Viewpoint

Vaccination Strategies for the Last Stages of Global Polio Eradication

Launched in 1988, the Global Poliomyelitis Eradication Initiative has enjoyed remarkable success. The WHO anticipates isolation of the last wild polio virus during late 2004/early 2005, paving the way for certification of a world free of polio in 2008. However, the ultimate objective of this campaign, discontinuation of polio vaccination, has been jeopardised by two recent developments: the characterisation of vaccine-derived polio viruses (VDPV), and renewed concerns over the risk of bioterrorism. The threat posed by VDPV has led the WHO to recommend discontinuation of OPV usage as soon as possible after eradication certification. Cessation of vaccination with OPV needs to be carefully designed to avoid creating conditions where VDPV will develop. For the longer term, strategies must be designed to guard against the risk of polio re-emergence due to long-term VDPV excretors, accidental release of wild viruses or bioterrorism. The main strategies under consideration are a "surveillance and response" approach or a continuation of vaccination with IPV. Choosing between these strategies will pose a major dilemma for India and for many other countries.

Keywords: *Poliomyelitis, Vaccine, Vaccination, Disease eradication.*

Current status of the Global Poliomyelitis Eradication Initiative (GPEI)

Launched in 1988 by the World Health Assembly, following the success of the world-wide eradication of smallpox in 1980, the Global Poliomyelitis Eradication Initiative (GPEI) has been remarkably successful, with reported cases of poliomyelitis decreasing from over 350,000 in 125 countries in 1988, to 682 cases and sustained circulation of wild virus in only 6 countries (India, Pakistan, Afghanistan, Nigeria, Niger, Egypt) in 2003(1). Three regions have already been declared polio-free (the Americas in 1994, Western Pacific region in 2001, and the European region in 2002), and wild polio virus type 2 has not been isolated anywhere in the world since late 1999. The World Health Organisation (WHO) anticipates the isolation of the last wild virus in late 2004 or 2005, probably in Nigeria, and the declaration of world-wide eradication of polio three years later, in 2008(1).

For ultimate success, three primary objectives of the GPEI must be met: certification of polio eradication, containment of preserved virus stocks and discontinuation of polio vaccination. However, the task of meeting these objectives has been complicated by two recent events: the characterisation of vaccine-derived polio viruses (VDPV), and a radical shift in perception of the threat of bioterrorism. These events have lead to a rethink of the widely-accepted idea that vaccination against polio will stop after global eradication certification.

Vaccine-derived polio viruses (VDPV)

VDPV are Sabin-derived strains that have re-acquired the transmission characteristics of wild polioviruses and can cause endemic and epidemic disease(13). Occurrence of VDPV has recently led the WHO to state that OPV usage will have to be discontinued globally soon after certification of global eradication (1). By definition, VDPV exhibit more than 1% nucleotide substitutes of the VP1 region of

the genome of Sabin viruses as a result of mutations. They also exhibit genetic recombination with other enteroviruses. Both changes are associated with reacquisition of neurovirulance(2). There are two types; cVDPV ("circulating" VDPV) and iVDPV (VDPV excreted by immunodepressed patients).

The ideal conditions for cVDPV circulation are deficiencies in hygiene and sanitation promoting circulation of polio viruses together with inadequate coverage of OPV, both routine and National Immunisation Days (NID)(2). VDPV-related polio outbreaks have been documented during 1983-1993 in Egypt(3), in 2000-2001 in Haiti, the Dominican Republic and the Philippines(4), and in Madagascar in 2002(5).

Patients with humoral immunodeficiency can excrete iVDPV for many years. To date, 19 iVDPV excretors have been identified including one subject still excreting iVDPV more than ten years after receipt of OPV(6). HIV patients in whom immunodeficiency is cellular rather than humoral do not appear to excrete iVDPV, studies being currently underway to confirm this(6). The number of iVDPV excretors throughout the world is probably extremely low, but their existence heightens concerns that neurovirulent viruses may continue to be excreted several years after the official declaration of polio eradication.

