures to redress the problem over such a long period of time is a dark chapter in the history of our Public Health. The situation was frustrating from the paediatrician's viewpoint, intolerable from a scientist's viewpoint, and unethical from societal viewpoint. On the science platform, a number of avenues were pursued in Vellore to make polio vaccination efficacious and polio prevention effective in the country, as will be detailed below. It is instructive to note that Brazil, another large country spanning the tropical and subtropical zones, also had a similar problem (Risi Jr 1984). From 1975 through 1980, the vaccination coverage with OPV improved, but polio continued to occur virtually unabated, with periodic outbreaks (Risi Jr 1984). In 1981 Brazil conducted two mass campaigns with OPV, targeted at under-five children to receive an additional dose each time, intending to continue this approach only up to 1984 (Risi Jr 1984). With the first two national OPV campaigns, the burden of disease declined dramatically (Risi Jr 1984).

India could not be brought to take polio prevention seriously while there were intriguing issues hidden below the surface of public knowledge. One example of this conundrum was that the Ministry of Health in charge of introducing OPV in India in 1979 had in 1974 closed down the only OPV-manufacturing unit in India at the Pasteur Institute at Coonoor, Tamil Nadu. Since then not a dose of OPV has been made in India. From 1978 until this day, India has been importing the needed OPV, either as finished product or as bulk concentrate for repacking after dilution.

As pointed out earlier, from the time of introducing polio vaccination as a national programme until the start of the polio eradication drive resulted in drastic reduction in polio incidence, more than 2 million children had developed polio for want of an effective vaccination policy (John 1984a, b). During this period more than a quarter million children had developed polio in spite of primary vaccination with OPV (John 1984a, b). Why did the disease burden fail to come down even a little bit once vaccination was introduced, but on the contrary why did it increase? There was a nation-wide epidemic of polio two years after OPV was introduced in the national EPI (Pillai 1981, Sundaravalli et al. 1981, Vijayan et al. 1985). These data were widely known, but they were simply ignored by the Government of India, which made no attempt to rectify this enormous problem until 1996 when polio control had to be taken seriously under international pressure for global eradication. In facing such seemingly callous attitude about a crippling disease of children, the immediate scientific challenges for us were to understand why OPV had geographic variation in host response and to design solutions to overcome the low VE.

The failure to control polio by the EPI was due to four factors, in my view.

(1) First, the coverage of 80% was reached slowly, leaving huge numbers of children unvaccinated. With new birth cohorts, the numbers of susceptible children accumulated and reached the needed threshold and outbreaks occurred, even

while the immunization programme was in progress. In many countries (e.g. USSR, USA) OPV was introduced in mass vaccination, resulting in rapid decrease in the incidence of polio, and then continued in the routine programme. Brazil successfully applied this tactic in 1981. Indeed, is not the major advantage of an orally given vaccine that it could be given on a mass scale?

(2) Secondly, the speed of immunizing infants was not sufficient to match the speed of wild virus infection, thus giving a false picture of vaccination coverage (further elaborated later).

(3) Third, 3 doses of OPV were simply too inadequate to protect a large proportion, estimated to be 30% of vaccinated infants and children, as will be discussed below.

(4) Finally, the rapidly expanding EPI was instrumental in injecting 3 doses of the triple antigen (diphtheria, tetanus, pertussis vaccine) to millions of infants and children, who were not protected from 'provocation polio' (see below) by adequate immunization using OPV (John 1984a,b, 1992, 1998a,b, Sundaravalli et al.1981, Wyatt 1985).

Unacceptably Low Antibody Responses in Children Given OPV

In 1968, I was invited to a WHO meeting (in Helsinki, Finland) of several global experts on polio, to discuss reports of less than expected seroconversion frequency after giving 'trivalent' or 'monovalent' OPV in two tropical countries, Singapore and Nigeria (Lee et al. 1964, Poliomyelitis Commission 1966). Since the potency of OPV given to children in these two settings had not been measured, the general suspicion was that the vaccine might have been inactivated in the warm tropical environment (Lee et al. 1964, Poliomyelitis Commission 1966). An alternate hypothesis was that intercurrent infection with other enteroviruses might have interfered with vaccine virus infection ('take'). Dr Sabin himself was present at this meeting and his opinion was that high maternal antibody was inhibiting vaccine virus take; he suggested that vaccination be deferred to the second year of life.

I agreed to conduct studies in tropical Vellore to measure the response of children to OPV, using financial support from WHO (John 1972, John & Jayabal 1972, John & Christopher 1975, John 1975, 1976). The first experiment was designed to answer several questions simultaneously. A fresh batch of OPV (Lederle) was obtained and held at –20°C. Its potency was tested before, during and after the study, and found to be unchanged from the original, recommended, titre. Nearly 200 preschool children were recruited with parental consent, and from each child stool samples were collected at weekly intervals. After the fourth stool was collected, a sample of venous blood was also collected and the child was given a standard dose of OPV (John & Jayabal 1972). Weekly stool samples were collected for two more weeks. This schedule of stool and blood collection was resumed 4 weeks after giving the first dose, so that the second dose of OPV was given 8 weeks after the first (John & Jayabal 1972). Four weeks later a third sample of blood was collected (John & Jayabal 1972). The sera were tested for the presence and titres of poliovirus neutralising antibodies and the stool samples were examined for the presence of enteroviruses (John & Jayabal 1972). The results showed that the overall seroconversion rates following one dose of OPV were only 19% to type 1, 60% to type 2 and 31% to type 3 (John 1972, John & Jayabal 1972). After two doses of OPV, the seroconversion rates were 35%, 76% and 48%, to the three polioviruses respectively (John 1972, John & Jayabal 1972). For comparison, seroconversion rates after one dose in South Africa (in temperate zone) were, 51%, 87% and 85% to the three types of polioviruses, respectively, and, after two doses they were 93%, 98% and 99% (Winter 1963, John 1972, John & Jayabal 1972). These data and seroconversion results from several other studies are compared in table 1.

Since OPV consists of three serotypes of viruses, the direct comparison of seroconversion rates between studies had to simultaneously compare three variables, which was cumbersome. To overcome this, we considered that each child could be counted thrice and the antibody response to the 3 serotypes could be cumulated,

Table 1. *A comparison of seroconversion rates and indices after giving one or two doses of OPV to children in various countries*[+].

	Seroconversion Rate (%) After one dose, to				Seroconversion Rate (%) After two doses, to				
Country	Type 1	Type 2	Type 3	SC Index**	Type 1	Type 2	Type 3	SC Index	Reference
USSR	92	84	70	82	N D	N D	N D	–	Khozinski et al. 1969
USA	ND*	N D	N D	–	93	100	88	94	Horstman et al. 1961
S. Africa	51	87	85	74	93	98	99	97	John et al. 1961
Singapore	N D	N D	N D	–	50	99	59	69	Lee et al. 1964
Nigeria	27	65	47	46	N D	N D	N D	–	Polio Commission 1966
India	19	60	31	37	35	76	48	53	John & Jayabal 1972

ND,* Not done * SC Index*, Seroconversion index
[+]Seroconversion index, explained in the text, helps to compare data as a single variable per study, instead of 3 variables for the 3 types of polioviruses. The studies that had tested seroconversion rates after one and/or two doses, as in the Vellore study, were chosen for comparison (*Adapted from & Jayabal 1972*).

when the result would become a single variable. This cumulative seroconversion response was termed the 'seroconversion index', which could be calculated by averaging the individual responses to the 3 viruses (John & Jayabal 1972, John 1976). Thus, the seroconversion indices of children in Vellore to one and two doses of OPV were 37 and 53, while they were 74 and 97, respectively, in South Africa (Winter PA D et al. 1963), as shown in table 1. In USSR the seroconversion index after one dose was 82 and in the USA after 2 doses it was 94 (Horstman 1961, Khozinski et al. 1969). Thus, the 'immunogenic efficacy' of OPV was found to be low in our setting, in spite of giving a vaccine with potency as per international standards. We obviously had a serious problem with sub-optimal efficacy of OPV, proven by clinical observation of primary vaccine failure and by laboratory confirmation with antibody measurement showing unsatisfactorily low seroconversion frequencies (John 1972, John & Jayabal 1972, John & Christopher 1975). Evidently, the reason for the observed clinical vaccine failure was the sub-optimal antibody response of children to the vaccine. Our studies confirmed the observations made in Singapore and Nigeria, and conclusively established that wide variations in vaccine efficacy occurred in different geographic regions, and the disturbing finding that the efficacy was much lower in India than in many other countries. This phenomenon is referred to as 'geographic variation' in response to vaccine (John 1989).

Vaccine efficacy (VE) is defined as the proportion of cases averted as a result of immune protection induced by vaccination. Since protection induced by polio vaccines is mediated through the production of virus-neutralising antibody, measuring antibody response to vaccination has been accepted as a surrogate marker for protective immunity. The proportion of vaccinated children mounting antibody response is termed seroconversion rate, which would be equivalent to VE. Obviously there is need for distinguishing between different expressions of VE. We have suggested that the term 'immunogenic efficacy' will denote induction frequency of neutralizing antibodies (seroconversion rate); 'clinical vaccine efficacy' will denote the measured VE under near-ideal circumstances of a clinical study, often of limited sample size; and 'field level vaccine efficacy' will denote the actual performance of a vaccine in the real world situation of the community at large with a vaccination programme (John 1993, John & Samuel 2000). The reason for the low field level efficacy reflected as vaccine failure cases was the low clinical vaccine efficacy, which in turn was due to low immunogenic efficacy of OPV, prevalent in India and in other developing countries in tropical and subtropical zone (Patriarca et al. 1991, John 1993, John & Samuel 2000).

