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Editorial

Will India need inactivated poliovirus vaccine (IPV) to complete polio eradication?

'*Everything is created twice - first in the mind, then on the ground*'

The present situation

Our immediate goal in India is to interrupt wild poliovirus transmission. In 2005 only 34 districts are infected, with 55 cases of type 1 and 4 cases of type 3 polio, an all-time lowest record (*http://w3.whosea.org/vaccine*). Cases are few and far between in time and space. Transmission chains have weakened under sustained heavy vaccination pressure. This year, monovalent type 1 oral polio vaccine (OPV) was used in site-specific surgical strikes and monovalent type 3 OPV will also be used soon. One dose of monovalent vaccine is immunogenically worth three doses of trivalent vaccine, accelerating the build-up of immunity in the shortest possible time. Optimistically, wild virus transmission could be interrupted within a few months, but the road map beyond remains unclear. It will be safer, hence wiser, to use IPV to conclude polio eradication. Delay in decision may create a situation in which we may not have what we need and cannot use what we have. An answer to the question in the title will emerge *post facto*, but by then the error might be too costly.

In 1978 our Government decided to use OPV exclusively, ignoring questions of its scientific validity. In 1988 the Government signed the WHO resolution for global polio eradication defined as '*zero incidence of wild poliovirus infection*', and continued the exclusive use of OPV. The third opportunity for policy review is now, but choices are more difficult than before.

Lessons from smallpox eradiaction

Smallpox (*Variola*) eradication is our guiding precedent. Post-eradication, smallpox vaccine (*Vaccinia*) was discontinued for epidemiological (absence of target disease), economic (unnecessary cost), and safety (vaccine adverse effects) reasons. *Vaccinia*, heterologous species to *Variola*, neither caused smallpox nor spread from the vaccinated to others. Discontinuing vaccination had no adverse epidemiological consequence. Contrarily, Sabin and wild polioviruses are one species. Vaccine-associated paralytic polio (VAPP) is identical to wild-virus-polio, only far less frequent. Sabin viruses are transmissible and may even seed circulation. During intestinal replication, shedding and transmission, they revert progressively towards wild-like genotype. Such 'circulating vaccine-derived polioviruses' (cVDPV) cause polio, usually in clusters. Seven cVDPV outbreaks have been recognised - in Egypt (during 1983-1993), Dominican Republic and Haiti (2000-2001), Philippines (2001), Madagascar (2001-2002 and 2005), China (2004) and Indonesia (2005). VAPP and cVDPV are ethically incompatible with eradication. Hence true eradication is '*zero incidence of poliovirus infection, wild or vaccine*'. Countries using OPV must achieve eradication in two phases, namely, W (wild viruses) and V (vaccine viruses), as shown below.

Eradication Phase	AFP due to vaccine virus	AFP due to wild virus	AFP due to non-polio cause
Pre-eradication	Yes	Yes	Yes
Phase W	Yes	No*	Yes
Phase V	No*	No*	Yes

AFP-Acute flaccid paralysis, the clinical presentation of poliomyelitis
*Absence of disease for three years in spite of sensitive surveillance is surrogate for zero incidence of infection

Can we safely stop OPV?

Many experts assume that OPV can be discontinued after achieving phase W and phase V will occur automatically. This simple approach is not safe. Near-hundred per cent vaccination coverage with multiple (>10) doses of OPV is essential not only to interrupt wild virus transmission, but also as a deterrent against the emergence of cVDPV. Viruses from the vial are safer than vaccine-derived viruses in transmission. The higher the immunity barrier constructed by vaccination, the lower the probability of vaccine virus transmission. When this deterrent is diluted, by the decline of the number of doses per child or of coverage with multiple doses, the consequence is to promote cVDPV. Such decline is likely to occur (intentionally or unintentionally) after we reach phase W. This scenario was the predisposing factor in six outbreaks of cVDPV.

Continuing OPV post-phase W is unethical on account of VAPP. Slow withdrawal is risky. What if OPV is stopped simultaneously in the country (or the whole world)? It is not known if the risk of cVDPV will decrease or increase in the sandwich period of time when recently vaccinated and virus-shedding children remain in proximity to unvaccinated children. If even one chain of transmission develops, the outcome may lead to cVDPV. This risk may be very low, but is not zero. If cVDPV emerges, it will be very difficult to control.

Is the risk of cVDPV, even as small as it might be, worth taking, considering the 4 billion dollars of direct expenditure and an estimated equal amount of indirect expenditure that the world has put in already for global polio eradication efforts? If cVDPV were to emerge, there will be a delay of one year or more before it is discovered. By then it would have spread widely, silently, even across national borders. Should we then flood the community with OPV (monovalent or trivalent) to eradicate the cVDPV, knowing that young children in surrounding communities will be naïve to polioviruses, wild and vaccine? Is it ethical or scientifically acceptable to re-introduce OPV into a world with no vaccination, when the probability of transmission and circulation will be higher than now? Are we willing to risk the entire investment of eradication for the sake of the cheapest or simplest of all future options? In the un-chartered sea ahead, are we confident our Titanic is un-sinkable?

