New polio vaccines for the post-eradication era

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# Glossary

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<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BSL</td>
<td>biosafety level</td>
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<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
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<tr>
<td>HEPA</td>
<td>high efficiency air (filters)</td>
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<td>IPV</td>
<td>inactivated polio vaccine</td>
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<td>mOPV</td>
<td>monovalent OPV</td>
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<td>OPV</td>
<td>oral poliovirus vaccine</td>
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<td>tOPV</td>
<td>trivalent OPV</td>
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<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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Executive summary

Wild poliovirus transmission is currently limited to several remaining foci in south Asia/Africa. This remarkable progress towards eradication of poliomyelitis has been achieved through the global use of oral poliovirus vaccine (OPV). The most important short-term programmatic priority is to achieve complete interruption of transmission of wild poliovirus. In the near future, however, it is anticipated that decisions will need to be made about vaccination strategies for the post-eradication era. This is to allow contingency plans and vaccine stockpiles to be developed for emergencies and to allow lead time to bring new vaccines, if needed, into use so the world can move from universal polio immunization to no polio immunization. These issues were reviewed by a group of experts meeting in Geneva, 19-20 January 2000.

At some time in the post-eradication era, immunization with OPV will stop - when and how is not yet decided. Although reappearance of poliovirus in a polio-free world is considered highly unlikely, contingency plans are required to ensure a rapid and high-quality response if needed and to minimize the probability or impact of a bioterrorist release of polio. The group recommended that in the post-eradication era control of a single serotype outbreak should be with mass campaigns of monovalent OPV (mOPV). This was because mOPV would provide a fast type specific immune response and prevent unnecessary seeding of additional viruses into the population. Thus a stockpile of mOPV of each type is required, some of which should be in multidose vials for immediate shipment and use. The size, locations and access criteria to the stockpile need to be determined. The group recommended that expertise and resources for manufacture and control of OPV be maintained in at least two facilities to service the stockpile. Plans for the stockpile need to be developed by WHO.

Although we are entering the end game for polio the group recommended there is still a need to consider new vaccines. One reason is because of biosafety concerns about manufacture of inactivated polio vaccine (IPV), in which wild type polio seed viruses are currently used. The use of non-wild strains, preferable the Sabin strains used to manufacture OPV, for future production of IPV was strongly recommended. Some manufacturers already had limited experience with Sabin IPV and it was recommended that this was reviewed as soon as possible.

Another reason to consider new vaccines was because of uncertainties of whether Sabin-derived strains, especially of type 2, would continue to circulate in a post-OPV era. The group thus recommended that the need for and options for reformulation of OPV be considered. Possibilities included omission of type 2 completely or substitution of Sabin 2 by a new strain. Several candidate new strains are available and cautious clinical evaluation was recommended to determine if any had advantages such as lower
transmissibility. The group acknowledged there would be substantial regulatory concerns over a reformulated OPV.

To take these issues further the group recommended that a meeting be convened to review the regulatory issues and additional research requirements for Sabin IPV and a reformulated OPV.
1. Introduction

Remarkable progress has been made towards eradication of poliomyelitis and as a result wild poliovirus transmission is now limited to several remaining foci in south Asia/ Africa. This has been achieved through the global use of oral poliovirus vaccine. The most important short-term programmatic priority is to carry out a final push to achieve complete interruption of transmission of wild poliovirus. In the near future, however, it is anticipated that decisions will need to be made about vaccination strategies for the post-eradication era. A previous WHO meeting (1) recommended that immunization against polio should eventually stop and that contingency plans should be developed for possible emergency vaccine use in the post-immunization era. The meeting also recommended that, among several possible strategies, consideration should be given to new candidate vaccines. It is urgent to do this now so that plans and vaccine stockpiles will be in place before immunization ceases. Moreover, new vaccines, if needed, will require a lead-time of at least several years to bring into use. The meeting therefore reviewed proposed contingency plans and current research on new candidate vaccines to determine the need for and feasibility of producing such vaccines, and to identify priorities for research.
2. Why emergency vaccination may be needed in the post-immunization era

