Controversies in Polio Immunization

Naveen Thacker and Niranjana Shendurnikar¹

Deep Children Hospital, Gandhidham and ¹Medical College, Baroda, Gujarat, India

Abstract. Vaccines against poliomyelitis have been in use for nearly five decades now and have played a major role in progress towards global eradication of the disease. Both the vaccines, (oral polio vaccine and inactivated polio vaccine) and their uses are still debated with particular reference to their selective advantages vs. disadvantages, choice for individual vs. community protection and their administration strategies. Further occurrence of vaccine associated paralytic poliomyelitis with oral vaccine assumes importance in the face of disappearing disease. Further availability of inactivated polio vaccine in India and its various schedules such as sequential and combination schedules show some promise for polio eradication.

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The era of polio vaccine development entered an important phase with the tissue culture cultivation of polio virus by Enders, Weller and Robbins in 1949 and the subsequent introduction of Salk inactivated vaccine in 1955 and Sabin live, attenuated oral vaccine in 1961.^{1,2} Repeated passages through tissue cultures and the purification processes eventually produced vaccine virus strains that were attenuated to the point of minimal residual neurotropism in monkeys and no virulence in chimpanzees¹.

In 1988 the World Health Assembly, the directing council of World Health Organization resolved to eradicate poliomyelitis globally by the year 2000. Since then remarkable progress has occurred in freeing 205 countries from poliomyelitis but the persistence and resurgence of disease in countries such as India, Pakistan and Nigeria has led to the shifting of the target to 2005.

Ever since the development of polio vaccines nearly five decades ago, debate continues to exist even today regarding their usage and administration strategies. Some of the aspects such as choice of vaccine for individual protection and eradication, whether to be used as a single vaccine or in a sequential pattern, safety concerns in the face of disappearing disease and vaccination schedules are being surrounded by controversies. More over the failure to achieve the target of polio eradication by year 2000 and the later resurgence of disease in 2002 has further raised few questions about the efficacy and eradication strategies.

ORAL POLIO VACCINE

Oral administration of OPV reproduces an infection which mimics a natural infection in the alimentary tract and which is capable of inducing resistance to re infection

comparable to that found in naturally immune hosts. Experimental trials in humans have indicated that the vaccines and their close contacts may subsequently shed the vaccine virus for up to several weeks/months and the person to person spread of virus can occur.²

OPV has been the vaccine of choice for routine immunization for most of the countries in the world for nearly four decades now. The choice of OPV for India has been based on the experience in over 120 countries including China, Indonesia and United States who have eliminated poliomyelitis using OPV. Its advantages are well documented including its low cost (approximately Rs. 3/-/dose), easy to administer even by volunteers and its ability to interrupt the spread of wild polio virus by inducing high level of gut immunity. However the vaccine has a limitation as a rare occurrence of vaccine associated paralytic poliomyelitis.³

Limitations of OPV

High levels of sero conversion have been attained in temperate/industrialized countries with two or three doses of OPV. Nonetheless in developing/non industrialized nations there is a wide variation in the serologic responses observed in children to oral polio vaccine. A review of 32 studies in developing countries found that after three doses of OPV, the mean proportion of infants with detectable levels of serum neutralizing antibodies was only 73% (range 36-99%) for type 1, 90% (range 71-100%) for type 2 and 70% (range 40-99%) for type 3 poliovirus.⁴ A large scale randomized trial in Brazil and Gambia has also confirmed these findings.⁵ Even after use in mass campaigns and giving 8 doses gaps in immunity have persisted in some countries, especially for type 3 polio virus.⁶

A study, which administered five doses of OPV at an interval of 4 weeks observed sero conversion rates of

Reprint requests : Dr. Naveen Thacker, Plot 208, Sector 1-A, Gandhidham - 370 201.