The Possible Reasons for Sub-optimal Seroconversion Rates

Warm Climate and Vaccine Virus Inactivation

The earlier preliminary observations of unexpectedly low antibody responses to OPV in

some tropical countries were without measuring the potency of vaccine used (Lee et al. 1964, Poliomyelitis Commission 1966, Ghosh et al. 1970). The poor antibody response was attributed to the warm climate, which might cause heat inactivation of the vaccine viruses. Obviously a vaccine with reduced potency would induce sub-optimal immune response. We formulated the scientific question to ask if OPV of good potency had VE similar to that in North America, Europe, South Africa, etc. The Vellore studies reviewed in this paper had disproved the explanation that loss of potency was the reason for poor antibody response (John 1972, 1975, John & Jayabal 1972, John & Christopher 1975). We had used OPV of recommended potency. Before and after the study, the potency of OPV was verified and found undiminished, without any heat inactivation. Yet the responses were poor in children, showing that loss of potency was not the reason for the geographic difference in response to OPV (John 1972, John & Jayabal 1972, John 1975, John & Christopher 1975). Obviously, vaccine has to be kept cold, and any chance of inactivation should be avoided, but there was no hope of improving seroconversion rates only by improving the cold chain and ensuring optimal potency of OPV. If vaccine is allowed to deteriorate, then we may obtain even worse result, as dictated by common sense.

Interference from Intercurrent Enterovirus Infection

Being a live virus vaccine, the process of immune response to OPV has to be preceded by vaccine virus 'take' (infection) in the gastrointestinal tract. It was reasonable to assume that the seroconversion rate was determined by the vaccine virus take rate, rather than by factors in the immune system determining antibody response after virus take. This question had been addressed in the early studies in which the virus take and antibody response were found highly correlated (John & Christopher 1975). Obviously, there was some factor that inhibited vaccine virus infection in spite of giving 10^5 to 10^6 median cell culture infectious dose ($CCID_{50}$) of each type of poliovirus as inoculum in each dose of OPV given to each child, each time. Could that be due to intercurrent enterovirus infections?

There have been studies showing that children in developing countries were frequently infected with enteroviruses (Feldman et al. 1970, John et al. 1970, 1978, John & Jayabal 1972, John 1975, John & Christopher 1975). Interference to vaccine virus infection due to such enterovirus infections was a readily invoked explanation for low frequency of seroconversion following OPV. As stated above, the first seroconversion studies had investigated if intercurrent infection with enteroviruses would interfere with the development of antibodies to vaccine viruses (John 1985b, 1985c). There was clear evidence that enterovirus infection up to four weeks prior to, or at the time of giving OPV, did not interfere with vaccine virus take and antibody response (John & Jayabal 1972, John 1975, John & Christopher 1975). Often there may be multiple enteroviruses found in stool samples of individual children, indicating that any interference between enteroviruses was only relative and not absolute (Feldman et al. 1970, John et al. 1970, 1978, John & Jayabal P 1972, John 1975, John & Christopher 1975). The numbers of receptor-bearing cells in the pharynx and small intestines are far too many to be completely blocked by one or a few enteroviruses currently infecting the individual. Moreover, there is no competition between the receptors of polioviruses and of other enteroviruses as they are distinct and independent (John & Walker 1999). Interferon response to an infection may mediate some interference over a subsequent infection. It is therefore commonsense to envisage that some degree of interference is possible in a person with one enterovirus infection, if the second virus inoculum is very small. However, the dose of viruses in OPV is extremely high, namely 10^5 to 10^6 $CCID_{50}$ of each type of virus. An important reason why such high inoculum doses are included per dose of OPV is that the three types of viruses in the vaccine may themselves compete for the same poliovirus receptors on mucosal surfaces (see below). Thus any interference either by pre-existing enteroviruses in the gut or between vaccine virus types themselves is unlikely to translate to lack of vaccine virus take. Indeed, in areas where OPV efficacy is excellent, viz. in North America and Europe, it is not unusual for a child to be simultaneously infected by the three poliovirus

types in the vaccine; occasionally by two, and infrequently by only one. The reverse is true in India, since many experience no infection, some are infected with one virus type, occasionally by two and infrequently by three (John & Jayabal 1972, John 1975, John & Christopher 1975).

In Western and several temperate zone countries, where the vaccine virus take rates (as indicated by antibody response rates) are high, a phenomenon of interference between vaccine virus types had been documented. This is referred to as 'inter-typic interference'. This was the main reason for increasing the virus content of individual types in the vaccine, with the most interfering type 2 reduced to the lowest titre in the vaccine. The OPV was formulated by balancing the amounts of the three virus types so that such interference would be minimum. Thus, a dose of OPV was standardized to contain 10^6 $CCID_{50}$ of type 1, 10^5 $CCID_{50}$ of type 2 and $10^{5.5\text{-}5.8}$ $CCID_{50}$ of type 3 viruses. As shown earlier, the first dose of such a vaccine was sufficient to achieve a seroconversion index of 75 to 80 in those countries. However, in India, the seroconversion index was only 37, thereby suggesting that there is an inhibitory factor on the mucosa of children in our settings. A careful analysis of seroconversion data showed that there was no evidence for inter-typic interference under field conditions in our setting (John & Jayabal 1972, John 1975, John & Christopher 1975). It was found that a child who responded to any one type was more likely to respond to another type, than a child who had not responded to the first (John & Jayabal 1972). This was equally applicable to any of the three types taken as the first type, and to any other as the second type (John & Jayabal 1972). Only rarely did a child get infected with all 3 types at once in contrast to the majority of children in the West getting infected with all 3. How do we reconcile the inter-typic interference phenomenon in the West and no interference in India? The most probable reason is that the inhibitory influence in our setting, referred to earlier, is stronger than the inter-typic interference in the West. When the inhibitory effect is low enough to be overcome by one type of vaccine virus, then it is easier for another type also to get infected. But overall, the rate of infection with any type was much lower in India than in the West.

Breast-feeding as a Potential Inhibitory Factor

Earlier, breast-feeding had been suspected to adversely affect the antibody response to OPV, but at the same time there were also studies that suggested no such effect (reviewed in John et al. 1976). Most mothers in India breast-feed their infants over several months, spanning the age at which they are given OPV. On the other hand the prevalence of breast-feeding was less in the West in the 1970s. We had earlier shown the presence of low levels of poliovirus neutralizing antibodies in breast milk of local women (John et al. 1973). The prevalence (probability of presence) of antibodies in milk was directly proportional to the titres of antibodies in the serum (John et al. 1973). Moreover, such antibodies continued to be present in milk as long as lactation continued (John et al. 1973, 1976). A definitive study was needed to see if breast-feeding should be withheld for any length of time before or after feeding a dose of OPV. Antibody responses were measured after one dose and after 3 doses, in 300 infants, divided in 6 groups. The rates of response were fairly equal among infants on unrestricted breast-feeding (with mandatory feeding between 30 min before and 15 min after giving OPV), infants in whom breast-feeds were withheld for three, four, five and six hours before and after giving OPV, and infants who were bottle-fed (John et al. 1976). Thus, breast-feeding was not the reason for sub-optimal immune response to OPV.

Inhibition by Maternal Antibody

As mentioned earlier, Sabin himself had proposed this reason to explain low seroconversion (Sabin 1964). The age distribution of polio cases showed that infants were at maximum risk to develop disease, therefore by extrapolation, obviously for poliovirus infection as well. Fifty percent of disease (and infection) occurred below 12 months of age (Ratnaswamy et al. 1973, Prabhakar et al. 1981, Sundaravalli et al. 1981, Hovi & John 1994, Singh et al. 1999); therefore infants were highly susceptible to poliovirus infection. Several surveys of poliovirus antibody prevalence had shown that maternal antibody declined rapidly and that virtually all infants were free of maternal antibodies by about 8 weeks. Finally, the seroconversion indices were relatively stable irrespective of the age at which the first and subsequent doses of OPV

were given (John 1984b). Even soon after birth the antibody response rate was no less than when vaccine was given any time thereafter (John 1984b). For these reasons, inhibition by maternal antibody could be excluded as a potential cause of poor antibody response rates in India.

Practical Methods to Improve Immune Response to OPV

Searching for Solutions

As elaborated above, even before India adopted the EPI and the 3-dose schedule of OPV in 1978, evidence had accumulated that the WHO-recommended 3-dose vaccination schedule was flawed for developing countries. By 1981 it was obvious that there were serious repercussions of inadequate or ineffective polio vaccination, by way of a massive nation-wide polio outbreak in that year. There was an increase instead of decrease in the number of cases reported, in other words, an enormous and worsening Public Health problem, to which the Government was not responding. Those who were in charge of EPI and polio control by vaccination had turned a blind eye to this paradox. It was felt that as scientists it was our scientific and ethical responsibility to design solutions to this problem so that the Government could modify its efforts to control polio in the country.

