Report of the meeting on the scientific basis for stopping polio immunization

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<tr>
<td>AFP</td>
<td>acute flaccid paralysis</td>
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<tr>
<td>CVID</td>
<td>Common variable immunodeficiency</td>
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<td>IPV</td>
<td>inactivated polio vaccine</td>
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<td>OPV</td>
<td>oral polio vaccine</td>
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<td>PID</td>
<td>primary immunodeficiencies</td>
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<td>VAPP</td>
<td>vaccine-associated paralytic polio</td>
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<td>VDPV</td>
<td>vaccine-derived poliovirus strains</td>
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<tr>
<td>XLA</td>
<td>X-linked agammaglobulinaemia</td>
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Dr R. H. Henderson, Assistant Director-General, on behalf of the Director-General, opened the meeting. Dr Walter Dowdle was elected as Chairman and Dr David Wood as Rapporteur. The agenda (Annex 1) and list of participants (Annex 2) are attached. Working groups organised to address specific issues are listed in Annex 3, and a list of working papers is attached as Annex 4.

Dr Henderson welcomed participants and noted the rapid progress towards eradication of poliomyelitis and wild type polioviruses. Circulation of wild polioviruses had been stopped in the Americas since 1991 and wild polioviruses were on the verge of eradication in the European and Western Pacific Regions. Wild poliovirus circulation had substantially declined in many of the remaining endemic countries of the Middle East, South-East Asia and sub-Saharan Africa. With this progress in mind it was timely to review available data and to identify what further studies were needed so that scientifically based policies of when and how to stop vaccination against polioviruses could be developed.

1. Introduction
2. Objectives

The objectives of the meeting were:

1. To review available scientific information and studies in progress relevant to making a decision on stopping immunization against poliomyelitis.

2. To define priorities for research relevant to recommending a strategy for stopping immunization which could be completed in the short term.
No country can safely stop polio immunization until wild polioviruses have been eradicated globally. Most countries currently use live, attenuated oral poliovirus vaccine (OPV) for infant immunization. Only a limited number of countries recommend an infant immunization schedule using only inactivated poliovirus vaccine (IPV). The rapid progress being achieved towards the global eradication of wild polioviruses makes it imperative that WHO be prepared to recommend a strategy for stopping immunization against polio when global eradication is imminent. This will permit the strategy to be implemented as quickly as possible after eradication is certified globally and maximize the benefits of eradication. WHO’s Plan of Action for Polio Eradication anticipates that the last case of polio caused by wild poliovirus will occur in the year 2000 and that global eradication will be certified in the year 2005. The single issue that dominates debate on strategies for stopping immunization is whether vaccine-derived poliovirus strains (VDPV) will continue to circulate after the use of OPV is discontinued. Should this occur, vaccine-derived strains could, theoretically, revert to fully neurovirulent strains. Persistent circulation could occur if VDPV excreted by the last cohorts of vaccinees established chains of transmission in new cohorts of non-OPV vaccinated individuals. Alternatively VDPV from persistently infected, immunocompromised individuals could potentially spread to and circulate in the general population.

Although the issue of persistent circulation of VDPV was actively debated prior to the introduction of the Sabin vaccine, only a limited amount of relevant research has been conducted in recent years. What research has been done is not widely appreciated in the scientific community. Because it will not be possible to absolutely disprove improbable or highly theoretical scenarios for persistent circulation, the controversy on stopping immunization may not be fully resolved prior to stopping immunization. However, reviewing available information and stimulating new research utilizing modern methods and studying areas where wild polioviruses have been eradicated will permit a strategy to be recommended on the best scientific evidence available.
Human populations and laboratory stocks are the only reservoirs of wild polioviruses. For the purposes of eradication, WHO recommends a strategy of laboratory-based surveillance for acute flaccid paralysis (AFP) to detect wild poliovirus transmission in human populations. AFP surveillance requires physicians and other health workers to report all cases of acute onset, flaccid (as opposed to spastic) paralysis among children less than 15 years of age. Cases are then subjected to clinical and epidemiologic examination. Two stool specimens are collected for examination in a WHO accredited virology laboratory to determine if poliovirus is the cause of paralysis. Satisfactory surveillance should detect at least one case of non-polio AFP per year per 100,000 children less than 15 years old with collection of two stool samples within 14 days of the onset of paralysis from 80% of AFP cases.

AFP surveillance may not detect every polio case and will detect less than 1% of poliovirus infections. However, experience with AFP surveillance in Latin America, and subsequently elsewhere, has shown that it is sufficiently sensitive to detect sustained wild poliovirus transmission in a community. Under conditions of good surveillance, a poliovirus genotype that is not detected for one year has disappeared permanently. WHO has established an independent Global Commission for the Certification of the Eradication of Poliomyelitis. At its first meeting in 1995, the Commission defined the parameters for certification. The overriding principle for certification is that countries, regions and eventually the world must demonstrate that no wild poliovirus has been found for at least three years under conditions of good surveillance. The Global Certification Commission will also require that the WHO global action plan for laboratory containment of wild polioviruses is fully implemented before the world is certified free of polio. The process of certification will thus provide the evidence that wild polioviruses are eradicated and adequately contained.