A previous WHO meeting concluded that immunization with OPV should stop when there was: assurance of the global eradication of wild polioviruses; assurance that wild poliovirus stocks were adequately contained; and evidence that OPV-derived strains would circulate for only a limited period of time in the post-vaccination era (1). Due to the magnitude of potential problems if polio did emerge in a future unvaccinated population, it would be irresponsible not to plan for this eventuality, however unlikely it may seem to be. Furthermore, although rational considerations show that polio is a very unlikely bioterrorist threat, this eventuality cannot be absolutely ruled out, and every reasonable step should be taken to minimize both the probability of a bioterrorist release and the impact should it occur.
3. Contingency plans

At least three scenarios can be envisaged for which it is necessary to prepare contingency plans in the post-eradication era. These are detection of circulation of (a) wild poliovirus (b) vaccine-derived viruses associated with clusters of paralytic cases, and (c) vaccine-derived viruses not associated with clusters of cases. Until very recently vaccine-derived viruses that caused clusters of cases had never been identified. However there appears to be at least one instance where vaccine-derived type 2 polioviruses may have assumed wild-type characteristics (including transmissibility and neurovirulence) and caused multiple cases of paralytic disease during the period of 1988-1993 in a densely populated, developing country with suboptimal vaccination coverage. No representatives of these lineages have been detected since February 1993, apparently as a result of well-conducted NIDs using OPV.

Outbreak control activities for vaccine-preventable diseases aim rapidly to increase immunity levels in the affected populations. Two vaccines could be available for polio control, OPV and IPV. There are also different formulations of OPV (i.e., trivalent [tOPV] or monovalent [mOPV]). The age groups to be vaccinated and the geographic focus for vaccination will depend on known or inferred patterns of age-specific susceptibility, and on the geographic spread of the virus as determined through disease and virus surveillance. As a general principle, vaccine should be used in a wider geographic area than where cases have already occurred and, at a minimum, should cover all children through age five years plus any older cohorts born since polio vaccination was stopped.

If there were to be a reoccurrence or outbreak of either wild or vaccine-derived poliovirus, it is most likely that only a single virus type would be involved, although two or even all three might theoretically appear together. It will be necessary to devise a global scheme to rapidly sequence all AFP poliovirus isolates eliminating unnecessary delays in testing. Given the very different ratios of paralytic cases to infections (1/200 versus 1/106), it is likely that the epidemic pattern in space and time would itself give a strong indication of whether a wild or vaccine-derived virus were involved.

The argument to utilize OPV vaccines in outbreak situations has been accepted widely ever since their introduction, and repeatedly justified by experience (Albania, Canada, Finland, Netherlands, USA, etc.). Importantly, such vaccines have been employed to combat outbreaks even in populations vaccinated with IPV (Finland and the Netherlands). There is little doubt that massive use of OPV will be the approach used to combat any outbreaks that occur of wild poliovirus, or vaccine-derived viruses that are associated with clusters of cases. However, unlike at present when trivalent OPV is used, there are several compelling reasons to prefer use of monovalent OPV in the post-immunization era. These include a more rapid immune response, a higher type specific seroconversion rate and, given that any outbreak is likely to involve only a
single virus serotype, the use of homologous monotypic vaccine will avoid unnecessary seeding of additional viruses into the population. These benefits of monovalent vaccine must be weighed against a potential increased risk of vaccine-associated paralytic poliomyelitis.

The response to the detection of circulating vaccine-derived virus not associated with clusters of cases is less clear. This is because use of OPV may perpetuate rather than eliminate this specific problem. Further research is urgently required to determine the likelihood of persistence of vaccine-derived strains in the post-eradication era and on the utility of alternatives to OPV for outbreak control for this scenario.
4. Development of new vaccines

There are uncertainties at present about how to stop vaccination against polio and how to deal with OPV-derived virus circulation in certain epidemiological situations. There may also be difficulties in continued manufacture of the currently available IPV in the post-eradication era because of biosafety concerns over the use of wild poliovirus seed viruses. For these reasons it was prudent to consider new vaccine candidates. A considerable amount of research on possible new vaccines has already been undertaken by a number of investigators.