Recommendation for 5-dose Primary Immunisation

There was an interesting mathematical relationship between the seroconversion indices after one and two doses as illustrated in figure 3 (John & Jayabal 1972, John 1993). After giving one dose, the seroconversion index was 37 in India and 75 in South Africa (John & Jayabal 1972, Winter et al. 1963). So the unresponsive 'deficit' was 100 – 37 = 63 in India, and 100 – 75 = 25 in South Africa. If the seroconversion index of first dose was applied to the deficit, we get 23 (63x37%) in India and 19 (25x75%) in South Africa, respectively, as the likely numbers of children who would respond to a second dose of OPV. If the observed index of first dose (37 or 75) and derived index of second dose (23 or 19) are added together we get 60 in Vellore and 94 in South Africa, as the likely seroconversion index for two doses of OPV as illustrated in figure 3. The indices obtained by actually measuring seroconversion after giving 2 doses were 53 and 97, very close to the calculated numbers. Using this approach we could predict the cumulative responses to each additional dose of OPV. In South Africa, the deficit after 2 doses of OPV would be 100 – 94 = 6 and a third dose would cover 5 more (6x75%), thus immunizing 99% (94+5). On the other hand, in India, the deficit after 2 doses would be 100 – 60 = 40 and a third dose would cover only 15 (40x37%), thus immunizing only 75% (60+15). These calculated numbers were nearly identical to the seroconversion indices observed in actual studies, namely 73% after 3 doses in Vellore, thus showing the validity of the mathematical estimation of response to each additional dose, which would add a progressively smaller number to the index (John 1976, 1984b, 1993). With five doses, the predicted seroconversion index would be 90 and the measured index was 89 (John 1976). Thus, the seroconversion indices obtained after measuring them were almost identical with the indices calculated mathematically, thereby validating the mathematical principle

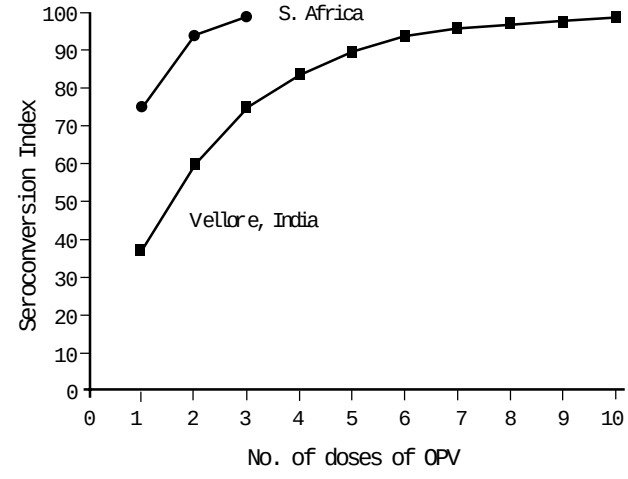

Figure 3. Graphs showing seroconversion indices following sequential doses of OPV in South Africa and Vellore, India, as constructed by mathematical derivation by applying the index of the first dose to the segment remaining seronegative after each subsequent dose (see text for details). The observed seroconversion index of second dose was 97 in S. Africa and the derived index was 94. The observed seroconversion indices in Vellore were 53, 73 and 89, against the derived values of 60, 75 and 90, respectively. The closeness of fit of the observed and derived indices is evidence that the mathematical method is valid. Note that the response of Vellore children to 3 doses was equal to that of one dose in S. Africa. The response to 5 doses in Vellore was equal to that of 2 doses in S. Africa. To obtain the response level of 3 doses in S. Africa, we need to give 10 doses in vellore.

behind it (John 1976, 1984b, 1993). To reach a seroconversion index of 99, that is, to achieve the predictable protection in near-100% vaccinated children, in other words the VE achieved by 3 doses in the West, we have to give 10 doses as shown in figure 3 (John 1993).

Based on the results of the field studies and mathematical prediction, as described above, we argued for a five-dose OPV primary immunization schedule in infancy in India, instead of the 3 doses recommended by WHO (John 1984b, 1993). India adopted EPI in 1978 and introduced OPV at first in urban populations and later in rural populations. Since the WHO vouched for the adequacy of 3 doses, the policy makers in India followed the WHO directive, ignoring both data generated in our own country demonstrating the inadequacy of 3 doses, and the simple solution to give 5 doses of OPV to each infant. Our field experience also showed that 5 doses would effectively control the disease (Prabhakar et al. 1981). This debate, regarding the inadequacy of 3 doses in India and the need to increase the number had continued for at least two decades without resolution, until 1995. Indeed there should have been no objection to this recommendation in the 1970s, since each infant had to be contacted five times for one dose of BCG, 3 doses of DPT and a dose of measles vaccine. If OPV was given at each contact, 5 doses could have easily been accommodated, thus inducing protective immunity in 90% of vaccinated children (John 1984b, 1993). Even that would be insufficient to give predictable protection to nearly all children, for which additional doses would be needed. Two further contacts are available, under the modified Universal Immunization Programme (UIP), once in the second year of life for DPT booster and once at about 5 years of age for DT booster, and on both occasions another dose of OPV could have been given, for a total of 7 doses of OPV during pre-school childhood. Vaccine efficacy of 90% would have provided better 'herd protective effect' than a 3-dose schedule with efficacy of 75% (John & Samuel 2000). For example, at 90% coverage, the effective protection ('herd immunity prevalence') would be 90x75% = 68% for 3 doses, but 90x90% = 81% for 5 doses (John & Samuel 2000). Oman, faced with the failure to control polio with 3 doses of OPV, had successfully achieved control when the 5-dose schedule was adopted (Sutter et al. 2000). Another country that used the 5-dose schedule and eliminated poliovirus transmission is Taiwan. The negative consequence of not accepting this simple remedial measure has been colossal. Literally lakhs of children in India, whose doctors and parents were told that 3 doses were sufficient, developed polio as they were inadequately immunized. Moreover, since the circulation of polioviruses had not been substantially retarded, the subsequent efforts for eradication became harder than anticipated.

Starting OPV Immunization at Birth

If we were to give 5 doses of OPV in infancy, without increasing the number of contacts of health workers with infants, then it was necessary to use the existing 5 contacts for UIP, namely at birth for BCG, at 6, 10 and 14 weeks for DPT doses and at 9 months for measles vaccine. Will a dose given to the newborn induce the same level of response as in older infants? This was directly tested and the results showed that OPV could be started from birth, without any lowering of seroconversion index (John 1984b). Thus a simple solution to overcome the sub-optimal vaccine efficacy of OPV was to liberalise the number of doses and to start immunization at birth, along with BCG, for which the health worker has to visit the neonate. Although this sounds simple and logical, it had been argued in discussions that 'if three doses do not work, thirty will not'. In the case of non-replicating antigens such as DPT or hepatitis B vaccine (HBv), the maximum response, both in terms of persons responding and in terms of antibody levels, is obtained with 3 doses. If there is no response (most unlikely for DPT but not so for HBv), the person is qualified non-responder. Against this background concept we had documented the incremental improvement in antibody response with each additional dose of OPV. Unlike for other vaccines given in 3 doses, OPV stimulates the immune system in a different sequence. For non-replicating antigens the first dose sensitizes, the second dose enhances sensitization and the third dose boosts for optimum response. For OPV, there is no such sensitization-boost phenomenon. Each dose is an independent stimulus, not enhanced by the previous dose. Thus

each time the result is a 'hit' or a 'miss'. Three doses are given in the West to have near 100% chances of 'hits' in every child. Our finding was that each dose had the same probability of infection; hence the value of additional doses to improve immune response. This observation became eventually necessary in planning the strategy of eradication of poliomyelitis, by repeatedly vaccinating the same children until each received at least some ten to fifteen doses of OPV. Unfortunately during the 1970s and 1980s the Government and WHO declined to increase the doses even to 5. However, in 1985 permission was given to give a dose at birth, in the case of institutional deliveries, but that dose was called 'zero dose' and would not be counted for assessing the three-dose coverage (Expanded Programme on Immunisation 1984, John 1985). Therefore it did not become the norm of practice in the EPI in India. We continued with the 3-dose policy until 1995, when polio eradication efforts began and the number of doses liberalized through supplementary immunization offering two doses to all children below 5 annually, irrespective of the number of doses taken previously.

Enhancing the Potency of OPV

Since the recommendation to increase the number of doses of OPV to improve vaccine efficacy was not acceptable either to the Directorate of Health Services, or to the WHO, two additional alternative approaches were tested to enhance protection in children. The first was to increase the virus content in the vaccine. With the help of the OPV production unit at Pasteur Institute, Coonoor, we prepared monovalent and mixed trivalent OPV with one $\log_{10}$ higher virus content than in the standard vaccine (John et al. 1976). Children were given one dose of these vaccines containing ten times higher virus content than the regular OPV (John et al. 1976). The seroconversion rates were: trivalent vaccine – 42%, 85% and 31% to types 1, 2 and 3 respectively (seroconversion index 53) and monovalent vaccines – 89%, 93% and 76% to the 3 types (seroconversion index 86) (John 1976). The seroconversion index 53 after a dose of trivalent OPV of enhanced potency was indeed higher than the index of 37 following a dose of standard vaccine, but still not in the satisfactory range of at least 70 as in the West. Therefore, even with such vaccine more than 3 doses would be necessary to get satisfactory seroconversion. Therefore, this approach was not going to be successful. Giving monovalent vaccines of enhanced potency would have improved the vaccine efficacy, but that approach was not considered to be feasible in our country (John et al. 1976). Even with monovalent vaccines of enhanced potency, each type would require 2 doses for achieving 98% seroconversion, for which the number of inoculations needed would be six. To give six doses of standard vaccine was an easier solution to the problem of insufficient VE to 3 doses, than giving 6 doses of OPV of enhanced potency.