AFP surveillance will also detect Sabin derived polioviruses, both as a cause of vaccine-associated poliomyelitis and, more often, as an incidental finding. However, the sensitivity of AFP surveillance for detecting circulating VDPV, particularly for strains with low neurovirulence, is unknown. Additional surveillance strategies may be required to know when VDPV cease to circulate.
5. Will vaccine strains circulate indefinitely?

Person-to-person transmission of VDPV from vaccinees to household and other close contacts is well documented. The crucial question which then arises is whether VDPV are transmitted beyond several generations or could circulate continuously in populations after OPV vaccination is halted. Relevant data are available from several countries where mass campaigns were the only method used to administer OPV. Starting in 1962, Cuba has immunized its children against polio solely through two annual mass OPV campaigns in February and April. OPV is not used at any other time during the year. Stool surveys from day-care centres in Cuba show that polioviruses are isolated from February through to June. Non-polio enteroviruses are isolated all year round with a peak in late summer. Sewage samples collected between August and December were negative for polioviruses but most yielded non-polio enteroviruses. A weakness of both data sets is that non-polio enteroviruses may have masked polioviruses in some samples. A serological study showed that only 7 out of 727 infants born in July and tested in February before the next mass OPV campaign had neutralising antibodies to poliovirus and in all seven the titres were low, most likely representing residual maternal antibody. Silent poliovirus circulation was also investigated in two surveys using paired sera. Children (24 in one study and 27 in the second) with no poliovirus antibodies in July had not seroconverted when tested again in January of the next year. Finally, all vaccine-associated paralytic polio (VAPP) cases have occurred in the period February to June - the months following the campaigns. Similar findings were reported from Hungary where, until the early 1990s, monovalent OPVs were used in three annual mass campaigns spaced one month apart. No supplemental doses were administered between campaigns. Enterovirus surveillance detected polioviruses only during the three months following the campaigns. Type 1 VDPV persisted longer than type 3, which persisted longer than type 2. All VAPP cases in Hungary clustered in the months immediately following the campaigns.

Genomic sequencing of poliovirus isolates provides a molecular marker which can be used to monitor circulation of VDPV. It has been estimated that poliovirus genomes evolve at a rate of approximately 1-2% nucleotide substitutions per year. Communities with poor sanitation, no wild poliovirus circulation and large susceptible cohorts may be at risk of persistent transmission of VDPV. Genomic sequencing has been done on 29 VDPV isolates from AFP cases from Brazilian communities with low OPV coverage. All isolates showed >99% similarity to the parent Sabin strains, providing no evidence for long-term circulation. These studies are being extended to include additional isolates from Brazil as well as other Latin American countries.
Studying VDPV isolates from countries using mass campaigns as the only method for delivering OPV would also be illuminative. The molecular clock used in these studies was calibrated using wild polioviruses and requires validation for VDPV.

Inactivated polio vaccine is used for routine immunization in the Netherlands. However, OPV was used in 1978 and 1992-3 to control polio outbreaks occurring in a religious group that refuses immunization. Serologic surveys in the years following each epidemic were consistent with the absence of poliovirus circulation in unvaccinated children from the religious group. From 1985 to 1990, Dutch enterovirus surveillance identified only 23 VDPV among 46,095 clinical samples analysed. These isolates invariably came from families with a history of international travel. Sewage waters are currently being sampled from localities where this religious group is concentrated. Any polioviruses isolated in this study will be analysed for evidence of genetic drift from the Sabin strains.

Recent polio outbreaks are due to wild strains rather than reverent, neurovirulent VDPV, suggesting limited transmission of VDPV. For example, polio immunization ceased abruptly in Chechnya with the onset of the secessionist movement in 1992. An outbreak of 143 polio cases occurred in 1995, caused by an imported, type 1 wild virus. Eighty-four percent of cases were less than two years of age. Immunity among unvaccinated children was, therefore, at low levels and implies quite limited, if any, community circulation of VDPV. An outbreak of 138 polio cases occurred in Albania in 1996. The first case was paralyzed 17 April, 10 days after the first of two rounds of a nation-wide campaign which immunized 98% (350,000) of children aged 2-59 months. Attack rates were highest in infants too young to be vaccinated, followed by young adults and teenagers. Since wild poliovirus was apparently introduced concurrently with the OPV campaign and cases were concentrated in populations normally in close contact with children, type 1 VDPV must be substantially less transmissible than the outbreak strain.

Taken together these studies suggest that VDPV will not persist in populations after cessation of vaccination although there are gaps in our knowledge especially with an increasing number of susceptibles.
6. Potential reservoirs of vaccine-derived poliovirus strains

As with wild polioviruses, there is no evidence for an animal reservoir of VDPV and survival of VDPV in the environment is finite. The only reservoirs of VDPV after cessation of OPV immunization will be laboratory stocks of virus. A global action plan has been prepared for containment of wild polioviruses but this plan does not address in detail containment of VDPV. This may be more difficult than containment of wild polioviruses since facilities likely to have materials that potentially contain VDPV will be more widespread. However the experience gained from implementation of wild poliovirus containment will provide a model and impetus for containment of VDPV.

