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Editorial

Establish herd effect to interrupt wild poliovirus transmission

Wild-virus polio cases in India in the first six months of 2006 (n = 70) have exceeded those during all of 2005 (n = 66) (*http://www.npsindia.org*). Transmission persists in western Uttar Pradesh (UP) with rising numbers and in Bihar with declining numbers. India and 3 other countries - Pakistan, Afghanistan and Nigeria, have failed to interrupt wild virus transmission in 2006. India was a leader in research on poliovirus epidemiology and vaccinology in 1970s and 1980s. Instead of assuming leadership in their application, India slipped to failure, only because science was ignored in public health policy.

One could defend that 2006 is an 'outbreak' year, as were 2002 and 1998 previously, at 4-year intervals. That is no consolation, as all subsequent efforts could not avert an outbreak. A call was made, in vain, for an exclusive internal Indian review of the scientific basis of the polio eradication interventions[1]. The force of transmission of wild polioviruses varies in populations and western UP may have one of the highest[2,3]. Vaccine efficacy of OPV also varies and it may be the lowest in western UP[3]. Among the many OPV response studies, one of the lowest recorded results in the world was in Delhi, close to the border of western UP[4]. A coincidence of these two adverse phenomena may explain the persistence of transmission[3]. India needs a way forward, based on tactics built upon scientific rationale and evidence.

Elimination of wild virus transmission is clearly impossible in 2006. Time over-run beyond the target year of 2000 has caused cost over-run. Globally over 4 billion dollars have been spent, while the original budget was only half as much. India had been spending more than what the country can afford, while other health programmes are being adversely affected. If India does not succeed by 2007, when wild poliovirus (along with new subtypes of influenza, SARS and smallpox) will become notifiable under the new 'International Health Regulations 2005,' the consequence could be embarrassing[5]. The delay has its local repercussions as well. According to rumour, health workers are losing faith in OPV as had many families in the past, as polio occurs in children despite taking 10 or more doses. Consequently the quality of immunization campaigns may deteriorate. If this state of affairs continues, improved intervention may not be implemented well. The longer the delay, the greater is the risk of losing much of the gains achieved so far. Any slip-up in immunization pressure may result in wild virus re-infection in other States and exportation to other countries. Urgent steps to design and deploy effective tactics to eliminate wild viruses in the shortest time are the immediate priority.

The elimination of a pathogen by immunization requires two elements - 'vaccine delivery' and 'vaccine effectiveness'. Unfortunately these were not optimized synchronously - when the programme improved on delivery, the inadequacy of vaccine effectiveness was not corrected. In recent years the pace of supplementary vaccination activities was more intense here than most, if not all, other places in the world. Western UP had 6 rounds of OPV campaign in 2003, 6 in 2004 and 8 in 2005. The quality of campaigns has been under close scrutiny and the coverage has been well in excess of 90 per cent each time. The average number of OPV given to under-5 children is 15. Other countries and other Indian States eliminated wild virus transmission with far less intense efforts[2]. The Government of India (GoI) and the National Polio Surveillance Project have so far spared no effort in their respective

managerial roles. The implementation partners, particularly the State Governments, UNICEF, Rotary International, the core group of non government organizations (NGOs), Indian Academy of Pediatrics and others have worked really hard; yet success has eluded them. Vaccine delivery of OPV has been excellent, if we ignore the low 'routine' vaccination rates.