Pulse Vaccination

Having noticed on several occasions the very low numbers of polio cases following periodic outbreaks of disease, we asked a simple question: can the simultaneous immunization of children in a community mimic immunologically and epidemiologically an outbreak of polio? Indeed, Sabin himself had suggested that OPV worked best when given in mass campaigns (Sabin et al. 1960). The rationale of Sabin was to flood the community with vaccine viruses in the hope that they would displace wild polioviruses. Our idea was to create an epidemic of infection so that the number of susceptible children would suddenly decline, upsetting the normal epidemiology of wild virus transmission. An experiment was designed in 1979 and commenced in 1980 January (John et al. 1983). In Vellore town (population 250,000), a polio surveillance system was set up, by pooling information on every child with acute onset paralysis coming to medical care (John et al. 1983). Field workers visited every medical institution known to receive children with AFP, on regular frequent periodic cycles and logged cases of paralytic illness. Competent medical staff confirmed or rejected the diagnosis of polio. During 21 consecutive calendar months from January 1980, 88 children with clinical polio, resident in Vellore, were detected, for a mean number of cases of 4.2 per month (John et al. 1983). There was no month without cases. Then after wide publicity and preparations, and with the full cooperation of the Municipal Health Officer and staff, 16 stations were opened on one day in October 1981, and OPV was administered to all children below 5 years (John et al. 1983). The operation was repeated in

November and December of 1981. From January 1982, for 9 consecutive months, there was not a single case of polio in Vellore. A cluster-sample survey showed that the 3-dose OPV coverage achieved thus far was 65%. Obviously, the apparent near 100% vaccine efficacy was not a direct effect of the VE of 3 doses of OPV (John et al. 1983, John 1993). One explanation that would fit with textbook description of OPV was that the vaccine virus would have established circulation in the community and in this manner nearly all children were immunized by repeated infections with vaccine viruses (Monto 1998). We questioned this, since we know that vaccine viruses are inefficient to infect even when given in huge quantities by mouth. If such spread were to occur, OPV should have much higher field level VE than documented so far. The failure to control polio in spite of high coverage with 3 doses stood in contrast to virtual elimination of polio by 3 doses given in pulse fashion. An alternate and more plausible explanation was that the simultaneous vaccination mimicked an outbreak and resulted in a sudden shrinkage of the susceptible pool of under-five children, thereby interrupting wild virus transmission in the local community (John 1993). This method of simultaneous immunization of eligible children was named 'pulse immunisation' (John et al. 1980, John & Steinhoff 1981, John et al. 1983, 1984). In order to investigate this hypothesis of sudden reduction in susceptible subjects, we conducted annual pulse immunization using measles vaccine, which does not cause any secondary spread from vaccinated children, and demonstrated the elimination of virus transmission from a community (John et al. 1984). The Vellore experiment with pulse polio immunization was repeated in October, November and December 1982, and once again, 9 months in 1983 were without polio in Vellore (Unpublished). We could not continue to give pulse immunization because the Municipal Health Officer was asked by the State Government not to cooperate (Pandian R, Personal Communication 1983); indeed, he was transferred to another town and we were informed that the Government of India did not approve of such campaign approach to immunize as it would adversely affect routine immunization and primary health care.

The Vellore experience of pulse immunization was replicated and upscaled in Madras city, to test if this approach was feasible elsewhere (Balraj & John 1986). The campaign of polio immunization was conducted in 1985 by public sector-private sector partnership, through 450 immunisation booths, during January, February and March of 1985 (Balraj & John 1986). We found that pulse immunization was a rapid method of increasing vaccine coverage in children, in addition to the intended effect on polio incidence (Balraj & John 1986). In spite of this new information, there was no change of heart for improving polio control either in the Government or in WHO.

The Potential of IPV as an Alternative to OPV

Immunogenic Efficacy of IPV in India

If the stumbling block for increasing the number of doses of OPV was the 'fixation' on 3 doses, believing that "if 3 did not work, 30 would not", we had to examine if the alternate vaccine, IPV, given in 3 doses would overcome the problem of low protective efficacy of OPV. Thus, as a potential alternative option to OPV, we had conducted several studies investigating the feasibility of IPV in our country. Until 1982/83 we used the old IPV in our studies, but since then we began using the modern IPV of enhanced potency (van Wezel A L et al. 1984, Simoes et al. 1985). The rationale of exploring the potential of IPV was that a very high degree of 'herd protective effect' had been observed in the USA and Finland as IPV was introduced (Nathanson 1982, Kim-Farley et al. 1984, Lapinleimu 1984).

The primary function of a vaccine is to offer immune protection to the vaccinated child. OPV had failed to do so in India in about 30% of children under the standard recommended dose-schedule stipulated by WHO. It is commonsense that such a vaccine cannot have sufficient herd effect, which requires very high VE (John & Samuel 2000, John 1993). The only way to improve protection and elicit sufficient herd effect to control poliomyelitis using OPV was to increase VE by increasing the number of doses to at least 7 per child, or resort to pulse immunization. Neither approach was accepted by the Government or approved by WHO in the early and mid-1980s. Fortunately, the marker of protection against polio was known to be the induction of virus neutralizing antibody. Therefore we could investigate the usefulness of IPV in India, in terms of seroconversion rates. If the vaccine

efficacy were to be found near-100%, then we could anticipate herd effect as was found in Finland and USA (Nathanson 1982, Kim-Farley et al. 1984, Lapinleimu 1984, John 1993, John & Samuel 2000).

At first we measured the immune response of children to the old formulation IPV, given in 3 doses 4 weeks or 8 weeks apart and found them to be extremely good, and equal to what would occur in developed countries (Krishnan et al. 1982, Krishnan & John 1983). Later we tested the modern IPV with enhanced potency and found that even two doses are sufficient to elicit near 100% seroconversion to the 3 types of viruses (Simoes et al. 1985). Being a relatively purified protein antigen, it can be injected intradermally in fractional dose, thus saving on cost; yet the antibody response was not compromised (Samuel et al. 1991). Indeed, with intradermal vaccination the booster immune response is vigorous and extremely high (Samuel et al. 1991, Samuel et al. 1992), compared to what can be achieved with repeated doses of OPV. In Oman and in Cote d'Ivoire, a proportion of infants had remained seronegative in spite of taking 3 or 5 doses of OPV (Morinier et al. 1993, Sutter et al. 2000). A single supplemental dose of IPV induced seroconversion to all 3 polioviruses in them 2 to 14 times more frequently than what was achieved by OPV (Morinier et al. 1993, Sutter et al. 2000). Undoubtedly, IPV is a far better vaccine than OPV in terms of immunogenic efficacy in tropical and other developing countries (Oduntan et al. 1978, Krishnan et al. 1982, Krishnan & John 1983, Simoes et al. 1985, Morinier et al. 1993, John 2000, Sutter et al. 2000). The geographic variation in immune response was confined to the orally given live virus vaccine, but not for the injected inactivated vaccine.

Protective Efficacy and Herd Effect of IPV

The geographic variation in efficacy of OPV is understandable, considering the facts that it has to infect the gastrointestinal tract to be effective, but there are structural, microbiological and functional variations in the gut mucosa of children and adults in countries like India, compared to those in countries like the USA or other rich nations in the temperate zone having high standards of sanitation and hygiene. On the other hand, IPV has much better immunogenic efficacy than OPV. However the question remains whether the immunogenic efficacy of IPV will be translated to protective efficacy and to herd effect in our settings with high endemicity of wild polioviruses. The 'force of poliovirus transmission' is higher in our environment than elsewhere (John 1993, John & Samuel 2000). IPV induces much lower secretory IgA production and transfer onto the mucosal surfaces in comparison with OPV (Ogra et al. 1968, Faden et al. 1990). However, we already knew that IgA response is induced more readily by infection than by stimulation by a non-replicating antigen. Thus IgA is a marker of infection and not necessarily of mucosal immunity. Moreover, IgA is not the only medium of local mucosal immunity (see later). To investigate the protective efficacy and herd effect of IPV, we conducted two field studies as described below.

The first vaccine field efficacy trial of IPV was conducted in a rural community of 50,000 population, from April 1980 through March 1983 (John 1993, John et al. 1987). Infants were given a DPT-combined IPV (quadruple vaccine), first using the old formulation IPV and later switching to the new IPV when it became available (John et al. 1987, John 1993). Among 3220 vaccinated children observed for 6911 person-years, none developed polio. In the adjoining half of the Block with 50,000 population, 3104 children (receiving DPT under the routine immunization programme then currently practiced) were observed for 6612 person-years, and 17 cases of polio were counted (John et al. 1987, John 1993). The field protective efficacy of 3 doses of IPV in this highly polio-endemic community was 100% (John et al. 1987, John 1993). This was consistent with the near 100% seroconversion rates described earlier. In addition, we believe that the total absence of polio even in the unimmunised segment of children in the community showed the presence of herd effect in the community.

Another field study was conducted to examine the effect of IPV immunization on the circulation of wild polioviruses in the community, which may reflect the presence or absence of herd effect, which in turn would reflect the mucosal immunity of vaccinated children. A rural community of 2130 was selected and starting from July1979 weekly stool samples were collected from all infants (John et al. 1987, John 1993). This cohort of infants formed

the control group. For infants born after 1 January 1980 three doses of quadruple vaccine (DPT and old IPV) was given, starting at 3 months of age (John et al. 1987, John 1993). Control (n = 94) and study (n = 82) children were followed up with weekly stool samples until they completed 3 years of life. Among the 4527 stool samples in control children 69 poliovirus isolations were made, for a rate of 1.52% (John et al. 1987, John 1993). Among 8159 stool samples in study children, the number of polio isolations was 49, for a rate of 0.52%. This difference, attributable to IPV immunization, was statistically highly significant (p <0.001) (John et al. 1987, John 1993). This finding confirmed markedly reduced virus circulation, which was the outcome of herd effect, which reflected mucosal immunity of IPV-immunised children against infection by wild polioviruses. The above two studies and all earlier immunogenic efficacy studies gave sufficient proof that three doses of IPV or even two doses, would be suitable in our routine immunization programme, and would be far superior to three doses of OPV or even five doses of OPV, in terms of reduction in cases and retardation of wild virus circulation.