Patients with primary immunodeficiencies (PID) especially of humoral immunity are a potential reservoir of persistent poliovirus excretion. X-linked agammaglobulinaemia (XLA) is usually diagnosed in developed countries in infancy or early childhood and the prevalence in one developed country is estimated at 1:700,000. Patients with XLA are prone to chronic echovirus and coxsackievirus infections of the central nervous system and a new antiviral drug, Pleconaril, is under trial for treatment of such infections. Common variable immunodeficiency (CVID) occurs in about 1:50,000 of the Caucasian population and often remains undiagnosed for more than five years during which time several doses of OPV may be given. The prevalence of XLA or CVID in developing countries is much less clear. In developed countries patients with XLA or CVID, once diagnosed, receive regular intravenous immunoglobulin replacement therapy which contains antibodies to poliovirus.

Persistence of Sabin derived polioviruses in immunocompromised individuals is documented in the literature. One study in a developed country showed that 28/30 antibody deficient individuals on immunoglobulin therapy excreted Sabin-derived polioviruses for < 1 month. However 2/30 individuals in this study developed long term (> 6 months) excretion of Sabin-derived polioviruses. Recently a Sabin type 1 virus from a patient with paralytic poliomyelitis and a Sabin type 2 virus from an asymptomatic individual were each found to differ at about 10% of VP1/2A nucleotides from the vaccine strains. Assuming a constant rate of genomic evolution, infections in these two immunocompromised individuals started about nine years earlier.

Research is in progress in both developed and developing countries in order to determine the prevalence of chronic poliovirus infection among immunodeficient persons. Stool specimens are being cultured from 150 persons with XLA and CVID attending a single clinic in the United Kingdom and 500 persons with specific
immunodeficiency disorders in the United States of America. Stool samples are also being cultured from a cohort of 39 immune deficient VAPP cases in the USA. Polioviruses isolated from these studies plus existing isolates from VAPP cases in the USA will be sequenced to measure genetic drift. However, genetic drift must be correlated with duration of infection in immunodeficient persons. Studies on the transmissibility of VDPV excreted by immunodeficient persons are needed, particularly quantitative sampling of stool specimens and throat swabs taken from such persons.

Patients with secondary immunodeficiencies such as HIV infection do not seem to be at increased risk of chronic poliovirus infection but further data are required.
7. Consequences of persisting circulation

The Sabin vaccine strains differ from their wild-type progenitors by, in the case of type 3, as little as 10 out of the approximately 7500 nucleotides of the virus genome. When fed to children the viruses are under selective pressure for growth in the human gut. Molecular studies of VDPV excreted by vaccinees shows that mutations appear as early as day five. The mutations may be direct back mutations to the wild type nucleotide but also may be more subtle. Thus a variety of second site mutations have been identified that restore various defective functions in the virus replicative pathway. Recombination between VDPV serotypes also occurs. Mutations selected to increase fitness for growth in the gut coincidently also confer reversion to neurovirulence in animal models. Therefore one consequence of persisting circulation could be emergence of VDPV with increased human neurovirulence. However, this does not necessarily follow since there is no direct relationship between animal and human neurovirulence. Furthermore, the likelihood, speed and extent of evolution towards wild type transmission properties such as a lower infectious dose, a longer duration of excretion, a higher titre of excreted virus, or better environmental stability are unknown. This is an area that needs further study, especially understanding the molecular basis of transmissibility.

A theoretical reservoir for the poliovirus genome is a recombinant with non-poliovirus enteroviruses. Although recombinants have been constructed by genetic engineering, most are impaired in replication. Further, only recombinants carrying the wild type poliovirus capsid could express poliovirus virulence. Without the poliovirus receptor, CD155, recombinants could not spread like wild virus in the host. However even recombinants with wild poliovirus capsids would not necessarily have wild type virulence since growth in neuronal cells depends on interactions between cell factors and elements from the non-coding region of the virus genome. Recent experiments have shown that not all enterovirus non-coding elements can function well in cells of neuronal origin. Therefore recombinants are most unlikely to pose a threat to eradication.

Transmission efficiency of polioviruses varies with several factors, especially correlates of hygiene. Estimates from pre-vaccine era seroprevalence data suggest basic reproduction numbers ($R_0$, the average number of transmissions from a single infected individual in a totally susceptible population) of two to five for wild polioviruses under good hygiene conditions and 10 to 15 in areas of poor hygiene. Hygiene conditions have probably improved in developed countries in the interim but may be comparable to the pre-vaccine era in crowded peri-urban slums in the developing
world. Though hard to interpret from the available literature, it appears that transmission risks are lower for VDPV than for wild-type viruses under similar conditions. The $R_0$ for Sabin type 2 is probably higher than for Sabin types 1 or 3.

