Immunisation against poliomyelitis: moving forward

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The worldwide campaign to eradicate poliomyelitis is nearing its 20th anniversary, and is 8 years over its original target date of the year 2000. During the past decade, the programme has encountered a number of unanticipated obstacles,7–9 which have led to renewed discussions about whether eradication of poliomyelitis is feasible and, if so, what is the best way to achieve it.4,4 To address these issues, we engaged more than 100 scientists from 18 countries—virologists, epidemiologists, public-health workers, policy makers, and representatives from the pharmaceutical industry—to review current progress and propose directions for the future. A series of panel discussions helped facilitate the exchange and analysis of new data and ideas on how best to use the existing vaccines against poliomyelitis, and on what role they might have in future immunisation programmes. Although differing viewpoints and perspectives have been aired to overcome current obstacles and move the eradication programme forward, new ideas and support are emerging with regard to several important issues.

The delay in completing the final stages of the eradication campaign, led by WHO, has been attributed to the failure of oral poliovirus vaccine (OPV) to interrupt circulation of wild virus in a few densely populated locations in Uttar Pradesh and Bihar in northern India, and the failure to immunise because of political turmoil or military unrest in northern Nigeria and remote areas of Pakistan and Afghanistan.7 These two factors have led to the resurgence of disease in more than a dozen other countries previously declared free of poliomyelitis. Reasons for the low efficacy of OPV in northern India are poorly understood. Each dose of vaccine is estimated to result in less than 10% seroconversion, requiring more than 15 consecutive administrations of vaccine to bring the population immunity to a desirable level.7 In this densely populated area with a high birthrate, a large proportion of very young children remain susceptible to poliovirus and serve as a reservoir to continue circulation of the virus. The recent introduction by WHO of supplementary doses of monovalent OPV into the immunisation schedule might help to reduce this reservoir, since the monovalent vaccine improves seroconversion rates for the relevant serotype compared with trivalent OPV,9 and campaigns in northern India have been increased to a monthly schedule and include targeted searches for infants not at home on the initial visit.

A new approach not previously recommended by WHO, but widely discussed in the broader scientific community, would be to add inactivated poliovirus vaccine (IPV) to the armamentarium of the eradication programme. Numerous studies have shown that IPV can induce high rates of seroconversion in tropical countries.9,8 The use of IPV in combination with OPV in infants could help close the immunity gap in this critically important age cohort, and tip the balance to eliminate wild poliovirus circulation. The initial reasons for the choice of OPV were its low cost, ease of administration, and its ability to induce herd immunity by person-to-person transfer. Data from developed countries suggest that IPV also has a herd effect, resulting from decreased transmission of wild virus to unvaccinated individuals when some of the population is immunised. Further studies are needed to determine how well IPV can reduce transmission in tropical settings and to assess its ability to stop wild poliovirus transmission and control outbreaks in the post-eradication era.

Although OPV has been the mainstay of the eradication programme, its continued use is ironically incompatible with the eradication of paralytic disease. Neuroviral vaccine-derived polioviruses (VDPVs) generated by reversion or recombination of OPV strains can circulate in poorly immunised populations and cause outbreaks of paralytic disease.10 Other VDPVs have been isolated from some immunodeficient patients who chronically excrete polioviruses, or from sources that do not allow them to be classified.2 These vaccine-derived viruses consistently emerge as a consequence of the inherent genetic instability of poliovirus. Initially, VDPVs were thought to be unfit, weak cousins of wild poliovirus, and therefore would only survive to a limited extent in field environments. However, experiments probing the mechanisms underlying the evolution and genetic flexibility of these viruses suggest that, if allowed to circulate, such strains will evolve in such a way as to be indistinguishable in virulence from wild viruses.11 Therefore, the world can never be considered free from the potential for paralytic poliomyelitis while OPV is being used, and indeed the term eradication must be redefined to include the elimination of both wild and vaccine-derived viruses. Several research groups have described potential vaccine strains with increased genetic stability,12,13 but their trials would face insurmountable regulatory and epidemiological challenges, so there has been little enthusiasm for their further development.

