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IPV Revisited. . . Yet Again !

INTRODUCTION

Several years back, we reviewed literature on Inactivated Polio Vaccine (IPV)(1,2) including immunogenicity, protective efficacy, safety profile, local immunity, herd protective effect, duration of protection, feasibility of introduction and cost considerations. Thereby we suggested its phased introduction in the routine immunization program, beginning with states free from poliomyelitis for at least 3-5 years(1,2). This was ignored amid the hype that eradication was 'just round the corner'; and could be accelerated by pumping in more doses of OPV. Further, evidence that vaccine associated paralytic poliomyelitis (VAPP) is a serious problem(1-4) was also downplayed(5,6). Naturally, the additional argument that India should indigenously produce IPV, rather than rely on imports was also drowned in the din (7,8).

It is, therefore, ironic that IPV is now regarded an essential tool that should be used in "campaign mode" and "given as per the availability of doses"(9). These recommendations of Indian Academy of Pediatrics experts, temporally coincide with availability of IPV in the Indian market. Although we were the first to suggest using IPV almost a decade back, we are in complete disagreement with the motives and methodology proposed recently by the IAP expert group. This article highlights the scientific arguments behind this disagreement and once again proposes a rational frame-work for India.

ISSUE 1: WHY IS IPV IMPORTANT IN INDIA?

1.1 There are four major reasons:

1. OPV used in the current manner has failed and cannot ensure eradication of poliomyelitis, at least in the near future. Therefore either it should be used more judiciously (strengthening routine immunization and down-scaling aggressive pulse polio campaigns) or we should switch to an alternate vaccine. Further, the current program in India is only focused at recording absence of virologically confirmed wild poliovirus cases (zero-polio status) for three consecutive years and calling this 'eradication', although this is not the true sense of the term(1).

2. Vaccine associated paralytic poliomyelitis is a significant problem(2,3); though it is being overlooked/suppressed. The more OPV is used, the greater the risk(6). There is also the ethical issue of continuing to expose children (especially in polio free areas) for the "sake of common good".
3. OPV derived virus can mutate, circulate and cause paralysis in an unpredictable manner(8) referred to as circulating vaccine derived polioviruses (cVDPV). There is also the risk of persistence in immunodeficient hosts (iVDPV) with the potential of causing paralysis.
4. Once eradication is certified (as per the WHO definition of zero-polio status for three years); individual countries will no longer be 'guided' on further action. They will be free to cease all vaccination or switch to exclusive use of IPV. Trivalent OPV will not be available except in WHO stockpiles! Naturally it will be unsafe to suspend all vaccination; hence by exclusion, India will have to switch to IPV.

1.2 However the current clamour for using IPV in India does not stem from these scientific arguments. It is proposed as yet another novel tool(9) to attain the WHO target of stamping out wild poliovirus cases to certify 'eradication' as quickly as possible.

ISSUE 2: HOW IS IPV TO BE USED IN INDIA?

There are basically six scenarios; these are examined below:

2.1 IPV in Campaign Mode in Endemic Areas

This has been recommended by IAP experts(9) for the 'hottest' districts of Uttar Pradesh to meet the WHO target (zero polio status by any means possible). However, as poliovirus does not respect district boundaries, all susceptible children in a larger area (perhaps the entire state) will have to be vaccinated with (at least) two doses of IPV. To ensure immunogenicity, the doses have to be spaced about eight weeks apart. If too close, (antibody) boosting effect of the second dose will not occur; if too far apart, it will be futile because the cohort will change significantly. Assuming two campaigns eight weeks apart (say at the end of January and March 2008), all children born after March 2008 will remain bereft of benefit, until the next campaign (when?). Thus, in practical terms it will leave many children unprotected; the very excuse for this exercise in the first place **(*Table* I)**. To ensure greater protection, the exercise will have to be repeated periodically (how often?), hoping meanwhile that none of the unprotected infants contributes to transmission.

***Table* I** also shows that this scheme requires approximately sixteen million IPV doses in the first

TABLE I THE ESTIMATED PROTECTIVE EFFECT OF USING IPV IN CAMPAIGN MODE EIGHT WEEKS APART IN UP AND BIHAR

State	Annual birth cohort	Births per month (approximately)	*Total No. of <2 children	†Fully protected	‡Partially protected/ unprotected	#Unprotected
Uttar Pradesh	5446538	453878	10893076	453878	907756	4084904
Bihar	2643840	220320	5287680	220320	440640	1982880
Total	8090378	674198	16180756	674198	1348396	6067784
% of annual birth cohort				8.3%	16.7%	75.0%

Assumptions for calculation purposes: • IPV (two doses administered eight weeks apart) has 100% protective efficacy; • 100% children are covered in the proposed manner; • Annual births are distributed equally in each calendar month; • Infant mortality rate is zero; • IPV doses are administered on February 1 and April 1 2008; • Only children under two years of age are eligible for this scheme of vaccination.