88.7%, 93.5% and 96.5% for type 1, 2 and 3 polio viruses respectively. It was postulated that the factors that contributed to lower sero conversion rates with three doses were overcome with the five doses of OPV.⁷ Several factors such as interference with other enteroviruses, presence of high levels of maternal antibodies, inhibition of type 1 and 3 virus from type 2 virus and diarrheal episodes have been advanced to explain sub optimal sero conversion to OPV in developing countries.⁷

Failure of OPV had been noted as experienced by the continuous outbreaks of polio among children in Gaza and the West Bank, despite the extensive use of OPV since late 1960s. Routine use of OPV supplemented by mass campaigns achieved an infant immunization coverage of 85% to 90% but was insufficient to control the disease.⁸ Approximately half of those children contracting polio had been partially or fully immunized but serologic surveys in 1970s revealed low seropositivity, perhaps related to inter current enteric infection causing viral interference.¹

A study in Brazil which evaluated the effect of diarrhea on OPV failure concluded that diarrhea at OPV receipt was associated with vaccine failure to poliovirus types 1 and 3 only after the second dose of OPV. These data support the current recommendations that children with diarrhea receive OPV and be re-immunized once their illness resolves. While the effect of diarrhea on vaccine failure may be limited to second dose of OPV, programmatic realities may preclude dose specific recommendations.⁹

The precise mechanisms by which mass immunization campaigns interrupt wild polio virus transmission are not exactly well defined. It has been believed that an increased number of doses in mass campaigns, leads to an increase in the levels of individual humoral and secretory immunity, thereby explaining the effectiveness of this strategy. Seroprevalence rates have been found to be consistently higher in children who have received additional doses through mass immunization than in children who have received all their doses through the routine immunization program, especially for type 3 polio virus. These findings suggest that adding further doses of OPV to the routine schedule is unlikely to have as great an impact on the immune status of children as administering the same number of doses during mass campaigns.¹⁰

Oral Polio Vaccine and Herd Effect

The spread of oral vaccine related polio virus from the vaccine recipients to contacts has long been thought to contribute towards the development of herd immunity particularly so in under developed/non-industrialized nations. Subsequent to the development of gut immunity which is believed to follow both OPV and IPV, the duration and quantum of polio virus excretion is diminished. With an increasing number of children getting immunized with either of the vaccine, they are no

longer likely to participate in wild virus transmission and the circulation of virus becomes slower and less intense. This would further lead to fall in the rate of infection and disease incidence in the unimmunized segment of population also. As the decline in the disease in the unimmunized segment is due to reduced frequency of infection, this is more appropriately referred as a herd effect.¹¹

Vaccine Associated Paralytic Poliomyelitis

Vaccine associated paralytic poliomyelitis (VAPP) is a rare but a serious consequence of the administration of oral polio vaccine. Vaccine virus progeny excreted by the vaccinees are known to mutate and it is theoretically possible that they could become neurovirulent and be capable of causing paralytic disease in the vaccinee or their contact.^{12,13} All strains of polio virus regardless of how highly attenuated, retain the property of multiplying in and destroying cells in the monkey spinal cord—the crucial test used to determine whether a strain is sufficiently attenuated and safe for human use.¹⁴ The mechanism of VAPP is believed to be mutation, or reversion of the vaccine virus to a more neuro tropic forms. These mutated viruses are known as revertants. Reversion is believed to occur in almost all the vaccine recipients but it only rarely results in paralytic poliomyelitis.¹⁵

The reported incidence of VAPP in industrialized countries including United States has remained fairly constant since the inception of OPV. Between 1980 to 1994, 133 cases of VAPP were reported in USA, of which 125 (94%) were associated with the use of OPV. The remaining cases were either imported or could not be definitely linked to the vaccine.¹⁶ Data from acute flaccid paralysis surveillance in Latin America showed an estimated risk of VAPP as 1 case per 1.5 to 2.2 million doses administered in 1989-1991.¹⁷ In England and Wales, the estimated risk of VAPP(1985-1991), was 1 case of VAPP per 1.4 million doses of OPV administered.¹⁸ Most of these studies have reported a substantially increased risk of VAPP following the first dose of OPV and that children with beta cell immune dysfunction were at higher risk of VAPP.¹⁹

The exact reason for the dose difference of VAPP are not known with certainty but it is probably because the vaccine virus is able to replicate longer in a completely non-immune infant. Such a prolonged replication increases the chances of emergence of a revertant virus that may cause paralysis.¹⁵

Except in Latin America (1989-91) and in India (1999) VAPP risk has not been estimated in tropical countries where the disease has remained endemic for long periods. Recently data on AFP surveillance has been analyzed to estimate the risk of VAPP in India. The study observed that a total of 181 AFP cases met the case definition for VAPP (AFP cases with onset of paralysis in 1999, residual weakness 60 days after onset of paralysis and isolation of

vaccine derived polio virus). The study concluded that the overall risk of VAPP was 1 per 4.1-4.6 million doses administered, recipient risk was 1 case per 12.2 million, first dose recipient risk was 1 case per 2.8 million and subsequent dose recipient risk was 1 case per 13.9 million. On the basis of the data from a highly sensitive surveillance system, it was concluded that the estimated risk of VAPP in India is evidently lower than that in other countries not withstanding the administration of multiple doses of OPV in mass immunization campaigns.²⁰