In the mid-1980s to late 1980s, various types of poliovirus antigens were investigated in depth for their immunogenicity. They included peptides, derived from the sequence of poliovirus proteins, the proteins themselves, and various attempts to express entire sequences of poliovirus in vectors such as vaccinia or the insect baculovirus. The conclusion at the time was that none of these approaches offered a practical way forward, and the existence of two highly effective vaccines made further development in a manufacturing or marketing sense unlikely. This is believed to remain the case at present, but it might be of interest to revisit capsid formation by non-polio expression systems such as DNA vaccines for the post-eradication era. This would be the only vaccine type not associated with a risk of poliovirus infection.

After wild-type poliovirus is eradicated, wild-type strains will require high levels of containment. The difficulty of reconciling containment with the production scales required for current IPV makes the use of attenuated vaccine strains for IPV manufacture attractive. The most promising attenuated candidate strains are the current Sabin strains used for OPV. The potential use of such strains for IPV production has been pursued extensively by three manufacturers but not so far as to obtain a licensed product. Potential differences in immunogenicity and antigenicity between Sabin and conventional IPV strains need to be investigated and may necessitate modifications in virus content and/or changes in the vaccination schedule for Sabin-derived IPV in order to achieve equivalent protection. In addition to live strains for which there is clinical experience, there are a number of other strains designed on molecular biological principles which are likely to be suitable for consideration as new IPV seeds.

Over the past 20 years the molecular basis of the attenuation of the Sabin vaccine strains has been studied in detail, and it is considered possible to exploit this understanding to create new live attenuated strains.

Kohara et al. (2) described the construction of an attenuated vaccine strain in which the capsid region of the type 1 Sabin vaccine strain was excised and replaced with the equivalent regions of the type 2 or type 3 Sabin vaccine strains. The rationale was that the type 1 strain is associated with the lowest rate of vaccine associated poliomyelitis of the three Sabin strains, of the order of a tenth that of the other two, and that at least some of the attenuating mutations lie outside the capsid region. The strains were
prepared according to good manufacturing practice (GMP), tested in the WHO neurovirulence test, found satisfactory and apparently have been tested in limited clinical trials.

Three groups have designed experimental strains based on understanding of the molecular basis of attenuation. In each case attention has focused on the 5' non-coding region which is involved in the initiation of protein synthesis, and in which each of the Sabin strains has been shown to possess attenuating mutations. Clinical trials would be necessary to evaluate whether any of the candidates had potential advantages over the existing Sabin strains. So far, clinical grade material was not available for any of these candidates.
After extensive consultation, WHO has developed a “Global Action Plan and Timetable for Safe Handling and Maximum Laboratory Containment of Wild Polioviruses and Potentially Infectious Materials” (3). These new provisions provide that, when polio eradication is achieved, all laboratories working with wild virus and vaccine production facilities producing IPV should work at a new biosafety level referred to as Biosafety Level (BSL) 3/polio. This exceeds Biosafety Level 2 by requiring double door entry to the laboratory; lockable doors; impervious and cleanable laboratory interiors; sealed perimeter penetrations; backflow preventors; inward directional airflows; high efficiency air (HEPA) filters and an autoclave in the laboratory. Facilities producing OPV would be, for as long as OPV vaccination continued, permitted to work at a containment level referred to as BSL 2/polio. In addition to current biosafety level 2 this requires laboratory staff to be immunized against polio; controlled and limited access to the polio laboratory; the use of wild polioviruses only when essential; and the secure storing of polio stocks.

