Why Has Polio Eradication Program Failed in India?

INTRODUCTION

Polio eradication program was launched in India in 1995, and global eradication was expected by end 2000. In addition to routine OPV vaccination, two rounds of pulse polio immunization (PPI) were introduced. In 1999 quantity of P3 vaccine viruses was increased from 500,000 to 600,000 per dose of two drops of OPV, and number of vaccination rounds were increased to 5-6 rounds per year for some states. In 2005 monovalent OPV1 (mOPV1) and later monovalent OPV3 (mOPV3) were introduced in Uttar Pradesh. It was stated that monovalent vaccines are 2-3 times more effective than trivalent oral polio vaccine. In year 2007 monovalent OPV1, and OPV3 were administered in Bihar also in addition to trivalent oral polio vaccine (tOPV). In 2007, number of vaccination rounds for Uttar Pradesh was increased to a round every month. But, polio has not been eradicated from India. On the other hand polio incidence has risen as can be seen in **Table I(1)**.

OPV has eradicated polio from most parts of the world, but has failed in India and few other countries. Why has OPV failed to eradicate polio from India? And why have we failed to find reasons for this?

WHY HAS OPV FAILED?

Majority of polio cases receive many doses of OPV before onset of paralysis (*Table II*). Inability to generate adequate antibodies to provide protection after appropriate number of doses of a vaccine, is known as vaccine failure. Factors for poor antibody generation by OPV may be in the vaccine and/or in the host. The nation has been repeatedly assured that the vaccine being administered is of high potency. Experts had stated: "Hence, it is very reassuring to note that the Oral Polio Vaccine (OPV) used in the country is adequately potent"(2), thus, it indicates that some factors in the hosts including co-infection

with other enteroviruses, malnutrition, and immunosuppression due to disease or drugs may be responsible for poor response to the vaccine. There are some observations suggesting that genetic factors may also play a role(3).

WHY HAVE WE FAILED TO FIND REASONS FOR POOR Performance of OPV in India?

Reasons for this can be discussed under two broad groups: (*i*) misconceptions regarding some properties of OPV, thus, missed to notice limitations or drawbacks of OPV; and (*ii*) some conclusive scientific evidence which emerged during eradication program was ignored and thus, missed the clues regarding reasons for failure to achieve polio eradication.

A. Misconceptions

1. *Herd immunity by secondary spread of vaccine viruses*. Oral polio vaccine has attenuated polio viruses which may induce immunity, but, do not cause active disease. These viruses replicate in the gut and are shed in feces. It was thought that these shed attenuated vaccine viruses, on reaching non-immune individual would induce immunity in this contact in similar way as had occurred in the vaccine recipients. It is called herd immunity because immunity has been induced without the contact taking the vaccine. "Widespread 'herd immunity' results, even if only approximately 66 percent of the community is immunized" (4,5).

Now it is known that this additional benefit of OPV almost does not occur, the nominal benefit which may occur could be the boosting effect on the already present immunity. The additional benefit of herd immunity does not occur because of two reasons: (*i*) attenuated polioviruses contained in OPV have markedly reduced infectivity, and (*ii*) low load of vaccine viruses spread through feces. There are about 1,000,000 type 1 polioviruses, about 100,000 type 2 polioviruses and about 600,000 type 3 polioviruses *i.e.*, about 1.7 million polioviruses in each dose of two drops of OPV. On the other hand,

YASH PAUL

 $TABLE \ I \ \ \text{Number of Polio Cases in Different States from 1998-2007 As on 8th March, 2008}$