INACTIVATED POLIO VACCINE (IPV)

Although inactivated (Salk) polio virus vaccine (IPV) was licensed in 1955, an enhanced potency IPV was developed in late 1970s to induce a more predictable and solid immune response and also requiring a fewer number of doses of the vaccine. An enhanced IPV has been available in USA since 1988.²¹ This vaccine is produced in vero cells and contains all the three types of vaccine related polio viruses.¹⁵ Certain issues such as immunogenicity and the lack of gut immunity of IPV restricted the widespread use of IPV but now adequate information has become available to derive satisfactory conclusions about these issues.

IPV is highly effective in producing immunity to polio viruses and providing protection from paralytic poliomyelitis.^{22,23} The vaccine is reported to be highly immunogenic with over 90% or more of vaccine recipients developing protective antibodies following two doses of vaccine.^{15,24,25} Subsequent evaluation of sequential IPV-OPV schedules in United States confirmed the high seroconversion rates following two doses of IPV. After two doses of IPV followed by two doses of OPV, 95% or more children developed antibodies to all the three serotypes of polio viruses.²¹

There had been earlier apprehensions about the likely short term effect of immunity following IPV but accumulating data has suggested that the protective antibodies persist for several years following primary immunization with IPV.²⁶ Some industrialized countries have become polio free using IPV but this vaccine has not been recommended by WHO for polio eradication in developing countries.²⁷ Several countries have used immunization schedules based on the sole use of IPV and these include Sweden, Finland, Netherlands and Iceland.⁸ The countries that have used a combination of OPV-IPV and have become polio free (Denmark, West Bank) have used a complex schedule of vaccine combinations that are not completed till the first birthday.²⁷

Enhanced Immunogenicity IPV

Enhanced potency IPV (eIPV) is a more potent IPV with greater antigenic mass with the potential to immunize adequately, using a reduced number of doses. Clinical studies have confirmed that 90% to 100% of children developed protective antibodies to all three types of

poliovirus after the administration of the currently available eIPV.²⁸

Multiple schedules of eIPV have been tested, as an eIPV-only schedule, sequential eIPV-OPV schedule, in combination with diphtheria/tetanus/pertussis, and as part of a number of investigational combinations including acellular pertussis, *Haemophilus influenzae* type b conjugate, and recombinant hepatitis B surface antigen.^{24,29} eIPV is now licenced for use in more than 60 countries worldwide.

Clinical trials have established the immunogenicity of two doses of eIPV given as primary immunization in the first year of life.³⁰ After the second dose, 100% of children had antibody titers greater than 1:16 against all three types. Significant boosts in antibody concentrations were noted after a third dose given at 18 months of age, with a 5- to 10-fold increase in GMT.³¹ The clinical efficacy of eIPV was 89% after two doses in a Senegal study.³² A study in the North Arcot Region of Tamil Nadu, India comparing the efficacy of OPV *vs* eIPV has shown the higher efficacy with later (66% *vs* 92%).³³ Greater immunogenicity and efficacy is seen with a three-dose eIPV schedule.³⁰ In one Canadian study, 98% of vaccinees seroconverted after two doses at 2 and 4 months of age. The third dose at 18 months increased seroconversion to 99.7% and had declined only slightly by the fourth dose at 4 to 6 years.⁸ The fourth dose produced virtually 100% positivity.

Combined Schedules of IPV-OPV

As it is important for polio immunization to be completed before 4 months in developing countries, a randomized multi-centered study was conducted with a simultaneous administration of OPV/IPV at the ages routinely recommended by WHO, in Gambia, Oman and Thailand. The study concluded that across the study sites IPV given at 6,10 and 14 weeks of age provided inadequate protection against polio virus. This is due to probably nearly waning age, with an interference from maternal antibodies and a shorter dosing interval. In contrast, the combined schedule with the simultaneous delivery of OPV and IPV at 6,10 and 14 weeks led to an excellent serologic response in three different parts of world, with mucosal immunity equivalent to that provided by OPV alone without the risk of VAPP.²⁷