The threat of bioterrorism

The terrorist attacks in September 2001 in the United States, and the dissemination of Bacillus anthracis spores in the mail, have changed the perception of bioterrorism as a remote hypothetical threat. Less widely known is the contamination of OPV batches in India with a live Type 2 polio virus (MEF-1). This wild-type virus was found to have caused seven cases of paralytic polio in Eastern Uttar Pradesh and Gujarat in 2002-2003, and could also be the causative agent of three cases which occurred in Eastern Uttar Pradesh and Bihar in 2000(7,8). If this was a deliberate act, the use of Type 2, which had not been isolated globally since 1999, indicates that the perpetrators wished to make it known. An attempt to silently damage the polio eradication program could have gone undetected for a long time if Type 1 or 3 wild-type polioviruses had been used, given their continued circulation in India. It is not clear whether OPV batches were contaminated by MEF-1 deliberately or by accident. However, this serves to illustrate that while polioviruses may not be the "best" agents for bioterrorism, they are easy to obtain, store and release into the environment undetected. In view of such threat, however slight, many countries refuse to countenance the risk of allowing generations of children to grow up with no immune protection against poliovirus, for which purpose inactivated polio vaccine (IPV) is used.

Discontinuation of Oral Polio Vaccine usage

In 2003, a WHO-convened group of experts recommended discontinuation of OPV use as soon as possible after global certification of eradication, given the risks posed by VDPV, a position which was endorsed by WHO(1).

How to safely discontinue OPV, without creating the conditions for the emergence of VDPV is being discussed(2). One worry is that the disappearance of wild polioviruses from much of the world and the prospect of global eradication will lead to less rigorous OPV campaigns and coverage, thus creating the conditions favoring transmission of OPV-derived viruses and the development of cVDPV. Two basic approaches could be

envisaged to eliminate OPV-derived viruses. The first involves massive OPV campaigns in the two years preceding discontinuation of OPV vaccination. In this way, levels of immunity within populations would be such that person-to-person transmission of vaccine-derived viruses would be short-lived (as they would soon reach immunised subjects and their intestinal immunity would halt or at least significantly decrease fecal excretion). This approach would not eliminate the risk of iVDPV excretion by immunodeficient individuals. The second option is to use IPV in order to ensure levels of immunity sufficient to prevent further circulation of the last vaccine-derived polioviruses. Some experts advocate discontinuation of OPV under an "IPV umbrella", only scaling down OPV usage when IPV coverage has reached sufficient levels to prevent circulation of OPV-derived viruses(9).

Containment of preserved wild viruses

In contrast to smallpox with visible clinical signs of infection, polio is visible in only one in approximately 200 children with virus infection. Consequently, poliovirus may circulate for months or years in a given population before a clinical case is seen, representing a major hurdle to detection and eradication. As with smallpox, the GPEI plan includes the identification of all laboratory sites likely to preserve wild viruses, the destruction of the vast majority of these stocks and the maintenance of only a very small number in well-documented and highly secure facilities for research purposes. The large number of laboratories in India(10) and throughout the world likely to be storing samples of poliovirus or stool samples that may contain poliovirus, make this a Herculean task, the magnitude of which is further increased by the threat of bioterrorism. Although poliovirus does not constitute the "best" instrument for bioterrorists, the possibility that it may be preserved in clandestine fashion for future use is a real concern.

Issues for the post-OPV discontinuation era

As for the global smallpox eradication initiative, the ultimate aim of the GPEI was to discontinue immunisation. The economic benefits of polio eradication and discontinuation of vaccination have been estimated at over $1 billion per year. This scenario requires some revision in the light of recent developments. In a context where the threat of bioterrorism cannot be ruled out and where neurovirulent viruses could survive undetected, high- and intermediate-income countries will not stop immunising their populations, even after eradication of wild virus has been proclaimed. IPV will continue to be used in these countries, in vaccine combinations, to guard against any remote risk of polio resurgence. For the other countries, according to current thinking, OPV vaccination will continue to be practised until 2008, when global certification is expected. After that time, OPV usage will need to stop.