S.No	States	1998	8 1999	2000	2001	2002	2 2003	2004	4 2005	5 2006	5 2007	CBR*
1	Andaman & Nicobar	0	0	0	0	0	0	0	0	0	0	19.1
2	Arunachal Pradesh	0	0	0	0	0	0	0	0	0	0	22.3
3	Dadra & Nagar Haveli	1	0	0	0	0	0	0	0	0	0	34.9
4	Daman & Diu	5	0	0	0	0	0	0	0	0	0	23.7
5	Goa	2	0	0	0	0	0	0	0	0	0	14.3
6	Kerala	0	1	0	0	0	0	0	0	0	0	17.9
7	Lakshadweep	0	0	0	0	0	0	0	0	0	0	26.1
8	Manipur	0	0	0	0	0	0	0	0	0	0	18.3
9	Meghalaya	0	0	0	0	0	0	0	0	0	0	28.5
10	Mizoram	0	0	0	0	0	0	0	0	0	0	16.9
11	Nagaland	0	0	0	0	0	0	0	0	0	0	11.8
12	Pondicherry	2	0	0	0	0	0	0	0	0	0	17.8
13	Sikkim	0	0	0	0	0	0	0	0	0	0	21.8
14	Tripura	0	0	0	0	0	0	0	0	0	0	16.5
15	Assam	1	0	0	1	0	1	0	0	2	0	26.9
16	Himachal Pradesh	0	0	0	0	0	0	0	0	1	0	22.1
17	Jammu & Kashmir	0	0	0	0	1	0	0	0	1	0	19.6
18	Tamil Nadu	91	7	0	0	0	2	1	0	0	0	19.2
19	Andhra Pradesh	96	21	0	0	0	21	1	0	0	5	21.3
20	Chandigarh	1	2	1	0	1	0	0	0	1	0	17.5
21	Chhattisgarh	15	3	0	0	1	0	0	0	0	0	26.7
22	Delhi	47	73	3	3	24	3	2	1	7	2	20.3
23	Gujarat	164	9	2	1	24	3	0	1	4	1	25.2
24	Haryana	39	19	4	5	37	3	2	1	19	6	26.9
25	Jharkhand	27	8	1	2	12	1	0	2	1	0	26.5
26	Karnataka	71	21	8	0	0	36	1	0	0	1	22.0
27	Madhya Pradesh	107	17	2	0	21	11	0	0	3	0	31.2
28	Maharashtra	121	18	7	4	6	3	3	0	5	2	20.9
29	Orrisa	49	0	0	0	4	2	0	0	0	1	24.3
30	Punjab	9	4	0	5	2	1	0	1	8	1	21.5
31	Rajasthan	63	18	0	0	41	4	0	0	1	3	31.2
32	Uttarakhand	36	16	1	3	14	0	1	1	13	6	20.2
33	West Bengal	26	21	8	1	49	28	2	0	1	2	20.6
34	Bihar	131	115	49	27	121	18	41	30	61	497	31.9
35	Uttar Pradesh	845	757	178	216	1242	88	82	29	548	339	32.8
Total cases in India		1934	1126	265	268	1600	225	136	66	676	866	
Biha	r and UP %age	50.46	77.44	85.66	90.67	85.18	47.11	90.44	89.39	90.08	96.54	

* CBR: Crude Birth Rate; Source: Mittal and Mathew(1).

one gram of fecal matter of vaccine recipient contains about 100 vaccine polioviruses(6). Thus, 17 kg of fecal matter may provide same quantity of vaccine polioviruses as are contained in one dose of OPV. How much antibodies would be generated by few thousand vaccine polioviruses spread through feces when many doses of OPV, each dose containing about 1.7 million vaccine polioviruses have failed to generate protective immunity?

During replication in the gut some of the attenuated vaccine polioviruses back-mutate and reacquire the neurovirulence and become capable to cause paralytic poliomyelitis(7). These mutant vaccine polioviruses can cause paralysis in the vaccine recipient, called recipient VAPP and through secondary spread in non-immune contact called contact VAPP. Melnick(8) was skeptical about the 'collective interest' of the community through benefit of herd immunity provided by the spread of live poliovaccine virus, and stated: "some people consider this spread into the community to be an advantage, but the progeny virus excreted and spread by vaccinees often is a mutated virus. Obviously it cannot be a safety tested vaccine, licensed for use in the general population".