There was a 'world congress on poliomyelitis and measles vaccines and immunization' in New Delhi during January 7 to 12, 1992, in which Dr Renu Patel, the then Professor and Head of the Department of Pediatrics in one of the Medical Colleges in Mumbai presented her experience with IPV. She was the project officer for Integrated Child Development Scheme (ICDS) in several slum communities in Mumbai. For several years during early and mid-1980s when 3-dose OPV coverages were 90% or more, polio had continued to occur at a rate of at least 5 cases per 100,000 population per year in all the slum communities. All cases were in children given 3 doses of OPV, highlighting the extremely high vaccination coverage, the vaccine failure phenomenon, and the absence of herd effect of 3 doses of OPV. In 1988, in one block of about 100,000 population she replaced OPV with IPV (3 doses per infant). From the next year (1989), that community did not have any case of polio until 1992, as long as the community continued with IPV. Intrigued by this finding, she introduced IPV in a second block one year later in 1989, and polio incidence fell to zero in 1990 and remained so until 1992. In 1990 one more block was brought under IPV and it became polio-free from 1991. A fourth block had been maintained on very high coverage with OPV and it continued to have vaccine failure polio each year. After presenting her data in the world congress, she returned to Mumbai when was reprimanded by both the State and Central Governemnt authorities for speaking publicly in favour of IPV, and was transferred out of Mumbai to a rural Medical College (Patel 1992, reconfirmed in 1998). Dr Patel was convinced that her transfer was a form of punishment Patel R, Personal Communications 1992, 1998.

Dr Meenakshi Mehta, Paediatric Professor in another Medical College in Mumbai presented data on 3-dose OPV failure in children in the same congress. After her return to Mumbai she was asked by the same authorities to give a written apology for speaking against the national policy on 3 doses of OPV and was warned not to speak on the low efficacy of OPV while in public service (Mehta M, personal communication 1992). I had presented the results of the Vellore studies on IPV at that congress. Upon my return to Vellore I too received a warning from the Ministry of Health and Family Welfare of the Government of India, through the Administration of the institution employing me, for having spoken on IPV while the national policy was to use only OPV. My credibility and credentials were checked out by the then Minister for Health (Bhan P, Personal communication 2002). I wrote a position statement confirming that our IPV studies were of a research nature and that IPV was being investigated in the light of the problems with OPV. The Administration refused to take any action against me for conducting scientific studies. With these, the matter was dropped. My request to modify the EPI schedule to include 5 doses of OPV in infancy in my position paper was not accepted by the Government.

The North Arcot District Vaccine Trial

The Indian Council of Medical Research (ICMR) was kept fully informed of the issues of the low immunogenic efficacy of OPV, the failing polio control programme, the suggested modifications of immunization policy, and of all research findings on IPV from our center. The ICMR has its own Enterovirus Research Centre in Mumbai, which has

been conducting investigations on polio and OPV for several decades. However, during the late 1970s and early to mid-1980s both the ERC and the ICMR (except for one Director-General, Dr C Gopalan, who wanted, but was unable, to get the Government policy revised) held on to the view that 3 doses of OPV were sufficient in the national immunization policy, in support of the prevailing WHO and Ministry of Health viewpoints. Only by mid-1980s the ICMR began getting concerned about the fact that polio was not getting controlled in spite of a nationwide immunization programme started in 1978/79.

By mid-1980s the ICMR was faced with the long series of publications from Vellore clearly showing that the national policy on polio prevention was grossly faulty.After much deliberation, the then Director-General of ICMR Dr V Ramalingaswamy requested us to establish a polio control demonstration project, including disease surveillance. We were asked to evaluate the potential of IPV for polio control, but the test license to import it was given by the Directorate-General of Health Services on condition that the results of the study will not be published. Therefore results will not be presented in any detail. The study was planned in the erstwhile North Arcot District (later divided into the Vellore and Thiruvannamalai Districts) with a population of 5 millions. The then Director-General of Health Services asked us to give OPV in one half of the district and IPV in the other half. Our reason to conduct this study in spite of the restriction on publication of results was our conviction that the Government was sincere and serious in looking at alternate strategies of polio control by using IPV. Disease surveillance for polio and other vaccine-preventable diseases was established, using pre-formatted post cards as the medium of reporting cases and networking private sector and public sector health care institutions for disease reporting (John et al. 1998). The District was divided in two halves and the northern region with high vaccination coverage and low polio incidence was given OPV and the southern region with low vaccine coverage and high polio incidence was given IPV. The schedule of IPV was 2 doses 2 months apart, along with DPT, starting at 2 months of age, and a third dose of DPT-IPV at the time of giving measles vaccine at 9 months. The schedule of OPV was to give 3 doses at 6, 10 and 14 weeks of age, at the time of the 3 DPT doses, followed by a dose in the second year of life and another at 4-5 years when DPT and DT boosters were due. We were able to obtain very good cooperation from both public and private sectors in health care and thus achieve high immunization coverage in both study areas (Balraj et al. 1990, Balraj et al. 1993). Near 95% coverage was obtained with OPV but the IPV coverage had lagged behind. Polio was controlled in both regions. In the OPV half of the district, the incidence of polio was 9 per 100,000 population in 1987 and it was brought down to 0.4 by 1992. In the IPV half of the district, incidence was 14 per 100,000 in 1987 and it was brought down to 0.3 per 100,000 in 1992. Thus, IPV reduced the incidence faster than OPV (unpublished). The major lessons learned were that disease surveillance was eminently feasible, post card was a suitable mode of rapid reporting, polio surveillance could easily be combined with other vaccine-preventable diseases as well, virological diagnostic facility was essential for polio control, and that private sector institutions and medical practitioners were fully cooperative for surveillance and disease-reporting (John et al. 1998). We found that with effective vaccination achieving very high coverage, either polio vaccine would control polio to very low levels of incidence, and that IPV was quite suitable for effective immunization even in our polio-endemic community. We did not attempt or achieve the interruption of wild virus transmission since the study was for five years.

The critical issue determining success of control of polio seemed to be the speed of covering infants and young children with adequate immunization. Earlier it was shown that the median age of polio, reflecting poliovirus infection in general, was between 12 and 18 months of age (Ratnaswamy et al. 1973, John 1984a, Sharma et al. 1990, Sharma et al. 1990, Hovi & John 1994, Ahuja et al. 1996, Singh et al. 1999). The speed and coverage of immunization had to match and exceed that speed in order to control the disease and retard the speed of transmission of the virus (John 1993). We found that 90% coverage of routine OPV or IPV doses given at the recommended age intervals (plus, in the

case of OPV two more doses in under-five age period) achieved sufficient speed of immunization, effect herd immunity and herd effect to drastically reduce the incidence of polio. It is critical to obtain the maximum prevalence of immunity due to vaccination during the first 6 months of age rather than achieving the same level of coverage by 12 months (John 1993). The WHO-recommended procedure of measuring 3-dose coverage of immunization by 12 months of age misses this critical point, and lacks the sensitivity to measure the speed of immunization, thereby adversely affecting the control of polio using OPV (John 1993, John et al. 2003). If the success of immunization is to be measured as vaccination coverage in infants, then it must be measured at 6 months of age instead of 12 months (John 1993). The ideal way to measure success is to monitor the incidence of disease by surveillance (John 1993, John et al. 1998).

Can Polio be Eradicated without IPV?

The safety problems of OPV were touched upon in the section of introduction. From the very early days of the use of OPV, the WHO was aware of the problem of vaccine-induced polio, called 'vaccine-associated paralytic polio' (VAPP) (Henderson et al. 1964, World Health Organization Consultative Group 1982). It was unwise to have chosen OPV for global use without establishing a surveillance system to detect vaccine efficacy on the one hand and vaccine safety on the other (World Health Organization Consultative Group 1982). Both VE and VAPP exhibit geographic variation (World Health Organization Consultative Group 1982, John 1989, 2002). The WHO Consultative Committee on OPV safety had actually recommended such surveillance, but EPI did not include it in its programme planning. Through EPI, the WHO was promoting 3 doses of DPT during early infancy and simply popularizing a combination product of DPT plus IPV would not only have avoided any VAPP, but also expedited the control and ultimate eradication of polio worldwide.

The very definition of polio eradication as *zero incidence of wild poliovirus infection* propounded by the WHO is faulty since the vaccine viruses are by themselves actual cause of polio not only in vaccine recipients, but also among close contacts who might be non-immune and susceptible (Henderson et al. 1964, World Health Organization Consultative Group 1982, Technical Consultative Group 2002, John 2002). Therefore I have proposed the refined definition of polio eradication as *zero incidence of poliovirus infection, wild or vaccine* (John 1996, 2000). This level of eradication can be achieved only by using IPV, since it demands zero incidence of vaccine virus infection. The Technical Consultative Group to the WHO on Polio eradication has recently estimated that the total number of cases of VAPP annually would be about 120, as long as OPV is used in all developing countries (Technical Consultative Group 2002). According to WHO, 120 VAPP cases are compatible with global polio eradication (Technical Consultative Group 2002). The estimate is flawed and the more realistic number would be in the range of 400-800 cases annually (John 2002). In 1999, there were 181 cases of documented VAPP in India alone, clearly showing that the estimate of 120 is quite unrealistic (Kohler et al. 2002). The continued occurrence of polio due to vaccine viruses cannot be tolerated as the world gets certified that polio due to wild viruses has been eradicated. Cases of VAPP are not compatible with the true definition of eradication for a 'polio-free' world. Therefore, I have strongly advocated that IPV should be introduced and OPV replaced by it as soon as wild poliovirus transmission is eliminated (John 1996, 2000, 2002)

Recently another risk from OPV has become evident, which also highlight the inescapable need for the replacement of OPV with IPV as soon as it is feasible. Sabin strains of vaccine viruses are reversible genetic variants of wild polioviruses. A single nucleotide substitution (point mutation) in the 5' non-coding segment of vaccine viruses, at position 480 from G to A in type 1 virus, at position 481 from A to G for type 2 and at position 472 from U to C in type 3 will re-establish neurovirulence (Evans et al. 1985, Kawamura 1989, Pollard et al. 1989, Skinner et al. 1989). The vaccine viruses mutate to neurovirulence quite frequently during multiplication, both in human hosts and also in cell culture (Minor 1982, Chumakov et al. 1992). Therefore, every dose of OPV already contains a minute fraction of neurovirulent revertants (Chumakov 1993).