Introduction of any new biosafety procedures for vaccine manufacture requires appropriate training of staff, perhaps building modification, and the new biosafety process requires validation and a mechanism to ensure compliance. Further discussion between WHO and the vaccine manufacturers is essential to develop practical and appropriate mechanisms to ensure production of adequate supplies of affordable polio vaccine, under safe manufacturing conditions, for use in the years immediately after polio eradication.
6. Conclusions and recommendations

6.1 Response to detection of an outbreak due to wild poliovirus or vaccine-derived polioviruses that are causing significant clusters of cases

It has long been accepted that wide-scale use of OPV is the preferred strategy for epidemic control of polio. There is little doubt that massive use of OPV will be the approach used to combat any outbreaks of wild poliovirus or vaccine-derived polioviruses that are causing significant clusters of cases. However, unlike the present situation when trivalent OPV is used, in the post-immunization era there are several compelling reasons to prefer use of monovalent OPV. These include a more rapid immune response; a higher type-specific seroconversion rate; and unnecessary seeding of additional viruses into the population. Pending a favourable review of the safety issues, the group recommended that:

- The outbreak of polio caused by wild virus in the post-eradication era should be controlled with mass campaigns with homologous monovalent OPV. Similar recommendations would apply to outbreaks with vaccine-derived viruses that are causing significant clusters of cases.

- WHO should undertake a review to determine whether current suppliers to the United Nations Children’s Fund (UNICEF) have licences for use of monovalent OPV and the specific countries where these licenses apply. If necessary, steps should be taken to assure these products are licensed for global emergency use.

- A stockpile of each of the three types of monovalent OPV vaccine should be maintained in case of an outbreak of poliovirus after cessation of vaccination. At least part of the stockpile should constantly be available in multi-dose vials (e.g. 20–100 doses) for immediate shipment.

- A preliminary estimate of the size of the stockpile is that it should be at least 500 million doses of each serotype. WHO should prepare a formal report that quantitates more precisely the amount of vaccine needed, taking into account not only epidemiological factors but also vaccine-manufacturing considerations such as the time to replenish any stocks that may be used. The revised estimate should also take into account the proportion of the stockpile to be stored as monovalent bulks and the proportion to be stored in multi-dose vials for immediate shipment.

- WHO’s formal report on the stockpile should indicate ways to assure that vaccine from the stockpile can be made available to any and every country needing it.

- Studies of the immunogenicity of single-dose monovalent OPV in low-hygiene settings should be considered to help establish the size of the stockpile and outbreak response strategies.
WHO should review the significance, if any, of waning gut-induced immunity and conduct studies if necessary to determine whether previously vaccinated persons will need to be re-vaccinated as part of outbreak response.

OPV vaccine manufacturing capacity must be maintained to meet global needs in at least two facilities. WHO should determine how the manufacturers are selected and funded. This production should be sufficiently regular to ensure maintenance of production capability and expertise, and should also be under appropriate biosafety containment levels. Expertise and appropriate resources for control of OPV should also be maintained in at least two national control authorities for batch release of the vaccines in the stockpile.

6.2 Response to detection of circulation of OPV-derived strains that have not caused clusters of cases

Whether vaccine-derived viruses could circulate in the post-eradication era and yet cause poliomyelitis at the low rates of the vaccine strains today is not yet certain. Nevertheless, as contingency plans have to be made now, the group considered how to respond to detection of circulation of OPV-derived strains. The use of homologous monovalent OPV to control circulation of attenuated OPV-derived strains may not be effective in terminating transmission in this circumstance. So alternative strategies may be required. The group therefore recommended that:

- Research on the transmissibility of vaccine-derived polioviruses is of high priority. Special studies should be conducted now in countries that have switched from OPV to IPV. In the future, studies should be conducted to monitor any persistence of vaccine-derived strains as other countries cease supplementary immunization and/or routine OPV vaccination.
- Should vaccine-derived OPV persist, research is required on the utility of different strategies, including use of current IPV to eradicate circulation of OPV-derived virus, especially in low-hygiene populations.
- If shown effective in controlling OPV vaccine-derived viruses in these environments, a global stockpile of trivalent IPV vaccine should be maintained.

