Poliomyelitis in Indian children who have received oral poliovaccine: Vaccine failure or low potency?

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Several studies from hospitals have reported that 10–45% of children with polio paralysis had received 3 doses of oral poliovaccine (OPV). Field studies have shown higher proportions. Paralysis following receipt of OPV by a child destroys the confidence of mothers in the vaccine. One reason for these failures is that OPV of low potency has been considered 'satisfactory'. Vaccine potency has been improved, but even if the total titre is satisfactory, there may be little of types 2 and 3. Mass immunization by Sabin Days may fail unless the vaccine provides full protection against all the three types. Spot diagrams of vaccine titres of tests on vaccine samples would give a clearer answer than the uninformative 'satisfactory'.

ALTHOUGH the efficacy of the oral poliovaccine (OPV) is estimated to be more than 90% (ref. 1), there is serious concern at the numbers of cases of paralysis where the children had received 3 doses of OPV: in 1988 14% of cases at Kalawati Saran Children's Hospital, New Delhi[2]. In the *National Review*, 'about 20–30% of children suffering from paralytic poliomyelitis were reported to be fully immunized'[3]. Recent papers have highlighted the problem (Table 1).

Reported cases

The number of reported cases has fallen dramatically in the last few years, but only one in ten cases was reported. We do not know if mothers who have been persuaded to have their children immunized, are likely to take them to hospital if the child is subsequently paralysed. Changes in the proportion and number of children who have received OPV but have still been paralysed must be treated with caution.

A household survey of 10,093 children in Pondicherry found 24 lame, of whom 60% had received 3 doses of OPV and another 20% had been partially immunized[4]. This is higher than the proportion reported from hospitals (Table 1) and suggests that hospital figures may not be typical.

Using local records

Hospitals collect records, yet seldom analyse or use them to monitor local conditions. The case histories of children with paralytic polio who attended a large hospital in Pondicherry (Table 2), show several points:

1. In the large and medium towns, there were few cases, suggesting that immunization rates were high. Of the 32 cases, 14 were paralysed in spite of receiving three doses of OPV.
2. There seemed to be poor immunization in two smaller towns.
3. There was little immunization in the villages and one town.
4. Cases who had received OPV might be older than those who had not:

There is no difference in the mean age of c 1.2 yr for those with 0, 1 or 2 doses of OPV. However, those who had received 3 doses of OPV had a mean age 5 m higher than the others.

It is disturbing that one half of the cases had received at least one dose of OPV and that 20% had received three doses.

Immunization failures

It is probable that most failures represent cold chain lapses, in that the vaccine given was of low or nil potency. We cannot judge how many represent real vaccine failures. Many causes for low conversion to protection have been suggested, but one has not received enough attention. It is known that malaria prophylaxis is ineffective when the person has diarrhoea as the drugs are not absorbed. Diarrhoea is frequent in India. A survey, from December 1987 to March 1988, of 14,880 children under 1 yr in seven areas, showed that

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Table 1. The proportion of children with paralytic poliomyelitis who had received doses of OPV

Year	Area	N	% of children immunized with 0	1	2	3	>3	Reference
1986–87	Delhi	74[§]	62		22	11	2	17
1988–89	Madras*	302	44		25	31		18
	Madras**	78	23	10	20	46		19
	Madras[†]	614	44		30	26		20, 21
1990	Marathwada	355	39		30	24		22
1990	Delhi	47			††	21		23
1991	Bangalore	40	65		10	25		24[#]
1990–91	Patna	96	52		33	15		15

Notes: [§]74 cases of severe acute paralytic poliomyelitis chosen from 1615 cases August 1986–May 1987.
*All children clinically diagnosed as APM May 1988–May 1989
**Cases 6–35 months from Madras city May 1988–May 1989
[†]Cases January 1988–September 1989 so include all cases in the other studies.
[††]Only 21% had received 3 doses of OPV
[#]Recalculated from Table 1 where the number with three doses is 11 not 10 and 5 of the percentages are incorrectly given.