There has been only one study regarding the incidence of VAPP in India by Kohler, *et al.*(9). Of 181 VAPP cases, 60 were recipient VAPP cases and 121 were contact VAPP cases. As individuals upto age of 15 years are included in surveillance for acute flaccid paralysis (AFP), those above 15 years of age who might have developed contact VAPP remain unknown.

Another point which needs mention is that the mutant vaccine derived polio viruses (VDPV) may circulate in the community, are called cVDPV and can cause outbreaks of polio caused by man-made mutant polioviruses derived from OPV. The Global Polio Eradication Initiative (GPEI) currently categorizes VDPVs as: (*i*) circulating VDPVs (cVDPVs) which emerge in areas with inadequate OPV coverage, (*ii*) primary immunodeficiency associated VDPVs (iVDPVs), and (*iii*) ambiguous VDPVs (aVDPVs), for which the clinical, epidemiological and virological data are insufficient for definitive assignment. Even the last two variants

could pose risks for the community, nature and extent of which are not fully understood at present.

Thus, contrary to the erroneous perception that secondary spread of vaccine polio viruses provides some benefit to the community, this may harm the community.

2. Is 100% vaccine coverage necessary? For a vaccine preventable disease where causative organism spreads from man to man, as happens in case of poliovirus, 100% vaccine coverage of susceptible population is not required. The immunized persons may provide protection to a non-immune individual without inducing immunity essentially by breaking the transmission of the infection or lessening the chances of a susceptible coming in contact with an infected individual. It is called herd protection(10). It seems bizarre that on the one hand property of herd immunity is attributed to OPV where non-vaccinated individuals may derive additional benefit; and on the other hand 100% vaccine coverage is mandated.

3. *Role of unvaccinated children:* A non-vaccinated child may develop polio or immunity following wild poliovirus infection; else, he/she may not get exposed at all. Thus, every unvaccinated child may not participate in wild poliovirus circulation. On the other hand, a fully vaccinated but unimmunized child can also participate in wild poliovirus circulation. But, only the unvaccinated children are blamed for failure of eradication program(11).

B. Scientific evidence which was ignored

1. *VAPP after subsequent OPV dose:* Risk of vaccine associated paralytic poliomyelitis (VAPP) is highest with the first dose of OPV(12-14). In a study by Kohler, *et al.*(9) there were 60 recipient VAPP cases; 9 children (15%) had developed paralysis following first dose of OPV, 4 (6.7%) after 2nd dose, 15 (25%) after 3rd dose and 32 (53.3%) after 4th or higher dose. NPSP data from Rajasthan for year 2000 showed that of 15 VAPP cases not a single case developed VAPP after the first dose of OPV(15).

Why few children in India developed VAPP following first dose of OPV? Plausible explanation

YASH PAUL

for this observation could be that in India the first dose of OPV is given soon after birth or by 6 weeks of age, and the persistent maternal antibodies prevent development of paralysis by mutant neurovirulent vaccine polioviruses as well as by wild polioviruses. Onset of paralysis after subsequent OPV dose, especially after 4th and higher dose, indicates that although maternal antibodies had declined or disappeared, OPV administered had failed to generate antibodies level required for protection. A child who develops paralysis after 12th dose of OPV proves that the previous 11 doses of OPV had not generated adequate antibodies, suggesting that children were showing poor response to OPV.

2. Decline in polio incidence was not uniform: Due to shortage of electricity to maintain proper cold chain, potency of OPV may be adversely affected. Environmental factors like overcrowding and poor sanitation help in quick transmission and spread of wild polioviruses in the community. Malnutrition, inter-current infections, immunosuppression due to disease or drugs in the hosts may be responsible for poor response to OPV. Shortage of health related infrastructure and health workers can be contributing factors for low vaccine coverage.

Why did children from different areas show different response to same OPV? Bihar and Uttar Pradesh have never been polio free since launch of polio eradication program. It can be said that all those factors which have adverse effects on polio eradication, exist in Bihar and Uttar Pradesh. But, similar or equally similar conditions exist in some of those states also where polio has been controlled. It would suggest that some genetic factors play important role in success or failure of eradication of polio by OPV in different populations.