Given the high levels of immunity in all human populations today, it is likely that the effective reproduction number (the actual average number of transmissions per infected individual) for VDPV will be less than one and therefore the number of individuals infected with VDPV will rapidly decline after cessation of OPV vaccination. However, the prevalence of immunity will also begin to decline in all populations through accumulation of new susceptibles. Intestinal immunity will decline more rapidly than humoral immunity. The effective reproduction number will gradually increase with the increasing susceptibility of the population. A simple mathematical model suggests that it is unlikely that VDPV will persist in good hygiene conditions. However, it is uncertain that transmission will stop in tropical developing countries. At least four studies are in progress on OPV circulation in developing countries, but efforts should target tropical countries where population density is high, hygiene poor and immunization coverage low.
8. Possible strategies for stopping immunization

While it is not possible at the present time to recommend a strategy for stopping immunization, only a limited number of possible strategies can be envisaged. As each of the possible strategies has vaccine supply and quality issues which must be addressed, the options must be assessed now.

If VDPV do not persist, the simplest and least costly strategy would be to simply stop immunization with OPV. Ideally, cessation would be coordinated between countries to reduce the chances of cross border transmission of VDPV. A final series of mass campaigns may be necessary to boost population immunity to the highest possible level. Another approach would be to stop administration of the three Sabin types sequentially. Because type 2 wild virus disappears quickly with effective implementation of immunization programmes, it would probably be the first vaccine strain removed. Either a bivalent type 1 and 3 vaccine or monovalent vaccines could be used. However, safety and efficacy trials would be required to gain regulatory approval for a bivalent vaccine. There was evidence from at least one country that VAPP rates were higher with monovalent type 3 vaccine.

If VDPV do circulate persistently, then IPV could be used for an interim period of, as yet, undefined length. However, the effectiveness and feasibility of this strategy must be validated. The immunogenicity of IPV in developing countries cannot be inferred from studies in industrialized countries. One recent study of IPV administered in developing countries using WHO’s current infant immunization schedule (6, 10 and 14 weeks of age) demonstrated a suboptimal serologic response to polioviruses. Low routine immunization coverage in populations at the highest risk for persistent circulation may also limit the effectiveness of an IPV strategy. If implemented IPV could be efficiently administered in combination product with DTP and, possibly, other antigens. Vaccine manufacturers indicated that 5-7 years would be required to establish a global IPV production capacity. These companies would also need to be assured that they would recover their investment before expanding their facilities. In order to evaluate an IPV strategy, it would be useful to monitor the disappearance of VDPV in polio-free countries changing from OPV to IPV. For data to be reliable and interpretable, future studies of IPV use in developing countries should guard against “contamination” of the study area with VDPV or circulating wild virus.

New vaccine strains for either OPV or IPV vaccine might be useful in the final stages of vaccination. Several candidates were proposed. For example, a more stable genotype of the Sabin type 3 strain that retains the attenuated phenotype has been created through molecular engineering. Such a virus could serve as a new
attenuated vaccine strain. A different approach has developed a virus chimera in which the IRES element (that controls initiation of polyprotein synthesis) of poliovirus type 1 (Mahoney) was exchanged to that of human rhinovirus 2. The chimeric virus had indistinguishable growth kinetics from the parent Mahoney in HeLa cells but did not replicate in human neuroblastoma cells. It was attenuated in both transgenic mice and monkeys. This virus could be a precursor of a new IPV seed that could reduce laboratory containment problems in the post-eradication era. Continued research on candidate new vaccines should continue, but an aggressive approach will be required from researchers, industry and regulatory authorities for any of the candidates to reach clinical trials.

Whatever strategy is used it will be necessary to stockpile supplies of both OPV and IPV, and to develop contingency plans, to respond should an outbreak of poliovirus occur in the future.
1. Substantial progress towards the global eradication of poliomyelitis and wild polioviruses by the year 2000 has been achieved through implementation of the four WHO recommended strategies: (1) high routine immunization coverage with OPV; (2) annual national immunization days delivering two supplemental doses of OPV to all children less than five years; (3) laboratory-based surveillance for acute flaccid paralysis and (4) house-to-house immunization campaigns delivering supplemental OPV in areas with persisting transmission of wild polioviruses. The WHO plan of action for polio eradication projects that the world will be certified free of wild polioviruses in 2005.

2. As a result of the initiative more OPV is being used than ever before. However, with eradication in sight it is appropriate to consider when and how vaccination against poliovirus can be stopped.

3. A major benefit of the eradication initiative is that wild polioviruses are eradicated in perpetuity and, as a result, vaccination against poliovirus will be unnecessary. Vaccination should stop when there is sufficient assurance that wild poliovirus circulation has ceased; when remaining wild poliovirus stocks are under maximum laboratory containment; and when there is sufficient assurance that VDPV will not persist in the community after vaccination ceases.

4. Global certification of eradication requires at least three years of intensive surveillance during which there is no evidence of wild poliovirus circulation anywhere in the world. It also requires that the global action plan for laboratory containment of wild polioviruses is implemented everywhere in the world. This will provide the evidence that wild poliovirus circulation has ceased and that all remaining wild poliovirus stocks are under maximum laboratory containment.