6.3 Continued research on new vaccines

There are uncertainties at present about how to stop vaccination against polio and how to deal with OPV-derived virus circulation in certain epidemiological situations. There may also be difficulties in continued manufacture of the currently available IPV in the post-eradication era because of biosafety concerns over the use of wild poliovirus seed viruses. The group therefore considered that it was essential that research be continued on new vaccine candidates. The new vaccine candidates may be new inactivated vaccines; reformulations of current live, attenuated strains; or new live attenuated strains. The group made separate recommendations for these different possibilities.
6.4 **New inactivated vaccines**

- The group strongly recommended production of future IPV from non-wild type strains, preferably the Sabin strains. This would simplify future containment requirements during vaccine manufacture and increase the safety margin in case of inadvertent release. At least three manufacturers have already had experience with IPV made from Sabin strains and at least one country was thought to be close to introduction of IPV based on Sabin strains.

- WHO should urgently convene a meeting of regulators and manufacturers, and also request scientific advice from regulatory authorities, to review the available information and determine the time-frame and possibilities of widespread introduction of IPV produced from Sabin strains. The review should determine what further research is required on production, quality control and evaluation of IPV produced from Sabin strains.

- The group recommended that new strains, in addition to the Sabin strains, be evaluated for use for production of IPV. Ideally these strains should be non-transmissible. They should also retain immunogenicity after inactivation. Information that would give an indication of the safety and transmissibility of new strains should be obtained to determine the appropriate biosafety containment level for production. WHO should coordinate the evaluation of promising new IPV strains.*

6.5 **Reformulation of existing live attenuated vaccines**

- The group was concerned over the recent evidence of a putative virulent vaccine-derived type 2 strain in one country and limited evidence of circulation elsewhere. The group recommended an urgent evaluation of all AFP poliovirus type-2 isolates to determine how commonly this phenomenon occurs. Full characterization of the current putative Sabin-2 derived outbreak strain is necessary to provide complete information on the derivation of the strain.

- In the light of this finding the group recommended that WHO reconsider evaluation of a bivalent type-1 and type-3 OPV as a means of determining if Sabin-derived type 2 would continue to circulate in the absence of vaccination. Additional reasons for considering a bivalent OPV were: the remaining foci of wild type-2 transmission were now extremely restricted; Sabin type 2 is the most transmissible strain in OPV; type 2 vaccine virus is most likely to circulate; and the only known case of long-term excretion in an immunodeficient person acquired by contact was a type 2. Furthermore, a bivalent OPV would prevent vaccine-associated cases due to type 2. These benefits of a bivalent vaccine must be weighed against safety and efficacy implications of removing the type 2 strain from trivalent OPV (4). WHO should, therefore, urgently convene an expert group to consider the regulatory concerns and clinical study designs for a bivalent OPV. This could be done at the same time as the meeting on IPV regulatory issues.

- If, as a result of the re-evaluation, a country made a change to large-scale use of bivalent vaccine then appropriate studies should be set up to monitor the circulation of type 2 in the population.

- Should vaccine-derived type 2 virus continue to circulate, research should be conducted into which strategies, including the use of IPV, can be used to terminate transmission.
6.6 New live attenuated vaccine candidates

- WHO should coordinate a step-wise evaluation of new candidate live attenuated strains to determine if any have potential advantages over the Sabin strains such as a lower transmissibility whilst retaining or improving on the safety and efficacy profile of the Sabin strains. As there are no models of transmissibility this would have to be done in phase 1 and 2 clinical studies. A less transmissible type 2 strain for OPV, for example, may preclude the need for a bivalent experimental intermediate.

- Given that the window of opportunity to do such trials may be narrow, initiation of the studies must be as soon as possible. The transmission properties that should be examined are the infectious dose required, and the titre and duration of excreted virus. Surrogates of safety and efficacy, such as molecular reversion rates, virulence in transgenic mice and neutralizing antibody responses, should also be evaluated in these initial trials.

- At least two candidate strains, one a type 2 and one a type 3, developed by Dr A Nomoto, Japan (2) have already been prepared as clinical grade material and have already been studied in clinical trials. WHO should review these results. If necessary, additional clinical trials should be conducted.