The deficiency of vaccine effectiveness had been staring at us for years, but only now have most stakeholders noticed it. Delivered doses were not providing protective immunity to a substantial proportion of children[2,3]. The effectiveness of a vaccine for disease control requires vaccine efficacy (VE) and herd effect (HE). Vaccination is primarily to prevent disease in the vaccinated individual when exposed to the pathogen. The probability of protection (immunity) is measured in a group of individuals and is expressed as vaccine efficacy. The protected individual may still get infected when exposed, but infection does not progress to disease; thus it is modified to a varying degree. Lack of protection in spite of vaccination is vaccine failure, the frequency of which is inversely proportional to VE. The modified infection in immunized individual has an effect on the quantum, duration or both, of pathogen-shedding, the essential link in the chain of transmission to new hosts. Even slight reduction of shedding (quantum or duration) decreases transmission efficiency. The more the proportion of subjects vaccinated, and the longer the vaccination pressure is sustained, the greater the reduction of transmission efficiency. This is the basis of HE, defined as the decline in incidence of disease (and infection) in the unvaccinated segment of a population in which a proportion is vaccinated[6]. The greater the fall in transmission efficiency, the slower will be the spread of infection and lesser the number newly infected. The slowing speed of spread is evidenced by rising median age by which 50 per cent of cases had occurred. As disease frequency is directly proportional to that of infection (in the non-immune), this upward age shift is the visible evidence of slowing transmission. The falling number of new infections is evidenced by declining incidence of disease among the unvaccinated. If these trends are sustained by sustained immunization pressure, there will be a cascading effect, resulting in downward spiral of falling incidence of infection - consequently, first disease incidence and eventually infection incidence will reach zero, and infection is eliminated from the community. Unless re-introduced from outside, infection cannot reappear.

The two factors for obtaining high HE are high VE and high vaccine coverage. The former is an attribute of the vaccine and the latter depends on the quality of the vaccination programme. It is therefore important to assess the VE, vaccine coverage and HE, in the districts where transmission has not been interrupted. The two signals of HE are an upward shift of the age of children with polio and a fall in incidence that is disproportionately greater than the vaccination coverage. What we see in western UP are the lack of upward age shift and slower fall of incidence than vaccination coverage. Well over two-thirds of cases continue to occur below 24 months of age, as had always been in the past. The median age continues around 12-18 months. As virtually 100 per cent are vaccinated with multiple doses of OPV, the fall in incidence is lesser than coverage. Both these signals point to a lack of HE. Since coverage is almost at saturation level, VE is clearly deficient.

All vaccines against anthroponoses (human-to-human transmitted infectious diseases) that protect against the infectious form of disease exhibit HE. Thus, diphtheria toxoid, whole cell or acellular pertussis vaccine, killed influenza, hepatitis A and poliovirus vaccines, capsular polysaccharide *Haemophilus influenzae* b and pneumococcal vaccines, live virus vaccines against polio, measles, *etc.*, have all been shown to exhibit HE in different parts of the world. The one exception, namely BCG, does not protect against the infectious form of tuberculosis and has no HE. Among all others OPV alone has wide variations of VE (hence HE also) in different geographic settings. They are very low in India[7-9].

Among the virus types in trivalent OPV, type 2 is more immunogenic with higher VE than others[4,7]. Type 2 transmission ceased in western UP in October 1999. This provides the clue that coverage using trivalent OPV was indeed high enough to eliminate

that pathogen against which VE was high. Western UP was the very last place on earth to interrupt its transmission highlighting the problems of this geographic population. In UP (and Bihar to a lesser degree) the VE of types 1 and 3 is unacceptably low. Even with near 100 per cent coverage trivalent OPV does not show sufficient or even detectable HE against them. This interpretation is critical for re-designing future interventions. The median age of polio remains at the 12-18 months level; nearly half the cases are in 10-dose-recipients; nearly all cases had taken at least 4 doses of OPV. These observations tell us two things. First, it will take more than 10 doses to immunize all infants against types 1 and 3. Second, the speed of wild virus transmission is faster than the speed with which children are being immunized. Unless infants are fully immunized by age 6-9 months, it seems unlikely that this vicious cycle will be broken. This translates to at least 10 doses of OPV given to infants by 6-9 months of age. Unfortunately this speed is not practical, since every month from birth every infant will have to be contacted. If monovalent types 1 and 3 OPV were to be used, the VE per dose will improve, and probably the number of doses needed may be somewhat less. This approach requires scientific validation by specific studies, but we do not have the luxury of time in our favour. As an aside, there is no scientific reason to continue giving type 2 vaccine to children. Since bivalent vaccine with types 1 and 3 is not licensed anywhere, the logical option is to use only types 1 and 3 monovalent OPV in a suitable sequential manner. The hidden advantage to this approach is a natural experiment, to document the probability of emergence of circulating vaccine-derived poliovirus (cVDPV) type 2, after that vaccine is discontinued.