5. Data from various sources indicate that VDPV circulate in communities for limited periods after cessation of immunization. The best evidence comes from virological surveillance after mass immunization campaigns in countries where supplemental OPV doses are not given between campaigns. Molecular evidence of minimal genetic drift in Sabin viruses isolated from vaccine-associated polio cases in areas free of wild poliovirus but with low OPV coverage also supports limited circulation. Furthermore, outbreaks of poliomyelitis in partially OPV immunized populations have always been due to wild type poliovirus and not Sabin-derived strains.

9. Conclusions
6. Whilst all available data suggest that VDPV will circulate for only a limited period when vaccination stops, there are gaps in our knowledge especially of what will happen when population immunity falls.

7. The literature shows that, under similar conditions, transmission rates are lower for VDPV than for wild polioviruses, and that type 2 is the most transmissible of the VDPV. However it is difficult to quantify these differences.

8. A better understanding is required of the transmissibility and persistence of VDPV, particularly in tropical countries with poor hygiene and substantial numbers of susceptibles.

9. Surveillance strategies currently in place are directed towards wild-type polioviruses. Further studies are required on the sensitivity of these and alternative strategies for detection of Sabin-derived polioviruses.

10. Laboratory stocks are a potential source of re-introduction of VDPV into a community after the cessation of vaccination. A global action plan has been prepared for containment for wild polioviruses and will have been implemented before the decision to stop vaccination is taken. This experience and plan should be extended to obtain effective containment of laboratory stocks of VDPV.

11. Persistently-infected, immunodeficient persons are also a potential source of continued seeding of VDPV into susceptible populations. A very few long-term (several years) excretors are well documented. Studies are in progress to better determine the prevalence of long-term excretors both in developed and developing countries. Treatment with antiviral compounds should be explored as a means of terminating long-term excretion of VDPV.

12. Sabin polioviruses rapidly mutate in vivo. A strong selection pressure is for growth in the human gut. A adaptation to the human gut coincidentally also confers increased neurovirulence in animal models. In addition to direct back mutation, a variety of second site mutations has been observed, which emphasises that the virus has a range of possible ways to restore defective function. The molecular basis of the lower transmissibility of the VDPV is not known. Consequently, the molecular changes required for reversion to wild type transmissibility are not known.

13. Recombination with other enteroviruses does not appear to pose a threat of continued circulation of VDPV.

14. There are several possible strategies to stop vaccination. Further studies of persistence of VDPV are required before a strategy can be recommended. If VDPV do not circulate persistently, then the simplest strategy is to stop OPV. The alternate strategy of sequentially removing the three types from OPV appears unlikely to be used because of the need for large safety and efficacy trials. If VDPV circulate persistently, then an interim period of IPV use may be required globally. Vaccine manufacturers believe that with appropriate financial arrangements, capacity could be expanded sufficiently within five to seven years. However, the effectiveness of an inactivated poliovirus-only strategy remains
untested. Whatever strategy is recommended, it will be important to coordinate cessation of OPV in all countries so that VDPV are not continually re-introduced across borders.

15. An alternate strategy would be to develop new, more stable attenuated polioviruses for OPV or genetically engineered viruses with lower virulence for the production of IPV. So far no such vaccines are licensed but several candidate strains are under development. A review of scientific, regulatory, ethical and economic issues for the potential use of new poliomyelitis vaccines is needed for this strategy to move forward.

16. Stockpiles of vaccine, both OPV and IPV, should be prepared for emergency use.
10. Recommendations

Vaccination with OPV should stop and vaccination with IPV can stop when there is (a) sufficient assurance of the global eradication of wild type polioviruses, (b) suitable laboratory containment of remaining stocks of wild polioviruses, and (c) evidence that VDPV will circulate for only a limited period in the post-vaccination era. Global certification will provide assurance of the absence of wild poliovirus circulation. Implementation of the global action plan for laboratory containment of wild polioviruses will provide assurance of suitable laboratory containment of wild poliovirus stocks. Additional studies are required now and should be coordinated by WHO to provide assurance that VDPV will circulate for only a limited period after cessation of OPV immunization.

1. Studies are required on the transmissibility of all three VDPV serotypes and their persistence in the general population.
   a) Population studies should be designed and conducted prior to the cessation of OPV vaccination to determine the behaviour of VDPV in the post-eradication era. In particular:
      - Countries with low OPV coverage but no circulating wild poliovirus should be monitored prospectively and retrospectively by virological surveillance after national immunization days and by molecular virological surveillance for genetic drift in Sabin-derived polioviruses.
      - Countries that make a coordinated switch from OPV to IPV vaccination schedules should be encouraged to compare the rates of disappearance of VDPV in different population groups within the country.
      - OPV challenge studies should be carried out in populations previously vaccinated with either OPV or IPV in countries now using IPV in which there is no live poliovirus (either wild or VDPV) circulation, to determine the duration of intestinal immunity in the absence of boosting through reinfection.
      - Theoretical analyses/modelling studies of virus transmission and persistence should be encouraged, taking into account population heterogeneity (especially age and social structure) and seasonality of transmission.
   b) Virological studies are desirable to determine molecular markers of poliovirus transmissibility and should take into account possible effects of virus recombinations.
c) An inventory of available published and unpublished epidemiological and virological data is required to better quantify the differences in transmissibility between wild-type and Sabin-derived polioviruses.