A controlled study was conducted in Karachi, Pakistan to compare humoral and mucosal immune responses against polioviruses in infants observed the addition of three doses of IPV to three doses of OPV induced a significantly higher percentage of seropositive children at 24 weeks of age for polio 1 (97% versus 89%, $P < 0.001$) and polio 3 (98% versus 92%) compared to the EPI schedule. Combined schedules of OPV and IPV in the form of diphtheria-pertussis-tetanus-IPV vaccine (DPT-IPV) may be useful to accelerate the eradication of polio in developing countries.³⁴ Clearly, both eIPV-only and eIPV/OPV schedules can be successful. In countries

where wild-type virus no longer circulates and where general hygiene is good, eIPV alone may be the vaccine schedule of choice.¹

Sequential IPV/OPV Schedules

Several United States trials have tested sequential eIPV-OPV vaccination schedules, comprising of one to three doses of eIPV, followed by one to two doses of OPV. Better immunogenicity resulted after three doses than after two doses of eIPV given as a primary series. Post-dose 3 and pre-booster titers were higher in infants given eIPV and OPV simultaneously at the third vaccination session than in infants who received two or three doses of eIPV followed by one dose of OPV.^{28,30}

Sequential eIPV-OPV may be the most efficacious tool for polio eradication. A number of countries have chosen to use such a combination, typically giving one or more doses of eIPV before boosting with OPV. This regimen is also likely to be safer than an early OPV schedule by substantially reducing VAPP among recipients and contacts. Experience now provides evidence for the safety and efficacy of such schedules.⁸ Israel, Gaza, and the West Bank have used a combination of an IPV (later eIPV) and OPV vaccination schedule since 1979, a revised practice begun owing to failure of the OPV-only regimen.³⁵

IPV and Mucosal Immunity

Concerns have been raised that inactivated polio vaccine would induce lower levels of mucosal immunity than OPV and that as IPV virus does not spread to the unvaccinated contacts as the live vaccine does, there may be less efficacy in preventing the circulation of wild virus.^{1,36} IPV and its enhanced version eIPV have now been shown to induce a substantial degree of mucosal immunity with a demonstrable protective effect.^{28,37} Several studies have indicated that the immunity with IPV induces IgA in nasopharyngeal and intestinal secretions, with higher titers seen in higher potency IPV.^{28,38}

In fact the immunity induced in pharynx is equivalent to that induced by OPV.³⁸ Reduced pharyngeal shedding with a decreased community transmission of polio virus in United States was demonstrated with the use of IPV in 1950s.³⁹ IPV has clearly provided effective community protection in countries that have maintained IPV only schedule.¹ Pharyngeal immunity though an important defence mechanism in countries where the droplet spread of polio virus is important, remains a relatively less important concern in India where the predominant mode of virus transmission is feco-oral route. The marker of gut immunity polio virus specific secretory IgA (pSIgA) titer in stool as well as pharyngeal secretions are found to be no different when eIPV and OPV are compared.³⁸

CONCLUSION

Summarily OPV is the vaccine which is economical, easy to administer even by volunteers and has an effective

ability to interrupt the spread of wild poliovirus by inducing high levels of gut immunity. Thus, it is the vaccine of choice which should continue to be used for polio eradication in countries like India, but has its own drawbacks like it needs multiple doses for individual protection, with a risk of VAPP and prone to interference with enteric infections, childhood malnutrition and requires stringent cold chain maintenance.

IPV is an ideal vaccine for an individual protection and its various schedules such as sequential and combination schedules show some promise for polio eradication. Some more studies are needed in this direction and it may be possible that such a strategy may be an answer to problem in areas facing outbreaks of the disease. Sequential IPV/OPV schedules can be considered as the first phase of transition towards an all IPV schedule for future. The cold chain and the safety concerns with the use of IPV have been well addressed by its use in the countries which are polio free or on the verge of polio eradication. IPV can be combined and used effectively as per EPI schedule. However, factors such as supply of vaccine, cost and trained man power and lack of feasibility for mass administration are likely to limit its wide scale use in a country like India.

Western hemisphere is now free of poliomyelitis due to high immunization coverage, intensive disease surveillance, active case investigation and an aggressive control of the outbreaks. In the face of the disappearing disease, concern for issues such as VAPP will also have to take a precedence.

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Controversies in Polio Immunization

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