The safer alternative for faster result is to vaccinate with 3 doses of IPV, which will provide better immunity than even 10 doses of OPV, in terms of higher proportion (virtually 100%) of infants developing immune response as well as achieving markedly higher antibody titres[7]. Thus, the addition of IPV appears to be the most promising way forward to interrupt wild virus transmission in the shortest possible time. This method need not drastically affect OPV delivery, either routine or in campaigns. Therefore it can be implemented without further studies, although the new tactic itself must be monitored for coverage and efficacy.

There are additional advantages to this approach. First, IPV protects against vaccine-induced polio (called VAPP *i.e.*, vaccine-associated paralytic polio). Currently 150-200 children get VAPP annually in India[10]. During the past decade 1500-2000 children were paralysed, but not recognized or compensated. There is no ethical justification to cause more disease due to the intervention, than the disease intervened against. Minimum ethical requirement is free treatment and rehabilitation of all children directly affected by the intervention meant for the benefit of the majority. To prevent VAPP is clearly an ethical necessity. Eventually India must discontinue OPV and the build-up of an IPV programme will help the transition to be risk-free from cVDPV[3]. By commencing an IPV programme now we will shorten the transition to the final phase of eradication, when OPV will no longer be in use[3].

What is the scientific evidence that IPV has HE? In many geographic settings it is highly immunogenic and has very high VE. Infants can be fully immunized by the age of 4-6 months, before they amplify and disseminate wild viruses in the community. Experience in USA and Europe has shown excellent HE[8]. Very few studies have been conducted in India on the immunogenicity and HE of IPV, but each of them had shown high immunogenicity or remarkable HE[8,9]. Based on such evidence, one private company manufactured DPT-combined IPV in 1986-87 but had to stop as directed by the GoI. In 1987, the GoI itself embarked on a mission to manufacture IPV in the public sector, to expedite polio control using both OPV and IPV and to gain experience with the latter. Concurrently a pilot project was approved in the North Arcot district in Tamil Nadu, to examine the potential of IPV in controlling polio and the results were highly encouraging. In 1988, the GoI committed itself on eradication by 2000 in the World Health Assembly (WHA), but gradually retreated from the 'open-minded' position on vaccines, to the exclusive use of OPV, against advice from scientists inside the country. The National Regulatory Authority declined

to license IPV in India and eventually the public sector IPV plant was also closed down. These strongly suggest an unscientific bias in favour of OPV and prejudice against IPV. Thus, India forced itself to use OPV exclusively for eradication, knowing fully well the possibility of failure. No pilot studies were conducted.

Pulse vaccination was shown to improve VE of OPV[9]. It called for 3 doses at monthly intervals, giving the health system the remaining 9 months of the year to improve the 'routine' immunization. Within 2-3 yr wild-virus transmission would have stopped in the easy States, but others would have failed. By examining the vaccination status and age of children with polio in the problem areas, the cause would have become clear - was it due to failure to vaccinate (inadequate coverage) or failure of vaccine (inadequate VE and HE)? The programme implementers did not think through these critical questions, but concentrated on the 'failure to vaccinate' theory and ensured very high, indeed one of the world's highest, vaccine coverage levels with multiple doses of OPV. Ignoring the 'failure of vaccine' side of the equation haunts the programme now. The lack of research in this enormously expensive and ambitious programme has resulted in the lack of timely grasp of the peculiar problem of very low VE and HE of OPV where they are most needed.

The lack of research on IPV, other than one successful study in Tamil Nadu, and the reluctance to take follow up action on its findings are further pointers to an unscientific outlook towards poliovaccines. One cannot revise the past, but can re-design the future. But, when the tactics are adjusted in future, to obtain high VE by using 3 doses of IPV or multiple doses of OPV (trivalent or better monovalent) by 6-9 months of age, or a suitable combination of both vaccines in sufficient number of doses, will the vaccine delivery arm of the programme remain robust and maintain the tempo to achieve high coverage? This is what the GoI must now ensure, while new tactics are designed and deployed.

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(*Note*: The views expressed are personal and not necessarily that of any organization with which the author is associated).

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