An alternate deterrent against cVDPV perhaps is wise, before withdrawing OPV. The only rational option, therefore, is to introduce IPV in preparation of withdrawing OPV. Scandinavian countries went from wild virus endemic state directly to elimination phase V, by the exclusive use of IPV. Germany, France, USA, Canada, UK, New Zealand and virtually all other rich countries went sequentially through phase W using OPV, and phase V using IPV. There is no alternative model available for India to adopt. The question posed in the title remains relevant only in developing countries, highlighting the rich-poor divide in risk-perception and risk-management.

Will IPV solve our problems?

The IPV solution of the cVDPV problem is fraught with formidable but not insurmountable obstacles. Globally the demand for IPV is more than its supply as it is made by only two European manufacturers. Short supply pushes price up, but rich countries pay the price for the safety of their children. India had contributed to this crisis by closing down (1993-1994) what was begun as a large public sector IPV production company in Gurgaon in1987-88. IPV was successfully manufactured in private sector, in Pune (1987-88), but that was also disallowed by the Government. Technology for its manufacture can be re-established if the Government so decides. If made here, the cost will be affordable.

Can we achieve 90 per cent coverage with three doses of IPV? If there is will, there will be a way. In Tamil Nadu, Kerala and Goa, DPT third-dose coverage exceeds 95 per cent, and IPV-combined DPT will simplify immunization. The reason of poor performance in other States is defective management, not public diffidence in vaccines. The success factors of Tamil Nadu must be replicated in other States not only to conclude polio eradication but also to prevent death due to measles and diphtheria. India signed the eradication-by-2000 pledge in 1988 but took no steps to accelerate polio control. In 1995-1996, with time running out, India resorted to management by crisis,

without a long-term plan. All hopes were pinned on OPV by campaigns, undervaluing routine immunization. Had our regular vaccine been DPT-IPV, and OPV was used in campaigns, we could have had the best of both vaccines, and eradication achieved earlier and cheaper, and the transition to IPV simplified. The bonus would have been the true strengthening of our universal immunization programme (UIP). Polio eradication would have actually been, and would have been seen to be, the fruit of UIP, instead of another 'vertical' project, perceived by some to be in competition.

We do not have direct evidence that IPV will act as a deterrent against cVDPV. It would have been safe to assume so, if we had data on its ability to interrupt transmission of wild viruses in developing countries. That no study had addressed this question illustrates the problem of man-made bias against IPV. India should have stayed clear of the Western controversy between the two poliovaccines. Indian studies had shown very low efficacy of OPV and very high efficacy of IPV. Western studies showed complete safety of IPV but not of OPV. Yet, India waited for the West to settle the controversy, but when they finally chose IPV, we are caught with our bridge burned behind us. Considering the high vaccine efficacy and herd effect of IPV in developed countries, and no evidence of their geographic variation in developing countries, we must assume that IPV will act as a deterrent against cVDPV. Clearly, every future option is based on assumptions. Therefore, now more than ever before, choice must be based on the safest assumption, which calls for wisdom and foresight.

Will the use of wild virus for manufacturing IPV pose a risk of accidental release at factory sites? Stringent containment measures are necessary, no doubt. The Japanese approach to this problem is to make 'Salk vaccine out of Sabin viruses' - so that the risk from stock live viruses is reduced. We do not seem to have the necessary time for capacity building to produce Sabin-Salk vaccine. We can transition from regular IPV to Sabin-IPV in due course. The priority must be to introduce IPV and discontinue OPV, for which the standard IPV could be used until Sabin-IPV becomes available.

Who must decide for India?

That there is no consensus among world experts on the need for IPV in developing countries points to the complexities behind the question. In a public health programme of such enormity and cost as global poliomyelitis eradication, one cannot wish away complexities. As far as India is concerned, we must face the question as a priority national issue, while the world experts grapple with it at global level. India's decision may even influence global thinking. Thus, we have an opportunity and an obligation to decide in our best interests, which will help other developing countries also. The Government of India must debate all options. If the consensus among experts chosen by the Government is that India will need IPV, then action is needed now. If IPV is not considered necessary, nothing changes for now. In any case, the decision must be taken by India now rather than waiting for a WHO decision, which may take time. The three possible approaches that WHO could adopt are: (*i*) to decline to give clear guidelines, letting countries themselves decide; (*ii*) to advise that OPV could be discontinued after wild virus eradication, and offer stockpiles of OPV in case cVDPV emerges; and (*iii*) to recommend IPV.

Conclusion

The question in the title deserves an answer. If IPV is considered the safer option, its production needs financial investment and time. Once standard IPV is made, switching to Sabin viruses as source material may be easier than starting de novo with them. Whatever the Government's policy - not to use IPV, or to use standard IPV, or Sabin-Salk vaccine, or the two in sequence - it must be articulated without delay.

(The views are personal and not of any organization with which the author is associated)

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