**Children born in 2006 and 2007*
†*Number of children born in 2008 who will receive 2 doses of IPV*
‡ *Number of children born in 2008 who will receive one dose of IPV*
# *Number of children born in 2008 who will not receive any dose of IPV*

year alone, that too assuming that the 'campaign' targets only infants less than two years old and not all susceptible children. The logistics of administering these doses within one to two days is staggering and includes training personnel to administer IPV, look for potential complications/ adverse effects and manage them. In addition, the risk of injection related paralysis needs consideration. Last but not the least, will the community accept campaign IPV, considering that till now they have been led to believe that 'campaign' OPV is the solution to the problem and also 'eradication is just round the corner'? Those resisting OPV for any reason are unlikely to accept a vaccine that is 'more powerful' than OPV.

It may also be mentioned in passing that using IPV in campaign mode has no comparable global precedence, although this has never deterred some experts from shying away from such schemes.

2.2 IPV in Routine Immunization in Endemic Areas

This appears scientifically attractive since it balances the demand to hasten zero polio status; at the same time curtailing the risk of VAPP. There are two problems with this approach; first it cannot achieve immediate zero polio status and will take 3-4 years for the entire community to be protected. The second is that it necessitates several million doses as outlined previously(8), which is prohibitively expensive at this stage since IPV is not produced indigenously. Last but not the least, this also will work only with more than 90% coverage sustained over 3-4 years, with such levels OPV also could achieve zero polio status and far more cheaply.

2.3 Phased Introduction of IPV in Routine Immunization Starting from Polio-free Areas

We have explored this option previously also(1,2). It seems the best approach because it accounts for the fact that indigenous production of IPV(8) will initially generate limited number of affordable doses, which will be adequate for states/ regions that are polio-free for 3-5 years or longer; there are 15 such states/ union territories at present. Competition between manufacturers and assured demand would increase production which would make a large number of doses available and affordable for other states. There is also the ethical consideration that has not troubled our policy-makers yet viz. the ongoing need to expose several children to the risks of OPV despite not requiring it themselves. In fact, had our suggestion been followed, India would not have witnessed the resurgence of poliomyelitis in at least eight states that were eligible for IPV several years back **(*Table* II)**.

2.4 IPV as a Post-eradication Measure

This is another theoretically attractive option except for two factors. First, it depends on achieving eradication which appears difficult with the current strategy. Secondly, it will be impossible to switch to IPV overnight for the entire cohort of 27 million annual births; although this is one of the options recommended by WHO. Alternatively, one would have to depend on either options 2.2 or 2.3 above with the disadvantage of having lost a number of years. Further, it may be pointed out that even by the current WHO definition of eradication, several states/union territories of our country qualified for this label years ago and should have been receiving IPV at this time in the manner that we proposed(1,2).

2.5 Sequential Use of IPV and OPV

Using IPV after some doses of OPV in routine immunization boosts antibody levels significantly more than with another dose of OPV. In

TABLE II STATES WHERE POLIOMYELITIS HAS RE-EMERGED AFTER A GAP OF THREE OR MORE YEARS

State	Last case seen in	Re-emergence of cases in
Himachal Pradesh	Prior to 1999	2006
Tamil Nadu	1999	2003
Chandigarh	2000	2006
Jammu and Kashmir	2002	2006
Assam	2002	2006
Madhya Pradesh	2002	2006
Rajasthan	2002	2006
Andhra Pradesh	2004	2007

children who do not seroconvert following a reasonable number of OPV doses, a single IPV dose can enhance antibody levels to the 'protective range'(10).

In the United States, all OPV schedule was replaced by a sequential schedule (two doses IPV and then two doses OPV) before total IPV(11). A sequential schedule of some (how many?) does of OPV and one or more doses of IPV may be scientifically acceptable, however, it must be remembered that as long as OPV is used, (more so before giving IPV) VAPP remains a risk. This was precisely why the United States was compelled to switch to exclusive IPV.

2.6 Using IPV Along with OPV

This strange suggestion is part of the IAPCOI recommendations(6,12). The argument therein is that OPV is mandatory in routine immunization by virtue of the national immunization schedule and in pulse polio campaigns 'by law'. Therefore the Committee is unable to conceive a scenario without OPV. On the other hand, arguing that OPV may not provide adequate individual protection and can cause VAPP(1-4,13), the Committee recommends that IPV be added for "children who can afford it". The opinion is that IPV will ensure individual immunity while OPV will assure community protection! This recommendation obviously appears to be aimed at boosting IPV sales rather than its scientific merits, that is why it is directed towards "those who can afford it". We fail to understand why a recommendation which has any scientific merit is made only for those who can afford it.