Several scenarios have been proposed to discontinue OPV use. One early idea was to synchronously stop OPV use throughout the world once wild polioviruses were no longer detected,14 avoiding the spread of VDPVs from countries still using OPV to those that have already stopped vaccination. This scenario would leave large populations in areas that did not adopt IPV vulnerable to disease if poliovirus re-emerged. Unfortunately, outbreaks are very likely to occur after cessation of OPV immunisation. Initially, it was thought that these

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outbreaks could be readily contained by local OPV administration.15 However, this scenario would, for the first time in human history, create large populations with no immunity to poliovirus and represents an experiment with potentially serious risks that cannot be accurately assessed. Unknown risk factors include the prevalence of chronic excreters, the long length of time that wild or vaccine-derived poliovirus can circulate without causing detectable disease, and the force of spread of virus and the severity of disease in immunologically naïve communities.16 Leaving populations in poor countries unprotected would create the possibility for pathogenic viruses to spread and reignite new epidemics, and would be unacceptable for a number of ethical and political reasons. The current spread of wild virus from northern Nigeria to surrounding countries has shown the havoc that poorly controlled spread could cause. The risk could be reduced by gradually replacing OPV with IPV, on a country-by-country basis, for at least an interim period until the risk factors can be better defined.

A gradual shift from OPV to universal use of IPV would help resolve a number of otherwise daunting tasks that will arise during the transition to a post-eradication strategy. Maintaining high population immunity throughout the world would minimise the risk of potential outbreaks caused either by re-introduction of poliovirus from facilities engaged in research, virus reference and production, or by release of a chemically synthesised poliovirus, a new threat that has been shown to be technically feasible.16 Economic and logistical aspects of creation and maintenance of a vaccine stockpile for response to outbreaks would be simplified, and the tactic of having to use OPV for emergency responses in an environment where a substantial part of the population has no immunity to poliovirus—fighting fire with fire—would be eliminated. Synchronous OPV cessation—a formidable political and logistical task—would not be required under this scenario. Industry in developed and developing countries would have time to develop and expand its manufacturing capacities to supply the world with IPV, and to accumulate experience and information about the safety of the transition.

High production costs have always been among the leading obstacles to large scale use of IPV in low-income countries. IPV manufacturers have repeatedly suggested that expansion of production could lead to substantial price reductions. Trials to reduce vaccine dosage and introduce intradermal delivery of IPV, eliminating the need for trained medical personnel to do conventional intramuscular injections, could further address these concerns and are already being sponsored by WHO. Intradermal injection of IPV has been shown in animals and human beings to produce higher immunity at reduced dosages of vaccine. Adjuvants can increase the immunogenicity of IPV, providing another possible route to dose reduction. Preliminary studies of novel adjuvants in animals hold promise of not only boosting humoral immune responses, but also increasing the ability of IPV to induce local (mucosal) immunity. Combining IPV with other antigens and an alum adjuvant seems to increase immunogenicity. The use of IPV-containing combination vaccines could substantially increase cost-efficiency of the product and its delivery, because it would simultaneously control a number of other vaccine-preventable diseases, with the added benefit of revitalising enthusiasm of local health workers and combating programme fatigue. IPV could then become part of routine worldwide immunisation programmes. Strengthening WHO’s Expanded Program on Immunization must become the next long-term goal of the international public health and infectious diseases community.

The establishment of production facilities in developing countries might also lead to cost savings, but concerns exist about containment of virus in new, less experienced facilities located in regions with potentially suboptimum immunisation coverage. To avoid this risk of release of wild virus strains, pilot projects are underway to develop IPV from attenuated (e.g. Sabin) strains; these projects could also link to the creation and maintenance of OPV stockpiles.17 IPV derived from Sabin products differ from conventional IPV in their immunogenicity in animals and human beings, as well as other immunoochemical properties.18 However, increasing the amount of type 2 and type 3 antigens and decreasing type 1 antigen was shown to produce IPV with immunogenicity comparable with that of conventional vaccines, albeit probably at increased cost.

In the interest of having a number of methods with which to undertake and safely complete the eradication and post-eradication effort, several potential drugs targeting different viral proteins are currently under investigation. Such drugs could be used to treat chronically infected individuals, as well as to treat—prophylactically or post-exposure—in outbreak settings.19 A new class of drugs targeting cellular chaperone pathways critical for viral replication was proposed; such drugs would suppress viral replication but would not allow the emergence of resistant mutants.20 Where do we go from here? We see broad continuing support for achieving the global goal of eradication of poliomyelitis, but with some new strategies that could be critical. These include: the use of IPV in conjunction with OPV to interrupt poliovirus transmission in high-risk areas; stopping OPV worldwide when IPV coverage makes it safe to do so; and continuing IPV with routine childhood immunisations. For the near future, continued global vigilance, surveillance, and vaccine response capacity will be needed to respond to the risks of variable immunisation coverage and susceptible subpopulations in some countries. Decisions about the future use of IPV will be needed soon if manufacturers are to accommodate any change in recommendations. Basic and field research will be crucial to better
understand poliovirus genetics and biology, investigate the role of antiviral drugs, and improve vaccines as part of an ever evolving strategy to eliminate poliomyelitis as a threat to all future generations.

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References