It was known since long that children in tropical and developing countries respond poorly to OPV(16-19). Poor seroconversion had been reported from India during 1970s(20-22). But, precise reasons for poor response were not known. The problem of non-responders to hepatitis B vaccine is known since 1980s and measles vaccine since 1990s(23). In 2004 Newport, *et al.* (24) reported role of genetic factors in antibody response to OPV. Because of genetic variations, antibody formation may be variable in different populations. The author had postulated(3) that some genetic factors may have played important role for poor response to OPV in children from Bihar and Uttar Pradesh because of the following obser-vations:

- (i) The states and union territories where decline in polio incidence occurred rapidly have higher Mongoloid, Negrito ethnic population, or had been Portuguese or French colonies before becoming part of independent India.
- (*i*) Even during years 2002 and 2006 when there was resurgence of polio incidence, polio cases did not occur in these states.
- (*iii*) It is unlikely that quick decline in some states could be due to better vaccine coverage and superior cold chain maintenance. High birth rate (*Table I*) in Bihar (31.9) and Uttar Pradesh (32.8) is offered as an explanation for difficulty in polio eradication. Dadra and Nagar Haveli, Meghalaya, Madhya Pradesh, and Rajasthan have crude birth rates of 34.9, 28.5, 31.2 and 31.2, respectively. Children from these states have shown better response than children from Bihar and Uttar Pradesh, despite a comparative birth rate.
- (iv) Children from Uttar Pradesh and Bihar are poor responders to current polio vaccines, Grassly et al.(25) estimated that per dose vaccine efficacy of trivalent OPV for type 1 was 9% (6-13%) for Uttar Pradesh, 18% (9-26%) for Bihar and 21% (15-27%) for rest of India; for type 3, efficacy was 9% (3-15%) for Uttar Pradesh, 22% (4-36%) for Bihar and 21% (8-33%) for rest of India. Thus, children from Uttar Pradesh show poor response to OPV type 1 and 3, while children from Bihar show slightly poor response to OPV type 1 but better response to OPV type 3. This different response to different strains in OPV by children from these two states can not be due to environmental factors, alone. It is thus possible that due to some genetic factors children from different populations show different response to OPV.

3. *Polio in vaccinated children:* It can be seen in the *Table II* that cases of paralytic polio are occurring

predominantly among the children who had received 4 or more doses of vaccine, and lately among those who had received more than 7 doses of OPV. On the other hand among the polio cases percentage of unvaccinated children is very low. It is being repeatedly stated that poor vaccine coverage is the reason for failure of the program. In case children develop paralytic disease after taking many doses of OPV, it means that many doses of vaccine had failed to provide protection.

Even after publication of study by Grassly, *et al.*(25) in 2006 the only remedial step taken was increase in rounds of pulse polio immunization in Uttar Pradesh and Bihar.

New Challenge: Sudden Rise in Polio Incidence

In the year 2005 only 66 confirmed polio cases were reported from India, the lowest figure till date, of these 4 were caused by P3. In 2006, 676 confirmed polio cases were reported, (P1:648; P3:28) Experts expected this rise as a part of 4 years cycle, similar to what happened in 1998 and 2002. But, it is worth noting that polio incidence in the following years i.e. in 1999 and 2003 was low, such pattern was not seen in 2007 (*Table I*). However the coverage for P3 was not adequate as for most of the rounds mOPV1 and tOPV were used only in routine immunization (RI). As RI coverage is so low, in effect most of the children in UP and Bihar did not get adequate P3 coverage. This is projected as the main reason for the P3 outbreak.

Three changes in polio scenario are being observed in India 2007 onwards: (i) there is a sudden increase in polio cases by P3; in 2007 out of 866 polio cases 786 cases were caused by P3; during

2008 as on 22nd March 2008, out of 150 polio cases 149 cases were caused by P3, (*ii*) number of polio cases increased in Bihar as can be seen in **Table I**, even during 2008 out of 150 polio cases reported from India 127 cases had occurred in Bihar, and (*iii*) large number of polio cases occur from June to September every year but, there is a sudden rise in polio cases, since November 2007 as can be seen in **Table III**.