In the post-eradication era, the hypothetical risk of resurgence of polio viruses will probably persist for many years. Such risks include iVDPV and other sources such as wild viruses persisting in remote locations, mishandled laboratory or manufacturing samples or bioterrorism. To plan for any eventuality, and tackle potential future polio outbreaks, a global "surveillance and response" system would include global virus circulation surveillance systems to detect the possible resurgence of polio viruses, large OPV stockpiles to control possible outbreaks, and processes to quickly implement vaccination in affected areas. To limit the circulation of VDPV, monovalent OPV, specific to the virus

type causing the outbreak, would be used to avoid needlessly re-introducing all three live virus types contained in current OPV(11). However, strains derived from OPV used to control outbreaks could themselves circulate in non-immune populations, in the vicinity of the OPV-vaccinated zone, thus posing the risk of VDPV spreading to unimmunized persons around the world. Strategies to overcome this eventuality are currently being explored(12). In addition to scientific issues, the costs of the various post-certification policies will need to to be assessed by each country, in order to make a decision on the best option, making this task highly complex.

Respective roles of OPV and IPV in the final eradication strategy

Since WHO mandated that OPV usage will need to stop, the days when the choice was OPV to IPV are over. The contribution of OPV to the current success of the poliomyelitis eradication strategy is beyond doubt. However, it is becoming apparent that ensuring the long-term global eradication of polio will be impossible without IPV. In a world in which wild virus has been eliminated, and in which routine OPV usage is no longer possible, use of IPV is the only way of preventing circulation of re-emerging polio viruses. IPV will provide collective and individual protection until the threat of resurgence of poliomyelitis virus, either through accident or malevolence, has disappeared.

Once OPV is discontinued, IPV represents the only option to maintain individual and collective immunity against polio. The debate on IPV usage in developing countries focuses on three issues: is IPV sufficiently immunogenic when given in the Expanded Program of Immunisation (EPI) schedule at 6, 10 and 14 weeks of life? Can IPV provide sufficient mucosal immunity to halt the spread of polio virus? And, lastly, is IPV not cost-prohibitive for the poorest countries?

IPV immunogenicity in developing countries

The immunogenicity of IPV has been most thoroughly documented in infants immunised in 2-4-6, 3-4-5 and 2-3-4 months schedules(14). One study of IPV given in the 6-10-14 weeks EPI schedule in Thailand(15) achieved seroconversion rates of 66%, 63% and 92% for polio types 1, 2 and 3 respectively. Other studies have shown better seroconversion rates with this schedule (16,17), although it has been suggested that the higher rates were in fact attributable to the concomitant circulation of OPV viruses. This issue was recently addressed in a study in Cuba, where the absence of circulating OPV viruses was demonstrated(18). In these conditions, IPV achieved seroconversion rates of 94.2%, 82.7% and 100% with the 6-10-14 weeks schedule, and 90.3%, 88.9% and 90.3% with a 2-4 months schedule, for polioviruses Type 1, 2 and 3, respectively.

IPV-induced mucosal immunity

IPV-induced mucosal immunity is critical to prevent excretion of neurovirulent polioviruses and to stop virus transmission. Polioviruses can be transmitted by the pharyngeal route, or by fecal-oral route. Both IPV and OPV provide good pharyngeal mucosal immunity. However, in countries where, because of sanitation conditions, fecal-oral is the more likely route vaccine-induced intestinal immunity may be important to halt viral circulation(19). Three studies showed that OPV provides superior intestinal immunity than IPV, although OPV does not totally prevent viral excretion even following challenge with Sabin virus(15,20,21). However, the impact of IPV on virus excreting is far from negligible; OPV and IPV, respectively,

are associated with 99.9% and 92% reductions in post-challenge fecal titres in comparison with unvaccinated subjects(21). These data may underestimate the effect of IPV, having been obtained in 1960's using the original Salk IPV rather than the more efficacious IPV vaccines enhanced potency currently.