Table 2. Cases of paralytic polio by OPV immunization status, 1988 and 1989 (author's analysis of data kindly supplied by S. Mahadevan)

	N	% cases who had received OPV doses 0	1	2	3	?
1 large and 1 medium town	32	16	19	16	44	6
2 smaller towns	30	53	27	10	10	
1 smaller town and villages	61	58	8	18	13	3
Mean age of paralysis		1.3 yr	1.1 yr	1.2 yr	1.7 yr	

in a two-week period, 14% had diarrhoea, defined as three or more loose motions a day[5]. The duration of the diarrhoea was not recorded but the survey indicates that each child may have four episodes of diarrhoea during the first year. Allowing for seasonal variation, diarrhoea may play a role in the poor response to OPV immunization.

Potency of the vaccines

The number of samples of OPV taken from centres and tested for potency has increased considerably (Table 3). The proportion judged satisfactory also appears to have risen. However, the titre of OPV considered satisfactory was $>10^{5.8}$ until 1990 when it was lowered to $>10^{5.65}$, the latter being less than one third the WHO recommended dose. 122 samples from 87 OPV distribution centres in Madras were taken[6]. All the first samples had titres $<10^{5.5}$. Later about 80% of samples had titres $>10^{5.84}$ and samples collected one year later were all $>10^{5.84}$. The visits to the centres and the results of the tests brought about an improvement of the cold chain. It seems an expensive way to ensure that instructions for using a vaccine carrier, not an ice bucket, etc. are carried out. It is also not clear whether visits were made at random times, not on a particular day and that samples were selected at random, there are very strict rules for the sampling of bottles for sterility in the pharmaceutical manufacturing industry. I have found no study where partly-used OPV vials were collected from immunization sessions.

It would be helpful if titres of vaccines tested were presented as scatter diagrams of log titre plotted against date, with points for each titration or dots of increasing size for multiple samples when many tests have been made. The basis for using a titre of $>10^{5.84}$ is that the titration itself is subject to random error due to small differences in sample volumes and difficulty in determining the end point. The WHO vaccine potency is $10^{6.14}$ with a titration margin of + or – $10^{0.3}$, i.e. $10^{5.84–6.44}$. This, however, is valid only if the mean value of titrations lies at $10^{6.14}$ with equal numbers of samples above and below.

In the samples tested[6], only two samples were $>10^{6.13}$ and 92 were $10^{5.84–6.14}$. Although the samples were considered satisfactory, there had been a loss of potency which would have been more evident with a plot of titre against time. Nevertheless, the improvement in titre of samples from 1988 coincided with a dramatic drop of about 75% of cases of polio seen at the Institute of Child Health, Madras. This suggests that previous disappointing results with OPV have been due, at least in part, to cold chain failures and defective vaccine; failures which can be rectified.

In one study, the potency of 2 samples of vaccine was found to be log $10^{5.4}$– log $10^{6.2}$ plaque-forming units and it was implied that these titres were acceptable[7]. The *British Pharmacopoeia* gives the minimum titre for triple vaccine as log 5.85. Although the difference between 5.4 and 5.85 seems small, it is actually the difference between 2.5 and 7×10^5 virions, almost a three-fold difference. WHO potency requirements for Triple OPV are

Table 3. Potency of samples of oral poliovaccines

Year		No of samples	% considered satisfactory	Log 10 titre for satisfactory	Reference
	1975	191	59		25
	1979	7	57	> 5.5	26
	1984	13	100	> 5.84	26
	1984	58	90		27
	1985	120	97		27
	1986	53	60		28
Jan	1987–				
Mar	1988	337	46	> 5.84	29 Note 1
	1988	460	40	> 5.84	30
	1989	433	56	> 5.84	30
May	1988	12	0	> 5.84	6
Apr	1989	12	100	> 5.84	6
	1986		65	> 5.8	31
	1990	6000	90	> 5.65	31
	1984	121	75		32 Note 2
	1985	139	66		32 Note 2
	1986	454	61		32 Note 2
	1987	1297	61		32 Note 2
	1988	1627	63		32 Note 2

Note 1: The samples were taken at primary health, district and immunization centres.
2: No definition of 'satisfactory' given.

not less than $10^{6.0}$, $10^{5.0}$ and $10^{5.5}$ for types 1, 2 and 3 (ref. 4), a total potency of $10^{6.15}$. A titre of 5.4 contains less than one fifth of the WHO recommended dose.