- Clinical grade material should be made from other candidate strains that have at least theoretical advantages over current Sabin strains for evaluation in phase 1 and 2 clinical trials.

- Candidate strains that show promise in these initial studies should be evaluated further for general safety as well as their potential to cause vaccine-associated paralysis.

- WHO should convene a working group to take this issue forward as quickly as possible.

6.7 Financing new vaccine development

- As there will be limited financial incentive for manufacturers to develop new polio vaccines, it is strongly recommended that WHO coordinates a plan for implementation of the necessary research for new vaccine development and that all sources of funds be sought including government funding agencies, foundations, etc.

6.8 Poliovirus surveillance and emergency response plans

The emergency response to a poliovirus outbreak detected after immunization has stopped will be greatly facilitated by using previously prepared plans of action, and using advice from institutions and individuals with expertise in polio outbreak control. The response to an outbreak will also depend on whether the virus is wild type or vaccine-derived. For these reasons the group recommended that:

- WHO should develop a model protocol for responding to polio cases and/or poliovirus infections in the post-immunization era. As part of the certification process of polio eradication, countries should adapt this protocol to local
conditions. The outbreak response should be based on the epidemiological circumstances and should involve the vaccination of, at a minimum, all children under five years of age, and all individuals born since cessation of vaccination in the populations concerned, which would extend appreciably beyond areas already known to be infected.

- **WHO** should ensure that the epidemiologic and virologic capacity for planning for and overseeing control of poliovirus outbreaks be maintained in the post-eradication era.

- **WHO** should coordinate research on ways to minimize delays from clinical onset of polio to sequencing of all poliovirus isolates.

- **WHO** should coordinate research on improved ways of detecting circulation of polioviruses in the absence of disease, including environmental monitoring.

- Current research on detecting long-term excretors of poliovirus, and development and evaluation of methods to treat such patients, should be continued and extended.
7. References


Annex 1: Agenda

Wednesday, 19 January 2000

08.30–08.45 Welcome and opening remarks
   M. Scholtz
   Introduction of participants
   Administrative announcements

08.45 –09.15 Progress towards Global Polio Eradication
   B. Aylward

09.15–09.45 Process of Certification and Containment
   H. Hull
   R. Sanders

09.45 –10.30 Summary of Meeting of Scientific Basis for Stopping Immunization
   D. Wood

10.30–11.00 Coffee break

11.00–11.45 Current research on stopping immunization
   R. Sutter

11.45–12.00 What is the potential for poliovirus to be used in bioterrorism?
   T. Treadwell

12.00 –12.30 Discussion

12.30 –14.00 Lunch

14.00 –14.30 Stopping a polio outbreak in the post-eradication era
   P. Fine
   Implications for future vaccines
   W. Orenstein

14.30–15.00 Discussion

15.00 –15.30 Potential new poliovirus strains for OPV and IPV production
   P. Minor
   K. Chumakov

15.30 –16.00 Discussion

16.00 –16.30 Coffee break

16.30 –17.00 Biosafety aspects of polio vaccine production
   M. Kennedy
   P. Saluzzo

17.00 –17.30 Discussion
Thursday, 20 January 2000

08.30–10.30 Group work

**Working Group 1**

Are new vaccines needed?
Safety in production
Transition from Sabin strains to no vaccination
Reserve against escape/bioterrorism

**Working Group 2**

Can new vaccines be brought into production?
Essential safety and potency criteria
Research needed
Estimated cost of research and potential funding sources
Taking vaccines from research labs to production (timeline)
Will new vaccines be accepted by national regulatory authorities?

10.30–11.00 Coffee break
11.00–12.30 Working group presentations
12.30–13.30 Lunch
13.00–15.30 **Large Working Group**

Which vaccine candidates should be supported?
Live oral vaccine strains
Inactivated strains

15.30–16.00 Coffee break
16.00–17.30 Final recommendations
Annex 2:
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Vaccine producers

Aventis Pasteur

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