The cost of IPV

The cost of IPV is often perceived as being too high for the poorer countries to afford. Indeed, it is paradoxical to consider paying more to vaccinate against an eradicated disease than to vaccinate against an existing disease. This notion incorrectly relies on OPV being an inexpensive vaccine. While it is true that one dose of OPV is inexpensive, in order to be effective (*i.e.*, to provide optimal seroconversion rates) and safe (*i.e.*, to avoid creating the circumstances for emergence of VDPV), OPV must be given not only with high routine coverage rates, but also through repeated vaccination campaigns such as National Immunization Days. A Mexican study has shown that the cost of OPV itself only represents 9.9-15% of the costs of an Immunization but that by five years of age, a Mexican child has received an average of 15 doses of OPV(22). In contrast, IPV is reliably immunogenic after 2 or 3 injections and does not require additional immunization campaigns to be effective(23). Therefore, a true comparison is not of the basic prices of OPV and IPV themselves, but rather the costs of vaccination programs with OPV or IPV. In this comparison, it is clear that OPV is not as cheap a vaccine to use as is often thought. In addition, while the current price of IPV is consistent with use limited to developed and intermediate-income countries, it is clear that adoption of IPV by large developing countries, such as India or China, would lead to increased incentives for more manufacturers to produce much larger quantities, and would drive prices down(23). Finally, further work is needed to assess the costs of using IPV or not using IPV over the longer term, to include the costs of maintaining effective "surveillance and response" systems compared with the costs of introducing IPV in routine vaccination programs.

Clearly, issues regarding post-eradication strategies are complex(24-27), and considerable efforts are currently being made under the aegis of the WHO to assess all possible scenarios, so that guidelines on OPV cessation and introduction of IPV can be designed(28).

Impact of future decisions regarding IPV usage

The decisions that must be made in the next few years concerning polio vaccination strategies are inextricably linked with wider considerations for the future. Until the start of the 1990's, vaccines used in public health programs were basically the same throughout the world, meaning that vaccine manufacturers were able to supply the same products to developed countries and, with a "tier pricing" approach, at much lower prices to developing countries. The existence of several vaccine manufacturers ensured a relatively stable supply to the poorer countries and competition guaranteed low prices.

Over the last few years, more technologically complex vaccines have been developed and manufactured, such as acellular pertussis and conjugated *Haemophilus influenzae* type b (Hib) and pneumo-coccus vaccines. Furthermore, the development of new vaccines goes hand in hand with the development of new combined vaccines designed to reduce the number of injections required. Hence the progressive development of a 'vaccine offer' suited to the richer countries' needs combination including acellular pertussis, IPV, Hib, *etc*. but which, in

the absence of large-scale demands, may become less and less affordable for the poorer countries. Current debate on the future use of IPV is complex, since it necessarily turns on a multitude of separate considerations. It is nevertheless important to understand that if radically different vaccination strategies are followed in the richer countries compared with the developing countries, this will only serve to widen the gap between vaccines intended for the rich and the poor countries.

Conclusion

After global eradication is declared, the risks of seeing a resurgence of polio are real. Countries such as India represent very large populations among which there are almost certainly undiagnosed immunodepressed patients excreting OPV-derived viruses, where it will be difficult to maintain high-quality virological surveillance over time, and where control of all wild polio viruses-containing laboratory materials will be complex. It will be critical, therefore, to maintain population immunity over the long term, to prevent circulation of re-emerging viruses. Once OPV is discontinued IPV will represent the only option to maintain individual and collective immunity against polio. However, in the face of other more burning health priorities, funding of routine IPV vaccination in India will be justified only if the costs (in the broadest sense of the term) of vaccinating with IPV are lower than the costs of not vaccinating with IPV over the long term. India and all other countries will have to gather data to assess the risks and advantages of each option and make a decision. Nevertheless, since viruses know no border, decisions made by each country will have an impact on its immediate neighbours and, beyond, on the global community. These dilemmas are the last challenges that the international community must overcome, if it wants to ensure the long-term success of the global eradication initiative and, to use the words of Dr. David Heymann of WHO(28), to "protect the investment" that all countries have made in their fight against poliomyelitis.

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