The other flaw with this scheme is that it shifts the onus of decision making onto individuals based on their economic status, rather than making the WHO responsible for failure to eradicate polio with OPV and the Government responsible for providing an essential vaccine on scientific grounds. There are less than a dozen countries using a combination of IPV and OPV in various schedules, but 9 of them use 2 or more doses of IPV besides OPV. There is no sense in following their experience because two doses of IPV administered eight weeks apart (or three doses four weeks apart) alone guarantees protection. Besides, none of these countries has been involved in a mass polio eradication campaign involving years (decades) of OPV.

ISSUE 3: WHAT WILL INTRODUCTION OF IPV IN THE ROUTINE IMMUNIZATION PROGRAM ENTAIL?

3.1 It entails a radical diversion from the current stand that India is witnessing the last few cases of poliomyelitis and eradication is in sight. It also requires shelving the 'short term target' of zero polio status in favor of the 'long term goal' of eradication. Program managers will have to be broad-shouldered and broad-minded to accept that the current strategy has failed.

3.2 The second challenge is the availability and affordability of several million doses of IPV. This issue is complicated by licensing of imported vaccine for sale in the open market; these manufacturers are keen that the vaccine be used liberally and several experts seem to be playing along this tune. One multinational giant even offered a couple of million doses of IPV free of cost; it is rumoured that this largesse coincided with the impending expiry date of a large stock and has since been withdrawn.

Market principles of indigenous production and healthy competition among multiple players will ensure affordability and availability, ensuring that Indians as a whole emerge the real winners. One of the advantages with IPV is that manufacturers are assured of a ready market of 75 to 100 million doses annually (depending on whether three or four doses including booster, are used in routine immunization) with a great additional potential for export. This is unlike the scenario for many other vaccines that take years from the stage of introduction to generating profit.

3.3 The third issue is the vaccination schedule. Logistically, it is easy to administer IPV with DPT. However as for DPT, immunogenicity of IPV is better with eight weeks interval between doses. One possibility is to ignore scientific arguments and use the existing schedule (as proposed for hepatitis B vaccine). The other view is to change DPT schedule

to 2, 4 and 6 months since the very premise for anticipating the first dose (to six weeks) and shortening the interval between doses (to four weeks) has neither been worked out in the Indian setting nor seems to have worked (fully 'immunized' infants continue to present with pertussis like symptoms). It has the indirect benefit that infants will be available for clinical examination, growth monitoring and development assessment at reasonable intervals throughout infancy and particularly when weaning is advised. It will also enable a rational hepatitis B vaccination schedule, since only the 0, 1, 6 months schedule has proven protective efficacy. This is in concordance with the original recommendations of IAPCOI made in 1991.

3.4 The fourth issue is training health care personnel to communicate effectively and administer the vaccine safely. The public will have to be taken into confidence and explained that our country has had to give up OPV because it has not produced anticipated results. It is possible, nay probable that shifting the focus (from innumerable OPV rounds targeted at a single disease) will enthuse the public to understand the importance of routine vaccination and strengthen the program. In any case, there is nothing to lose and much to gain.

3.5 Another important consideration is to assess what will happen if our country fails to develop a rational policy with regard to IPV. IPV is already available over the counter and presently the decision to use it (or not), rests mostly with individual physicians who may not have the time or energy for convoluted scientific arguments and prefer to follow personal beliefs or the advice of 'friendly' industry representatives. The haphazard use of IPV will result in communities where some children are protected (as individuals) admixed with others who have variable degrees of protection offered by varying number of OPV doses. In the event of polio cases occurring, there will be no way of sorting out the mess and developing a proper strategy taking the entire community into account.

SUMMARY AND CONCLUSIONS

- IPV should have been introduced in India in a phased manner as proposed several years ago, but it is still not too late if we are sincere to achieve the goal of eradication of poliomyelitis (as opposed to the milestone of zero-polio status).
- Using IPV in campaign mode is unlikely to result in eradication.
- IPV should urgently be considered in the routine immunization program, beginning with states that are polio-free for 3-5 years.
- IPV used in the routine immunization program should be procured through indigenous production to keep it affordable.
- The major challenge to the rational use of IPV in India is the fixed mindset of those in charge of leading / advising / controlling the polio eradication program.
- IPV could be introduced (singly or as a combination) in routine immunization by altering the current schedule to the scientifically appropriate 2, 4, 6 months scheme.
- Discussion and debate on the issue of IPV should be encouraged rather than suppressed in order to ensure that children of our country get the 'best deal'.

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