In Japan, where wild viruses were eliminated many years ago, river and sewage waters carry vaccine-derived viruses shed by vaccinated children (Yoshida et al. 2002). Among the strains of polioviruses in the environment, 69% of type 1, 92% of type 2 and 55% of type 3 viruses were found to be neurovirulent revertants (Yoshida et al. 2002). This is clearly a signal for the hidden risk inherent in the continued use of OPV. As long as immunity levels are maintained high with early vaccination of all children, the risk of infection by vaccine-derived neurovirulent mutants will remain low. However, if vaccination slackens, then the risk of infection from environ-mental source may increase.

Contrary to commonly held belief that vaccine viruses spread efficiently among contacts of vaccinated children (Jamison et al. 1993), attenuation had actually resulted in very low infectivity and transmissibility of vaccine viruses between human subjects (John 1993). The genetic changes responsible for this modification of property have not been investigated. Recently the phenomenon of vaccine-derived viruses establish-ing wide circulation in the community has come to light. In the Dominican Republic and the adjacent Haiti, a vaccine-derived type 1 virus circulated silently for about 2 years and then showed up in an outbreak of paralytic polio lasting from July 2000 to January 2001, until effective control measures by way of intensive vaccination succeeded in eliminating it from transmission (Kew et al. 2002). Although named circulating vaccine-derived poliovirus (cVDPV), in reality it was a 'vaccine-derived wild-like' (VDWL) virus. A total of 22 paralytic cases were virologically confirmed from the time investigations began in October 2000 (Kew et al. 2002). Several cases were missed by not being investigated in a timely manner. Approximately 200 infections with type 1 wild virus results in one case of polio (John 1985, Sutter et al. 1991). Therefore, the outbreak involved at least 4400 children from October 2000 to January 2001, but the number infected prior to the detection of this virus cannot be estimated. A cluster of 3 cases of polio due to VDWL type 1 virus was detected in the Philippines in 2001 and another cluster of 4 cases due to VDWL type 2 virus in Madagaskar in 2002 (Ayelward & Wood 2002 Personal communication). A strain of VDWL type 2 virus had circulated in Egypt from 1988 to 1993 and caused 30 cases of polio (Ayelward & Wood 2002 Personal communication). The occurrence and spread of VDWL viruses are rare and unpredictable events. However, declining coverage of OPV immunization resulting in increasing proportions of non-immune children mixing with vaccine-virus infected children, seems to set the stage for their emergence and spread. Thus, the continuing use of OPV is fraught with risks, but the discontinuation of OPV also poses similar risks, namely the emergence of VDWL viruses replacing wild viruses in Nature. The only way this situation can be avoided is by withdrawing OPV under cover of immunity provided by IPV.

Yet another problem is chronic infection and prolonged shedding of vaccine-derived neurovirulent revertant viruses by a small number of individuals with primary immunodeficiency (Bellmunt et al. 1999, Minor 2001). So far 19 cases have been described, each person shedding virus for a few to several years (Wood 2002, Personal communication). They were detected in England (8 cases), USA (7 cases), and in Japan, Argentina, Taiwan and Iran (one case each). The longest recorded duration of chronic infection and virus shedding in one individual is 15 years (Minor 2001). Although no secondary spread of virus has been documented from them, they may act as a source of virus after polio eradication and discontinuation of vaccination, when susceptible children may come into contact with them. Since 'incidence' refers to new infections, these chronic infection cases do not contradict the definition of eradication as 'zero incidence'.

It seems inevitable that polio eradication will be fully achieved and concluded by IPV replacing OPV worldwide (John 1996, 2000, 2002).

Animal Model Studies to Understand Vaccine Functions

Much of our findings described above were contrary to the textbook teaching on IPV and OPV (Jamison et al. 1993, Monto 1998, Wright et al. 2000). New data that are contrary to the generally accepted paradigm may be called 'anomalies' (Kuhn 1996, John 2001). The OPV paradigm has been that it mimics natural infection, induces mucosal immunity to protect not only from

disease but also from infection, spreads widely and immunizes children around, and that it would eliminate wild virus transmission when 3-dose coverage reaches some 80-85%. Most of our data were 'anomalies' contradicting the paradigm (John 2001). On the other hand, the IPV paradigm is that it is unsuitable in polio-endemic countries, does not induce mucosal protection, and has to be given repetitively to achieve immunity. Our data contradicted this paradigm also (John 2001). Yet, in spite of reporting our data through innumerable publications in peer-reviewed Western and Indian journals, the evidence and consequent recommendations were not accepted either in India or outside, with the exception of Taiwan and Oman, after polio outbreaks that occurred while they were following the 3-dose immunization schedule. Therefore the onus was on us to prove if our findings could be validated through additional or alternate methods. The accepted approach in such situations is to develop an animal model and explore the basic interactions between the host and the virus, wild or vaccine. We had earlier found that the common bonnet monkeys (*Macaca mulatta*) are susceptible to infection with wild and vaccine polioviruses. To confirm that the monkey gut is similar to human gut, we examined it in great detail and documented the presence of gut associated lymphoid tissue, which is similar to that of humans, including Peyer's patches, lymphoid follicles, M cells and intraepithelial lymphocytes (Samuel et al. 1992a, Samuel et al. 1992b).

We have examined mucosal (gut) immunity induced by oral infection in the monkey (Selvakumar et al. 1989). Monkeys that were orally inoculated with wild poliovirus type 1 shed virus both in the throat and in faeces for 18-20 days. Two weeks after cessation of virus shedding, monkeys were reinoculated and to our surprise, all were infected and shed virus in the throat and faeces for the same duration and in similar quantities, showing the total lack of mucosal 'protective immunity' after one infection (Selvakumar & John 1989). The third inoculation resulted in much shortened duration of infection and about 90% decrease in virus quantity in the faeces, suggesting the presence of partial protective immunity (Selvakumar & John 1989). We concluded that repeated infections are necessary to induce sufficient mucosal immunity to prevent reinfection (Selvakumar & John 1989). Had we investigated so, in all probability we would have found IgA antibody on mucosal surface, but we did not have the necessary facilities or funding. This finding offers an explanation why repeated doses of OPV have to be given to the same children, with virtually 100% coverage, before wild virus transmission could be stopped, in developing countries, as have been found in the eradication campaign. Why is this not applicable in developed countries in which regular childhood vaccination was sufficient to eliminate polio? The VE of 3 doses of OPV is low in developing countries and the force of wild virus transmission very high (as simulated in monkeys with heavy virus inoculum, 100 median monkey infectious doses), unlike in developed countries in which VE is very high and the force of transmission of wild virus very low (John 1993, John & Samuel 2000). To illustrate, the median age of polio has remained at 12-18 months in India from prior to introducing immunization, during the years of immunization and even after intensification of immunization for eradication, confirming very high force of transmission as well as absence of herd effect of vaccination with OPV (Ratnaswamy et al. 1973, Maiya et al. 1981, Hovi & John 1994, Singh et al. 1999). On the other hand the median age used to be about 10-15 years in Western countries before it was eliminated, reflecting the very low force of transmission. In India 100% of children were infected by wild polioviruses by 5-10 years of age (John et al. 1970), whereas in the West some 20% of the population would remain uninfected throughout life as a result of low force of transmission.

The inescapable conclusion from all the above observations is that the protection against disease and mucosal protection from infection are dichotomous attributes of 'immunity' against poiloviruses. This phenomenon was clearly demonstrated in the monkey model (Selvakumar et al. 1989). There have been 'natural experiments' illustrating the phenomenon of the dichotomy between protection against disease and mucosal

immunity against infection following immunization with OPV (Kim-Farley et al. 1984, John 1985, Sulekha et al. 1990, Sutter et al. 1991). After achieving excellent control of polio using OPV in Taiwan, and while high immunization coverage was maintained, an outbreak of polio due to type 1 virus occurred there in 1982 (Kim-Farley et al. 1984). The investigators could not find the reason for the outbreak, the largest ever recorded, since they had assumed that the OPV paradigm described above was true (Kim-Farley et al. 1984). Therefore they attributed the outbreak to suspected unimmunised pockets of population sustaining virus transmission and seeding the outbreak. By reanalyzing their data it could be shown that there could not have been sufficiently large unimmunised pockets to explain the outbreak; on the other hand data clearly indicated that immunized and protected children, who constituted the vast majority, actually contributed to the epidemic by participating in virus transmission (John 1985). Other investigators have later confirmed this phenomenon in other similar outbreaks in well-immunized communities in Oman and Kerala State in India (Sutter et al. 1991, Sulekha et al. 1990). Thus, there was excellent agreement between our field observations, animal experiments and outbreak situations in Taiwan, Oman and India, regarding the inadequacy of protection from infection induced by OPV unless given repeatedly, even to children immune against polio paralysis.

Having found that IPV had unexpected herd effect in our community setting (an anomaly against the paradigm), just as was found in USA or Finland, we explored the possibility of gut immunity induction by IPV (Selvakumar & John 1987). Monkeys given 3 doses of IPV responded with high humoral antibody production. Such monkeys resisted infection after oral inoculation, for up to 12 months (Selvakumar & John 1987). In spite of feeding 100 median monkey infectious doses, no animal shed virus either in the throat or in the faeces (Selvakumar & John 1987). Thus, immune stimulation by the non-replicating parenteral antigen had induced strong mucosal protective immunity (Selvakumar & John 1987).