Why sudden rise in polio incidence by P3 has occurred? Although precise reasons for the sudden rise in number of polio cases in Uttar Pradesh and Bihar have not been investigated, but, it could be that polio viruses have developed some sort of 'vaccine resistance'. There is the possibility that primary vaccine failure may result in 'vaccine pressure', leading to the development of mutant polioviruses strains that are 'resistant' to the antibody produced by the vaccine(24). In the past this phenomenon had been observed with measles vaccine(26-30). It is akin to 'drug resistance' developed by microorganisms.

As stated already Bihar and Uttar Pradesh have never been polio free, and administration of mOPV1 and mOPV3, and increased rounds of vaccination have failed to control incidence of polio in these two states. On the other hand, proportion of polio cases which was about 90% during 2004-2006 had increased to 96% in 2007 as can be seen in *Table I*. It strongly suggests that some genetic factors in children from these two states are responsible for poor response to the currently administered trivalent and monovalent oral polio vaccines.

The probability that children from Uttar Pradesh and Bihar show poor response to OPV due to some genetic factors should be explored, and efforts

1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
15%	14%	14%	9%	16%	14%	4%	0%	3%	1%
47%	45%	28%	31%	41%	35%	11%	11%	10%	3%
32%	34%	35%	41%	33%	34%	41%	44%	22%	12%
7%	8%	23%	18%	11%	17%	44%	45%	65%	85%
	1998 15% 47% 32% 7%	1998 1999 15% 14% 47% 45% 32% 34% 7% 8%	1998 1999 2000 15% 14% 14% 47% 45% 28% 32% 34% 35% 7% 8% 23%	1998 1999 2000 2001 15% 14% 14% 9% 47% 45% 28% 31% 32% 34% 35% 41% 7% 8% 23% 18%	1998 1999 2000 2001 2002 15% 14% 14% 9% 16% 47% 45% 28% 31% 41% 32% 34% 35% 41% 33% 7% 8% 23% 18% 11%	1998 1999 2000 2001 2002 2003 15% 14% 14% 9% 16% 14% 47% 45% 28% 31% 41% 35% 32% 34% 35% 41% 33% 34% 7% 8% 23% 18% 11% 17%	1998 1999 2000 2001 2002 2003 2004 15% 14% 14% 9% 16% 14% 4% 47% 45% 28% 31% 41% 35% 11% 32% 34% 35% 41% 33% 34% 41% 7% 8% 23% 18% 11% 17% 44%	1998 1999 2000 2001 2002 2003 2004 2005 15% 14% 14% 9% 16% 14% 4% 0% 47% 45% 28% 31% 41% 35% 11% 11% 32% 34% 35% 41% 33% 34% 41% 44% 7% 8% 23% 18% 11% 17% 44% 45%	1998 1999 2000 2001 2002 2003 2004 2005 2006 15% 14% 14% 9% 16% 14% 4% 0% 3% 47% 45% 28% 31% 41% 35% 11% 11% 10% 32% 34% 35% 41% 33% 34% 41% 42% 7% 8% 23% 18% 11% 17% 44% 45% 65%

TABLE II Number of OPV Doses Received by Polio Cases, 1998-2007

Source: www.npspindia.org, Accessed on 2nd Feb, 2008.