2. Studies already in progress should be encouraged and expanded on the potential of immunodeficient individuals to re-seed VDPV into communities after cessation of OPV vaccination.
   a) The prevalence of primary immunodeficiencies should be identified in a variety of countries through primary immunodeficiency registers (where they exist); networks of immunologists and/or paediatricians; and hospital based screening for patients with recurrent infections.
   b) Immunodeficient individuals should be screened for long-term excretion of polioviruses, as should:
      • AFP cases one year or more after onset of paralysis:
      • Immunodeficient patients known to have VAPP.
   c) Patients with secondary immunodeficiencies, especially those with HIV infection and chronic lymphatic leukaemia, should also be screened for long-term poliovirus excretion.
   d) Viruses from immunodeficient patients should be characterised for genetic drift to estimate the duration of excretion.
   e) Efficacy studies of antiviral agents to stop long-term excretion in immunodeficient individuals are in progress in the USA and U.K., and if effective, should be extended to developing countries.
   f) The transmissibility of viruses from long-term immunodeficient excretors should be studied by quantitative stool and throat swab culture of individuals and selective sewage sampling of hospitals with immunodeficient patients in countries where OPV immunization is not used.

3. Studies are required on appropriate surveillance strategies for VDPV.
   a) AFP surveillance should be reviewed to determine what further useful data could be obtained on VDPV.
   b) WHO global poliovirus laboratory network procedures should be reviewed to determine what further useful data could be obtained on VDPV, and the value of setting up a database of VDPV.
   c) Environmental surveillance sampling strategies should be developed for application after cessation of OPV vaccination.
   d) Consideration should be given to regular surveys (environmental, serological, and stool) of unimmunized populations in countries that use OPV vaccination.
   e) Further developments of laboratory methods are required, in particular:
      • simplified procedures for detection of genetically drifted VDPV;
      • validation of genetic drift as a correlate of circulation/excretion time;
      • improved sampling and analytical methods for environmental surveillance.
4. Studies are required to evaluate potential strategies for cessation of vaccination. In addition to the studies outlined above, the following studies should be conducted:

a) WHO should investigate how stopping OPV could be coordinated to reduce cross border transmissions of VDPV.

b) To determine the effectiveness of an IPV strategy in interrupting circulation of VDPV, the circulation of VDPV in countries switching from OPV to a pure IPV strategy should be closely monitored. Conducting such a study in a tropical developing country would be particularly important. The cost and logistical problems encountered in implementing a change to IPV should be studied so that other countries may benefit from the experience.

c) Genetically stable OPV strains or new less virulent IPV seeds are in development. For development to continue at a pace which could make these vaccines available should they be needed, a working group of researchers, manufacturers, regulatory authorities and programme staff should be convened to identify:

- the best candidate strains;
- the regulatory issues involved in introducing new live attenuated poliovirus vaccines;
- the studies that would be needed to assess the strains;
- the anticipated costs of this strategy;
- the most rapid way to proceed if suitable candidates are identified;
- the potential use of such strains in serum neutralising antibody assays in the post-eradication, post-vaccination era.

5. To further define policies for stopping vaccination against polioviruses the WHO Technical Consultative Group should regularly review results from these additional studies.
Annex 1: Agenda

Monday, 23 March 1998

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<tr>
<td>09.00</td>
<td>Welcome remarks</td>
<td>R. Henderson</td>
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<tr>
<td>09.10</td>
<td>Objectives of meeting</td>
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<tr>
<td>09.10</td>
<td>Introductory remarks</td>
<td>J. W. Lee</td>
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<td>09.20</td>
<td>Introductions and election of officers</td>
<td>H. Hull</td>
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<td>Administrative announcements</td>
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1. **Global progress and possible strategies for stopping immunization**

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<tr>
<td>09.30</td>
<td>Progress towards Global Polio Eradication</td>
<td>H. Hull</td>
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<td>09.45</td>
<td>Possible strategies for stopping immunization</td>
<td>S. Cochi</td>
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10.00 - 10.30 **Discussion**

10.30 - 11.00 Coffee break

2. **How will we know when polio virus is eradicated?**

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<th>Time</th>
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<th>Speaker</th>
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<tr>
<td>11.00</td>
<td>WHO strategy for poliovirus surveillance</td>
<td>B. Aylward</td>
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<tr>
<td>11.20</td>
<td>Ability to detect poliovirus in clinical samples</td>
<td>B. Schoub</td>
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<tr>
<td>11.40</td>
<td>Sensitivity of different methods to detect poliovirus in a population</td>
<td>M. Pallansch</td>
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12.00 - 12.30 **Discussion**

12.30 - 14.00 Lunch break

3. **Will vaccine derived strains circulate indefinitely after eradication?**

<table>
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<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker</th>
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<tr>
<td>14.00</td>
<td>Circulation of vaccine-derived strains following mass immunization in Cuba</td>
<td>P. Mas Lago</td>
</tr>
<tr>
<td>14.20</td>
<td>Circulation of vaccine-derived strains following mass immunization in Hungary</td>
<td>I. Domok</td>
</tr>
<tr>
<td>14.40</td>
<td>Experience with circulation of vaccine-derived strains in the USSR</td>
<td>S. Drozdov</td>
</tr>
</tbody>
</table>