There were already two scientific observations that had questioned the then prevailing teaching about mucosal immunity. One, breast milk was shown to have virus neutralizing antibodies, proving that local stimulation was not the only reason for local, mucosal, secreted antibody (John & Devarajan 1973). Evidently, there was more to mucosal immunity than the IgA antibody production and transport, induced by local infection by poliovirus on pharyngeal or small intestinal mucosa (which of course is possible only with OPV, but not with IPV). The presence of antibody in milk was determined by the height of antibody level in the serum (John & Devarajan 1973). The second observation was that the non-replicating poliovirus antigen in IPV given parenterally to a primate model induced strong local mucosal protective immunity against a large dose of virus challenge, again proving that local induction of immune response by prior infection was not necessary for local immunity (Selvakumar & John 1987). In the past investigators had examined mucosal immunity by measuring IgA antibody levels in mucosal secretions (Ogra et al. 1968, Faden et al. 1990). Only local infection will induce high local IgA production and secretion on to the mucosal surface. Thus, by measuring IgA levels, only one aspect of local immunity is assessed, namely the secretory IgA levels (Ogra et al. 1968, Faden et al. 1990). As clearly shown in the first set of animal experiments, such local stimulation of immunity by one infection was not strong enough to resist re-infection (Selvakumar & John 1989). IPV induces only low levels of IgA antibody, thus suggesting that there are other mechanisms of local immunity than local induction of IgA by infection (Ogra et al. 1968, Faden et al. 1990). Local immunity defined as 'the inhibiting influence on local infection' may be mediated through the spill-over of IgG antibody, which was most probably the mechanism of strong gut immunity following IPV inoculation (John 1993, Selvakumar & John 1989). We did not have the facilities to explore this further; also our purpose was not to understand the mechanism of immunity, but to investigate if it was present or absent. The animal experiments supported the field experience with both vaccines.

The excellent herd protective effect of IPV as found in the early experience of countries that used IPV extensively (Finland, USA, Sweden, France) can only be understood on the basis of such explanation. More recently there is increasing appreciation that the non-replicating *Haemophilus influenzae* type b vaccine, consisting of a protein-conjugated carbohydrate capsular antigen, has unexpectedly high herd effect, virtually eliminating colonization even in unimmunisad children, which can be explained only on the basis of mucosal immunity (Takala et al. 1991, Murphy et al. 1993). Pertussis vaccine consisting of antigens given parenterally also results in excellent herd effect, consequent to mucosal immunity (Trollfors et al. 1998). Thus, the dogma that only OPV has mucosal immunity and that IPV does not have mucosal immunity is not based on science, evidence or observations, but on the basis of a paradigm repeated often enough. Indeed there have been studies investigating mucosal immunity against OPV in children given IPV or OPV and they found it in both groups. Under such study conditions, OPV induced slightly better protection, not absolute, but slightly better, than IPV did, to re-challenge with the homologous OPV viruses. That IPV also did induce protection was generally ignored (reviewed in John 1993). The mucosal immunity is determined by the height of humoral immune response, which can be modified according to the antigen content of the vaccine used. The modern IPV is a superior immunogen compared to OPV and old IPV (John 2000).

Why did Indian Public Health Authorities Ignore Indian Data?

In spite of the continuing high incidence of polio and extensive publications providing a menu of solutions, the Government continued strictly following the 3-dose recommendation, irrespective of its level of protective efficacy. In 1984, due to increasing demand to liberalize the number of doses, the WHO finally agreed to accept a dose of OPV at birth, but it was not to be counted for coverage evaluation (Expanded Programme on Immunization 1984). It was therefore called 'zero dose', meaning thereby that it was of no consequence as far as EPI was concerned (Expanded Programme on Immunization 1984). The immunization coverage evaluation continued to use 3-dose coverage as the end point, not 4 doses. Most countries and programs simply ignored this additional dose since it was not to be counted against the required 3 doses. Why would the WHO and our own Health Ministry over-defend OPV to the point that they put the very same children on whose interests EPI was established, and who trusted the Government stand on the number of doses, at unnecessary risk of developing polio due to vaccine failure? There must have been issues hidden from public's eyes and we will explore this further.

From the year EPI was introduced in India, there was no decline in the reported numbers of polio in the country for many years, as stated earlier. In the absence of disease surveillance, India had been following a 'sentinel hospital' reporting system, which continued until 1996 when it was replaced by a nation wide surveillance of acute flaccid paralysis (AFP). The sentinel reporting system accounted for about 10% of the total cases of polio (Basu 1981, John 1984a, Singh & Foster 1998). During ten years from the establishment of EPI there was no decline in the annual numbers of reported cases of polio. Indeed there were huge, nationwide epidemics of polio in 1981 and in 1987, while polio vaccination was being implemented as a national programme. Admitting failure to control polio in spite of massive inputs into the Expanded and Universal Immunization Programmes would have forced the Ministry to examine if the immunization policy was sound; had that been done, the problems with OPV would necessarily have had to be admitted. In my opinion, it is reasonable to suspect that pressure was on the Ministry not to question the efficacy of OPV. Such pressure would not have come from vaccine manufacturers since the easiest solution was to increase the number of doses in the recommended schedule. Decades later, India had to abandon the efforts to manufacture IPV on account of extraneous pressure (Bhargava 1999). The source of such influence on India, which ultimately resulted in literally lakhs of children developing polio paralysis, and delaying the control and ultimate eradication of polio, is not known for sure, but all circumstances point towards the WHO as its likely source.

The WHO had funded my own early studies on OPV (John 1972, John & Jayabal 1972, John 1975, John & Christopher 1975). The findings of poor immunogenic responses to OPV and vaccine failure resulting in polio in 'fully' immunized (according to WHO) children, as well as the various steps towards solving this problem, were regularly reported to the funding agency. WHO experts did not take into account these data while formulating their policies for the developing countries including India. As WHO ignored these findings, so did the Government of India also ignore them and a nexus was likely.

That Indian Public Health authorities ignored Indian data is unarguably evident from the events that followed the introduction of OPV in the country. The seriousness of polio as a public health problem was established through several studies (Basu 1981, Prabhakar et al. 1981, John & John 1982, Joseph et al. 1983). The inadequacy of a 3-dose OPV immunization schedule was repeatedly shown (John 1981a,b,c, 1984c, 1985). The Ministry of Health of the Government of India, under which the Expanded Programme on Immunization was operating, was unresponsive to the need to improve protection of children against polio. Why such unresponsiveness happened is an issue being raised here not to simply find fault, but to understand the phenomenon. If we want to prevent repetition of similar behavior in other areas of Public Health, then we must understand the under-lying principles that made our Public Health leadership ignore for nearly 20 years such overwhelming scientific evidence that the policy adopted in 1978 was faulty, and thus put our children at unnecessary risk of paralytic polio. The most likely explanation is that the decision-makers relied on blind acceptance of directives from experts outside the country, who either disbelieved the investigations in India and their results, or had some hidden but specific reasons to sweep the problem under the carpet.

There have been other examples of a similar nature, in which our interests were not fully satisfied when interventions were introduced in the country. For example, in the 1960s there was the push for amino acid supplementation to treat kwashiorkor, while Indian data had clearly shown that even peanut would cure it (Webb et al. 1964). More recently there has been pressure on India to use synthetic vitamin A as a supplement to be given in campaigns (along with polio vaccine during pulse immunization) to improve blood vitamin level, while we had virtually controlled vitamin A deficiency in the population by improving nutrition through food availability and health education (Indian Academy of Pediatrics 2000). These examples do have resemblance to the control of polio in that, in each case there was a particular product that was given undue importance as a solution to a real and pressing problem. Here we will confine discussion on OPV.

Globally experts in Public Health and in Health Care Services, as well as member nations, especially among the developing countries, look up to the WHO for guidance on specific issues of policies, priorities and processes. By and large the WHO has given high quality and credible advice on most matters concerning health. The EPI itself is an example of the preeminent position of WHO as the world leader in promoting Public Health. It was designed so well that member countries had simply to adopt the guidelines to establish their own in-country EPI programmes. Even though member nations are free to develop their own policies using WHO policies only as guidelines, in reality many developing countries blindly adopted them without assessing their appropriateness within these countries. As stated above, even before the 3-dose OPV schedule was adopted in India from the WHO EPI, it had been clearly shown that 3 doses were grossly inadequate in Indian children. It was most unlikely that the Public Health authorities were not reading journals in which the early data on problems with OPV efficacy were published. The subject had become hotly debated in various forums. A demand was made in 1981 for a national policy on poliomyelitis (John 1981a). A cost-benefit analysis of polio prevention and the economic loss due to uncontrolled poliomyelitis was also published in 1981 (John 1981b). A documentation of high prevalence of polio in rural areas and more importantly a demonstration of effective control by the 5 dose-schedule was published in 1981 (John 1976, Prabhaka et al. 1981). In another publication in 1981 the

question of how to control polio was discussed (John 1981c). Fervent pleas were made in Indian journals of Communicable Diseases and Public Health for urgent action to control polio and how to achieve it (John 1985b). The magnitude of the problem of polio had been repeatedly documented. In addition, the fact that it had not come under control due to faulty intervention was highlighted repeatedly

The WHO experts on EPI and poliomyelitis might have probably believed in the beginning that 3 doses of OPV were sufficient for immunizing children everywhere. But WHO could not have been unaware of the efficacy problems repeatedly reported from India, but the experts obviously ignored them. Even if it was a genuine error of judgment to begin with, when it was proved wrong by the accumulation of evidence from many developing countries WHO should have acted if the error of judgement was genuine (Patriarca et al. 1991, Sutter et al. 1991, Kim-Farley et al. 1984, John 1985a). The fact that WHO experts did not revise the policy by liberalizing the number of doses of OPV suggests the possibility that there was bias in their viewpoint. Were the experts concerned with the possibility that their credibility would be affected if they accepted that the vaccine efficacy of 3 doses of OPV was unsatisfactory and that infants should be given at least 5 doses? Was there any reason why WHO experts could have been biased in favour of OPV ? In 1972, Dr Albert Sabin donated stocks of his vaccine virus strains to the WHO (Magrath et al. 1993). Thereafter WHO did most probably have a special interest in propagating this vaccine in preference to the alternate vaccine, namely IPV. When WHO designed the Expanded Programme on immunization (EPI) and formulated policies, OPV was included and IPV excluded. The unbiased approach should have been to give an option to member countries to choose.