In India it is even more important than in the temperate countries that the vaccine contains more than the minimum titre. Arya has pointed out that although the total titre of the vaccine may be within acceptable limits, there may be little, if any, of types 2 and 3 (ref. 8). Sokhey *et al.*[9] actually state that 'in no case should vaccine with virus titres <log $10^{6.0}$ for type 1, 5.0 for type 2 and 5.5 for type 3 be accepted'[9].

Discussion

Personal experience suggests that immunization cover may not be as complete as official statistics imply. One reason is 'many immunization teams are squeezed between seniors demanding returns and children reluctant to bare their bottoms. It is no wonder that the numbers of immunizations recorded often bear little relation to the numbers actually given'[10].

The authors of one study suggested that 'there is low credibility of OPV immunization in India in view of the high mortality in partially immunized children'[9]. This statement was based on a mortality of 11% among 143 unimmunized children and 30% among 48 'partially immunized' (although fully immunized children are mentioned, none appear in the text). The authors suggested that 'one of the explanations could be the adverse effects of OPV, which have not been studied so far and therefore, needs further investigation.' Two letters critical of these remarks followed[11].

The children studied by Mathur *et al.*[12] were admitted to the paediatric wards and were not typical of polio children: only 26% were under 1 year and the gender ratio was 2.3 males to 1 female. For children brought to hospital, about half are under 1 year and the gender ratio is about 1.5:1.0 (ref. 13).

Injections given for fever affect very markedly the severity of paralysis in polio following 1 or 2 days later[13] and in that study almost all the deaths followed multiple injections. No information about injections was given by Mathur *et al.*[12].

One study of paralytic polio compared 52 children who had received 3 doses of OPV with 30 children with no polio immunization[14]. They found more extensive paralysis and greater severity among the fully immunized children. However, 60% of the immunized children had received an injection prior to paralysis compared to only 10% of the unimmunized. This was one of few studies where the polio type was found: for type 1, 77% of the unimmunized, but only 25% of the fully immunized. This suggests that the vaccine may be lacking in types 2 and 3 (see above) as most studies have shown that about 70% of cases are caused by type 1. It is not clear why there should be such a difference in the injections given to the children. It is possible that mothers who accepted immunizations were more likely to take the child to a doctor, who would give an injection: 37% of the immunized children came from social classes I and II compared with only 7% of the unimmunized children.

The latest study concluded that 14 paralysed children who had received 3 doses of OPV had less severe paralysis than 82 with 0 to 2 doses[15]. The basis for admit-

tance was not detailed. One difficulty is that paralysed limbs, particularly those which have not been injected, sometimes recover some power[13].

Conclusions

As immunization cover in India is increased and the number of cases of polio falls, study of polio becomes more difficult. Age, gender, vaccine status and injections may all affect the chance of paralysis and its severity. Unless co-operative studies are made, individual hospitals may lack enough cases to make meaningful comparisons.

Children who receive OPV with low virion numbers may not develop immunity to types 2 and 3 and, in spite of multiple doses, may remain at risk. A vaccine of low potency will remain a problem even with National Immunization Days when all the children under 5 years are given OPV. Even doubling the dose of vaccine will be ineffective if there is too little type 2. Surveillance of cases for the virus type is necessary. If the Eradication Programme is successful, the problems will disappear, but eradication is a hope not a certainty.

Vaccine failures must seriously undermine the confidence of mothers in immunization. I have found no survey of mothers' attitudes to immunization which explores the effects of vaccine failure in the village. However, at meetings with over 150 primary health workers in Madras, all agreed that other mothers refused immunizations for many months after paralysis in a child who had received vaccine[16].

Words convey hidden meanings and the use of 'immunization and vaccine failures' suggests that the vaccine itself is at fault. It might be better if we used 'received OPV' rather than immunized or vaccinated.

If polio is to be eradicated, we must improve the virus titre of the vaccines, make the cold chain more efficient and improve the studies of vaccine cover and cases of paralysis.

A few children succumbing to polio after receiving OPV may be enough to destroy mothers' confidence in the immunization programme[16].

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