15.00 - 15.30 **Discussion**
Monday, 23 March (continued)

15.30 - 16.00 Coffee break
16.00 - 16.20 Circulation of polio viruses in the Netherlands A. van Loon
16.20 - 16.40 Circulation of vaccine-derived strains in Brazil after eradication E.M. da Silva

16.40 - 17.30 Discussion

Tuesday 24 March, 1998

4. Potential reservoirs of vaccine-derived strains after eradication

08.30 - 08.50 Environmental reservoirs for polio viruses W. Dowdle
08.50 - 09.10 Immunodeficiency syndromes and risk of persistent infection with polioviruses D. Webster
09.10 - 09.30 Excretion of vaccine-derived strains by immunodeficient persons in Europe D. Wood
09.30 - 09.50 Excretion of vaccine-derived strains by immunodeficient persons in the USA O. Kew

09.50 - 10.00 Discussion
10.00 - 10.30 Coffee break
10.30 - 10.45 Excretion of vaccine-derived strains by immunodeficient persons in developing countries N. Halsey

10.45 - 11.00 Discussion

5. Consequences of persisting circulation

11.00 - 11.20 Reversion of vaccine strains to neurovirulence and increased transmissibility P. Minor
11.20 - 11.40 Do recombinants with other enteroviruses pose a threat to the eradication initiative? E. Wimmer

11.40 - 12.30 Discussion
12.30 - 14.00 Lunch break
14.00 - 14.30 Transmissibility and persistence of OPV viruses: implications for the global eradication initiative P. Fine
14.30 - 14.50 Ongoing research on persistent circulation R. Sutter

14.50 - 15.30 Discussion
15.30 - 16.00 Coffee break
16.00 - 17.30 Working groups

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1 See Annex 3 for composition and topics assigned to working groups.
Wednesday, 25 March 1998

6. If vaccine-derived strains circulate, will IPV interrupt circulation?

08.30 - 08.50 Feasibility of a global IPV strategy and sequential removal of Sabin strains
J. Milstien

08.50 - 09.10 Immunogenicity of IPV in developing countries
P. Wright

7. Other strategies for stopping immunization

09.10 - 09.30 Prospects for better polio vaccines
E. Wimmer

09.30 - 10.00 Discussion

10.00 - 10.30 Coffee break

10.30 - 12.30 Working groups

12.30 - 14.00 Lunch break

14.00 - 15.30 Review of working groups reports and recommendations

15.30 - 16.00 Coffee break

16.00 - 17.30 Conclusions and recommendations
Annex 2:
List of participants

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Dr B. Aylward, EPI
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WHO Regional staff

Dr C. de Quadros, Director SVI, AMRO
Dr George Oblapenko, Medical Officer, Polio, EURO
Dr C. Maher, Technical Officer, EPI, WPRO
Annex 3: Working groups

Working Group 1

Topic: Transmissibility of vaccine-derived strains and the potential for their persistence in the general population

- What epidemiological and virological studies will be required to clarify the difference in transmissibility between wild type and Sabin polioviruses?
- What population studies can be designed and conducted prior to the cessation of OPV to determine the behaviour of OPV vaccine in the post-eradication era (i.e., ‘natural experiments’ to determine the potential for OPV persistence in a population with increasing susceptibility)?
- How can we determine the extent of Sabin polioviruses reverting to wild-type transmissibility and its implications?

Composition of Working Group 1

Dr V. Agol (Chair)
Dr Roland Sutter (Rapporteur)
Dr Paul Fine
Dr Olen Kew
Dr Edson da Silva
Dr Neal Nathanson
Dr J. Almond
Dr R. Crainic
Dr Wang Ke An
Dr Harry Hull
Dr Ciro de Quadros
Working Group 2

**Topic: Excretion of poliovirus by immunodeficient persons**

- What studies are required to determine the potential of immunodeficient individuals in developing countries to serve as long-term reservoirs of Sabin polioviruses?
- What studies should be conducted to determine the capacity of current or soon-to-be available therapies to clear long-term excretors of Sabin polioviruses?
- What studies are required to determine the extent of spread from long-term excretors of SABIN polioviruses to the general population (i.e., potential for ‘reseeding’ of the general population)

**Composition of Working Group 2:**

Dr D. Webster (Chair)  
Dr Barry Schoub (Rapporteur)  
Dr Ilona Carneiro  
Dr David Wood  
Dr Rebecca Prevots  
Dr I. Dömök  
Dr N. A. Halsey  
Dr T. Miyamura  
Dr S. Plotkin  
Dr Rudi Tangermann  
Dr Benjamin Nkowane  
Dr Susan Robertson

Working Group 3

**Topic: Surveillance strategies for vaccine-derived viruses in the post-eradication era**

- What studies should be conducted to determine whether AFP surveillance will be sufficient to detect circulation of vaccine-derived viruses in the post-eradication era?
- What studies are required to determine the most appropriate strategy for detecting vaccine-derived viruses following eradication?
- What studies are needed to determine whether targeted surveillance in high-risk areas, rather than global surveillance, would be sufficient for detecting OPV circulation following eradication?
**Composition of Working Group 3**