The problems with OPV were two: its low immunogenic and protective efficacies in developing countries and its adverse effect, namely vaccine-virus induced polio (called VAPP) in developing and developed countries. As I had illustrated above, the WHO ignored the efficacy problem for over two decades and advocated only 3 doses of OPV for individual children. The Government of India blindly adopted the WHO policy and disallowed additional doses, even though the vaccine was very cheap and five contacts with each infant were needed to give vaccines other than OPV. Giving one dose of OPV at each contact was necessary from both scientific and ethical viewpoints. Adding more doses would have opened the issue of low efficacy, and resulted in the admission of the problem, which WHO had always denied officially. Any adverse comments on OPV were apparently unacceptable. Ultimately the polio eradication efforts demanded a very liberal policy towards the number of doses per child, which was forced on WHO by the experience of national immunization days in Latin American countries (Risi Jr 1984).

A brief review of the history of certification of the safety of OPV was published recently (Robbins 1999). It was licensed in the USA in early 1960's as monovalent vaccines and later as trivalent vaccine, without adequate field evaluation within USA, as they had been used earlier in Singapore and on a very large scale in the USSR and East European countries (Robbins 1999). Only after beginning to use the vaccine did USA experts realize that the vaccine was not completely attenuated (Henderson et al. 1964). The vaccine-virus polio was indistinguishable from natural polio, for which reason many clinicians would have confused the former with disease due to wild virus infection acquired prior to vaccination. Albert Sabin did not ever accept that his vaccine could cause polio (Sabin 1964). When the WHO conducted an evaluation of the safety of OPV, Sabin was included as a member of the Consultative Group, a questionable decision indeed (World Health Organization Consultative Group 1982, John 2000). The final report of the Consultative Group declared that OPV was "one of the safest of vaccines in current use", while presenting evidence to the contrary (World Health Organization Consultative Group 1982, John 2000). Since no other vaccine in current use, then or now, is less safe than OPV, the phrase quoted above was sufficient to mislead Public Health leaders in developing countries (John 2000). The Consultative Group also cautioned: "*Since…neurovirulence tests for safety do not prove the innocuity of a vaccine with absolute*

certainty, it is essential that every programme of poliomyelitis immunization should include a continuous and effective system of surveillance" (World Health Organization Consultative Group 1982). India failed to establish such surveillance and our children suffered the consequence. For this lapse on the part of our own Directorate of Health Services, no one outside India can be blamed. Lack of even a rudimentary surveillance resulted in India not officially recognizing either the low protective efficacy of OPV, or the frequency of vaccine-induced polio. Introducing DPT on a large scale, without adequately protecting children against polio was alleged to have resulted in very large numbers of "provocation polio", a well known complication of intramuscular injections in children in polio endemic communities (John 1992, 1998c, Wyatt 1985, Sutter et al. 1992).

The Indian Council of Medical Research had been receiving all our research reports, but it neither agreed nor disagreed with the findings. If it had agreed, then it had to advise the Directorate of Health Services to re-examine and revise India's policy on polio prevention. If it had disagreed, then independent investigation had to be established to see if my findings were reproducible or not. Indifference to the findings was unfortunate. India must learn from these mistakes so that we become more self-reliant and more independent in making our own policy decisions. Overall, about 300,000 children developed polio paralysis due to 3-dose OPV failure, as a consequence to teaching the health care workers and parents that 3 doses were sufficient. An additional number, estimated to be over one million, developed polio due to provocation by DPT and other injections while protection against polio was not provided (John 1998c).

Ultimately our political system woke up and decided to address the issue of lack of control of polio in spite of a national programme to control it (Bhargava 1999). In 1988 the Technology Mission to the Prime Minister called a meeting of national experts in New Delhi, and a decision was made to establish a modern vaccine manufacturing institution with technical collaboration with French scientists (Bhargava 1999). This unit was to manufacture IPV, cell culture rabies vaccine and measles vaccine, all based on a highly efficient system of cell culture on micro-carrier particles, a technology that would have been highly beneficial to India. After progressing forward for some years, this unit was closed down in mid-1990s due to some disagreement between the Ministry of Health and the French collaborators (Bhargava 1999). Apparently the Ministry refused to license IPV in India; even today, while this review is being written, IPV is still not licensed in the country. It is important to recall here that India had a successful OPV manufacturing unit in the Pasteur Institute in Coonoor (Tamil Nadu), which had produced at least 6 batches of good OPV, but as soon as it became obvious that India will require huge quantities of OPV, as the WHO was establishing the EPI, in 1974, this unit was closed down (Balasubramanian 1975). Since then India has not indigenously manufactured one drop of OPV; all vaccine used in India has been imported either as finished product or as bulk concentrate for dilution and repacking. Forces have always been active to prevent India from becoming self-reliant in decision-making and/or becoming self-sufficient for OPV or IPV. Our own leaders seem to have assisted in this negative process. Fortunately the present Public Health and Science leadership of the country have grasped the complexities of polio immunization and moves are afoot to manufacture IPV indigenously, in the private sector.

How to Manage the End Stage of Global Polio Eradication

The ultimate goal of eradication is to be able to stop polio immunization without any risk of re-emergence of polio. Such discontinuation of immunization will apparently save the world the equivalent of over one billion US dollars annually. Every country will share in this saving. However, we cannot discontinue immunization until we are confident that poliovirus will not reappear from any source. The first phase of eradication efforts is aimed at eliminating wild polioviruses from human communities and the environment. As long as humans are not infected, polioviruses may survive in the environment only for very short periods. Therefore, the end stage of polio eradication may be defined as the interval from the time of

documenting the elimination of wild viruses to the time we can confidently discontinue all polio immunization.

If wild viruses are eliminated using OPV, vaccine virus-induced polio will continue to occur. It appears that the frequency of occurrence of vaccine polio is proportional to the incidence of polio in the pre-vaccine era (John 2002). USA had an average annual burden of about 10,000 to 15,000 cases in the pre-vaccine period, and about 10 cases of vaccine polio each year for two decades during the exclusive use of OPV. China had 40,000 to 50,000 cases of wild virus polio per year, which have been replaced by about 40-50 cases of vaccine polio. India had some 200,000 to 400,000 annual cases of polio prior to immunization and we may expect at least 100 to 200 cases of vaccine polio in their place. As long as this problem continues, we cannot claim that we have eradicated polio (John 1998).

If polio immunisation with OPV is discontinued one day without immunization using IPV, every child born thereafter will be fully susceptible to poliovirus infection. The vaccine viruses have a tendency to remain in the intestinal tracts of immunized children for a few weeks. While these viruses are shed into the environment, there is risk for the susceptible infants to get infected. This may lead to polio due to vaccine progeny viruses. In addition, such vaccine-derived polioviruses have a tendency to back-mutate to neurovirulence. If back-mutation causes the vaccine-derived neurovirulent mutants to acquire transmission efficiency, then they become very much like their wild counterparts (vaccine derived wild-like). If these events occur, then polio immunization will have to be reintroduced immediately, perpetuating the problem. For these reasons, it will be unwise to discontinue OPV immunization, unless we are able to provide immunity to new birth cohorts using the non-replicating IPV. This will ensure that children will be protected from infection and disease by vaccine-derived viruses. Vaccine viruses tend to die out in communities more rapidly than wild viruses. Therefore, after an interval of 5 –10 years when no live poliovirus will be used, but children will be protected with IPV, the world could safely discontinue all polio immunization.

If this scenario becomes more widely accepted, then India will need IPV, preferably combined with DPT in a combination vaccine against four diseases. The time to seriously consider this option and to take steps towards achieving it, is now, in 2003. As soon as India is certified free of wild poliovirus infection (anticipated or rather hoped for, in 2006 or 2007), we must introduce IPV, preferably as DPT-IPV, into the routine immunization programme and endeavor to ensure coverage achievement of at least 80-85 % of infants in every population unit. For a short period, perhaps 3 years, OPV should be given exclusively in pulse programmes while IPV is given in the routine immunization programme. During this period we have the opportunity to improve DPT-IPV coverage to 80-85%. Once we reach this target, we can safely stop OPV and thereafter continue only with IPV, until we are absolutely sure of the absence of VDWL virus in any community. Obviously our AFP surveillance has to be maintained along with the network of polio laboratories.

Epilogue

Important lessons in science, science policy and the faith or confidence of policy-makers in scientific evidence, as well as their self-esteem, self-reliance and autonomy are to be drawn from this case study. Such lessons are needed to guide us in our interventions against the innumerable health problems other than polio facing the country. As highlighted earlier, this paper is predominantly a review of work done in the author’s laboratory over three decades. The greatest discouragement we felt all along our journey of the pursuit of science and solutions to problems through science, was the utter lack of demand for the scientific work from the policy makers. The large number of publications on this subject from our laboratory is the testimony, to our perseverance in the hope that these data would become necessary the day we take the fight against polio seriously. This happened in the latter half of 1990s and thereafter, giving us the feeling of gratification for the efforts put in earlier.

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