Month	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
January	112	36	36	7	18	51	4	10	8	24	110
February	32	22	10	1	8	16	3	5	9	14	40
March	42	11	10	3	7	9	1	1	8	14	_
April	26	8	20	3	16	7	1	2	13	14	_
May	49	39	6	4	42	5	9	2	36	32	_
June	118	69	8	13	117	7	14	6	76	30	_
July	324	142	25	30	251	25	13	3	121	64	_
August	418	187	39	62	280	29	18	6	114	78	_
September	283	193	32	33	334	30	18	14	137	82	_
October	170	195	31	38	247	20	32	7	71	98	_
November	226	155	31	43	180	16	14	7	55	199	_
December	134	69	17	31	100	10	7	3	28	217	_
Total	1934	1126	265	268	1600	225	134	66	676	866	150

TABLE III MONTHLY RECORD OF POLIO CASES

Source: www.npspindia.org, as on 22nd March, 2008.

should be made to find a vaccine which will be more effective in children from these two states. Otherwise, we will have to extend the deadline again and again after introducing new strategies which may fail again as has happened in past. The present pattern of polio cases where number of polio cases by P3 is very high in Bihar, should be a reason for concern. Grassly, et al.(25) had stated that children from Bihar show very good response to OPV3 thus occurrence of high number of polio cases by P3 in Bihar indicates that because of some mutations poliovirus type 3 has either become more virulent or become resistant to antibodies generated by OPV3 and thus there is a likely risk of epidemic by P3 in near future. It can be said that some children from Uttar Pradesh and Bihar are poor responders to OPV, thus, OPV has failed to eradicate polio from India. It also appears that polio viruses, especially type 3 have mutated and become resistant to antibodies generated by OPV(31). It appears that polio eradication strategy was based on the presumption that OPV will eradicate polio, because, it was supposed to do so.

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KEY MESSAGES

- OPV has brought down the incidence of polio cases, but it cannot eradicate polio from India.
- · Children from Uttar Pradesh and Bihar show poor response to the currently available oral polio vaccines.
- Current rise in polio cases by P3 is an issue of concern. It is likely that poliovirus type 3 has mutated and is not affected by antibodies produced by OPV type 3.
- There is an urgent need for re-evaluation of polio vaccines and eradication strategy.

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INDIAN PEDIATRICS

VOLUME 45-MAY 17, 2008

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Polio Eradication and Environment

Whenever we talk of dealing with infections, we think only in terms of research and development of vaccines and drugs. What we forget are the basics *i.e.*, poor environmental sanitation and public health system. This holds as much true in the case of Polio Eradication Program (PEP) as for others. Consider the following quotes:

ENVIRONMENT: THE MISSING LINK IN POLIO ERADICATION PROGRAM

"Improved sanitation explains the virtual eradication of Polio from the USA in the early 1960s, when only about two-thirds of the population was immunized with the Salk vaccine, and the subsequent absence of circulating wild–type polio viruses in the United States and Europe. Poor sanitation and crowding have permitted the continued transmission of poliovirus in certain poor countries in Africa and Asia, despite massive global efforts to eradicate polio, in some areas with an average of 12-13 doses of polio vaccine administered to children in the first 5 years of age"(1).

"The science, applied in repeated vaccination campaigns, had also begun to perplex the public why repeated doses? Hasn't my child been protected enough? Why must we do it round after round year after year? And why is my child still infected by polio when he has been vaccinated many times"...... In industrialized countries children were sufficiently protected after receiving three doses of OPV, usually through routine immunization. For developing countries, epidemiologists had yet to determine exactly how many doses were enough due to the presence of a host of other viruses in unhygienic environments. The practice of open defecation and fecal contamination of drinking water easily precipitated viruses' transmissions. Children's vulnerability to infections and diarrhea somehow reduced the efficiency of each dose of OPV in fighting the poliovirus. More than three doses were thus required for developing countries, delivered through the NID, a supplementary immunization activity to bring additional dosage to children, including newborns. For India, where 80% of its rural population had no toilet at home, the Ministry of Health and Family Welfare recommended eight to ten doses for each child"..... "There was also a difference between protecting the child from the virus and eradicating the disease...... A child adequately protected from the virus would not lead to disappearance of the disease in the environs. As long as there were other children unvaccinated or inadequately protected with enough dosage, the virus would continue to thrive. As the virus was discharged from the guts of infected children or adults by means of feces, the untreated human waste often ending up in open sewers, lanes and riverswould become the source of transmission for others. Once out in the open, the virus looked for human