Dr E. Mendelson (Chair)  
Dr A. V. Loon (Rapporteur)  
Dr Mark Pallansch  
Dr Walter Dowdle  
Dr Sergei G. Drosdov  
Dr P. Laturnus  
Dr Pedro Mas Lago  
Dr Hinda Triki  
Dr V. Caceres  
Dr George Oblapenko  
Dr B. Aylward  
Dr Ana-Maria Henao-Restrepo

**Working Group 4**

**Topic:** Prospects for alternative vaccination strategies

- What are the potential strategies for stopping immunization following the eradication of wild-type poliovirus?
- What studies are required to evaluate those alternative strategies which are operationally feasible?
- What is the possibility and feasibility of developing a Sabin poliovirus vaccine which is less susceptible to genetic mutation and what studies will be required to evaluate such a vaccine prior to general use?

**Composition of Working Group 4**

Dr E. Wimmer (Chair)  
Dr Steve Cochi (Rapporteur)  
Dr Philip Minor  
Dr Peter Wright  
Dr Hiroshi Yoshikura  
Dr Julie Milstien  
Dr Francis Andre  
Dr M.R. Fibi  
Dr So Hashizume  
Mr C. Maher  
Dr David Featherstone  
Dr Yuri Pervikof
Annex 4:
List of documents

Draft agenda, WHO/EPI/POLIO/SIM.98.01
List of participants, WHO/EPI/POLIO/SIM.98.02
List of working papers, WHO/EPI/POLIO/SIM.98.03

Agenda item 1

Progress towards Global Polio Eradication (including current status of EPI),
WHO/EPI/POLIO/SIM.98.WP1.1 (H. Hull)*
Possible strategies for stopping immunization, WHO/EPI/POLIO/IM.98.WP1.2
(S. Cochi)

Agenda item 2

WHO Strategies for surveillance, WHO/EPI/POLIO/SIM.98.WP2.1
(B. Aylward)
Ability of currently available methods to detect polio virus in clinical samples,
WHO/EPI/POLIO/SIM.98.WP2.2 (B. Schoub)
Sensitivity of different methods for detecting polio virus,
WHO/EPI/POLIO/SIM.98.WP2.3 (M. Pallansch)

Agenda item 3

Evidence from Cuba on the circulation of vaccine-derived strains,
WHO/EPI/POLIO/SIM.98.WP3.1 (P. Mas Lago)
Circulation of vaccine-derived strains following mass immunization in Hungary,
WHO/EPI/POLIO/SIM.98.WP3.2 (I. Domok)
Experience with circulation of vaccine-derived strains in the USSR,
WHO/EPI/POLIO/SIM.98.WP3.3 (S. G. Drozdov)
Circulation of polio viruses in the Netherlands,
WHO/EPI/POLIO/SIM.98.WP3.4 (A. van Loon)
Vaccine-derived strains circulation in Brazil after eradication,
WHO/EPI/POLIO/SIM.98.WP3.5 (E. M. de Silva)

* The name of the person who presented each working paper appears in brackets, after the the paper’s title and reference code.
Agenda item 4

Environmental Reservoirs for polioviruses, WHO/EPI/PO LIO /SIM.98.WP4.1 (W. Dowdle)

Immunodeficiency syndromes likely to result in persistent infection with vaccine viruses, WHO/EPI/PO LIO /SIM.98.WP4.2 (D. Webster)

Excretion of vaccine-derived strains by immunodeficient persons in Europe, WHO/EPI/PO LIO /SIM.98.WP4.3 (D. Wood)

Excretion of vaccine-derived strains by immunodeficient persons in the USA, WHO/EPI/PO LIO /SIM.98.WP4.4 (O. Kew)

Excretion of vaccine-derived strains by immunodeficient persons in developing countries, WHO/EPI/PO LIO /SIM.98.WP4.5 (N. Halsey)

Agenda item 5

Reversion of vaccine strains to neurovirulence and transmissibility, WHO/EPI/PO LIO /SIM.98.WP5.1 (P. Minor)

Do recombinants with other enteroviruses pose a threat? WHO/EPI/PO LIO /SIM.98.WP5.2 (E. Wimmer)

Literature review and model of persisting circulation of vaccine-derived after eradication, WHO/EPI/PO LIO /SIM.98.WP5.3 (P. Fine)

Ongoing research on persisting circulation, WHO/EPI/PO LIO /SIM.98.WP5.4 (R. Sutter)

Agenda item 6

Feasibility of a global IPV strategy and sequential removal of Sabin strains, WHO/EPI/PO LIO /SIM.98.WP6.1 (J. Milstien)

Immunogenicity of IPV in developing countries, WHO/EPI/PO LIO /SIM.98.WP6.2 (P. Wright)

Agenda item 7

Prospects for better polio vaccines, WHO/EPI/PO LIO /SIM.98.WP7.1 (E. Wimmer)