

3.3 Development of products for the global OPV cessation phase

Milestones 2005

⇒ **Milestone 1: Local strategies to reduce VDPV risks will be introduced.**

Status: Ongoing.

Monitoring of subnational immunization coverage is ongoing. All poliovirus isolates are screened for discordant results and a protocol for identifying iVDPVs has been established.

⇒ **Milestone 2: Feasibility of incorporating the detection and immediate notification of circulating polioviruses into IHR/GOARN will be assessed.**

Status: Achieved.

Polio was incorporated into the IHR (2005) which is the version approved by the World Health Assembly in May 2005. It will come into effect in mid-2007.

⇒ **Milestone 3: Monovalent OPV, IPV and trivalent OPV stockpile sizes will be defined for the post-OPV era.**

Status: Achieved.

A global stockpile will consist of 750 million doses of each of the three OPV serotypes.

Funding is pledged from GAVI/IFFIm to initiate a stockpile and a tender will be issued in late 2006.

⇒ **Milestone 4: Third edition of *Global Action Plan for Laboratory Containment of Wild Polioviruses (GAP III)* published.**

Status: Ongoing.

All four components of GAP III were developed by end-2005 and will be consolidated into a version for public consultation by mid-2006.

Risks associated with OPV cessation

The ability of Sabin vaccine viruses to mutate and acquire greater transmissibility and neurovirulence necessitates an eventual end to the use of OPV. While the current risk posed by wild polioviruses remains far greater than the risk of vaccine-derived polioviruses (VDPVs), the number of wild viruses is rapidly decreasing; and as long as OPV use continues, the threat of VDPV will persist. A threat, if not addressed, could negate the eventual achievements of polio eradication. It is for this reason that OPV is considered incompatible with a polio-free world and the eventual global cessation of OPV has been recommended by the ACPE once wild poliovirus eradication has been certified.

Vaccine-derived poliovirus (VDPV)

Concerns over the risks presented by vaccine-derived poliovirus (VDPV) took centre stage in 2005 as the driving force behind the need for OPV cessation following the global eradication of polio. This was further highlighted by three well documented outbreaks during the year in Cambodia, Madagascar, Indonesia. In addition, the detection of vaccine-derived poliovirus in Minnesota, USA, among a religious group objecting to vaccination demonstrated that no country is safe from VDPVs.

A VDPV case is defined as a live, attenuated strain of the virus contained in the oral poliovirus vaccine (OPV) which has mutated and reverted to a neurotropic form and acquired enhanced transmissibility characteristics. The genome of VDPV differs from the parental Sabin strains by 1% or more. VDPV can be further classified as:

- a) iVDPV (*immunodeficient* excretors of vaccine-derived polio) isolated from immunodeficient patients who have prolonged infections after exposure to OPV;
- b) cVDPV (*circulating* vaccine-derived polioviruses) that are associated with sustained person-to-person transmission resulting in at least two patients with paralytic manifestations; and
- c) aVDPV (*ambiguous* vaccine-derived polioviruses) which are either clinical isolates from patients with no recognized immunodeficiency and not associated with an outbreak, or environmental isolates whose ultimate source has not been identified.

The four cases of VDPV detected in Madagascar this year were considered to be cVDPV, as were the 46 cases found on Madura Island in Indonesia in 2005. The latter represents the largest cVDPV outbreak to date.

The programmatic experience of controlling these outbreaks, and comparing these with those caused by wild poliovirus, suggest that fewer rounds of supplementary immunization activities are needed to eliminate the circulation of VDPV.

Risk mitigation: strategy and tools

A comprehensive approach must be taken to optimize the management of the risks of either the re-emergence of polio due to a cVDPV or re-introduction of either a wild or Sabin poliovirus, following the global interruption of wild poliovirus transmission. Progress on these risk management strategies is detailed in this section.

Containment of wild and Sabin polioviruses

Substantial progress has been made in 2005 in laying the foundations for the long-term containment of wild polioviruses and – for the first time – Sabin vaccine strains. The 3rd edition of the Global Action Plan for Laboratory Containment of Wild Polioviruses (GAPIII) will outline the key management strategies to reduce the risk of inadvertent re-introduction of poliovirus after eradication and OPV cessation.

In addition to the experience gained through the preparation and implementation of the 1st and 2nd editions of the GAP, four major areas of work are informing the development of GAP III, with a target date of late-2006 for distribution for public comment.

First, the long-term programmatic needs for poliovirus have been defined in terms of both the types and minimum number of poliovirus-containment facilities that may be required during and after OPV cessation. A minimum number of facilities (target < 20) with the capacity to store and handle poliovirus will be required indefinitely for essential IPV production and quality control, research, and diagnostic functions.

Secondly, a detailed assessment was conducted of the facility-associated risks of potential community exposure to polioviruses after eradication and OPV cessation (Dowdle W. R., et al., Containment of polioviruses after eradication and OPV cessation: characterizing risks to improve management. *Risk Analysis*, 2006 - in press). This assessment provided the basis for designing risk-appropriate biosafety measures (or ‘primary safeguards’) for facility storing or handling polioviruses after eradication.

As a third element of work, an assessment was conducted on the consequences of a poliovirus release during or after OPV cessation (Fine P. E. M. and Ritchie S., Consequences of release/reintroduction of polioviruses in different geographic areas after OPV cessation.

Risk Analysis, 2006 - in press). This article identified and analyzed the factors influencing the range of consequences that might result from the re-introduction of a wild poliovirus or Sabin strain (from a self-limited infection to re-established endemic transmission), as the basis for recommending ‘secondary safeguards’ that should be in place in any country or area choosing to store or handle polioviruses after OPV cessation. Finally, specific standards were developed for the management of poliovirus bio-risks in the limited number of essential facilities that will handle or store such viruses following OPV cessation.

By late 2005, this work was being consolidated into an overall poliovirus biocontainment strategy for the OPV cessation and post-OPV phases of the Global Polio Eradication Initiative.

Vaccine Stockpile

A significant achievement in 2005 was the development in record time of monovalent oral polio vaccines, for both type 1 and type 3 polio. Four manufacturers developed and received regulatory approval for use of mOPV1 in 2005. These vaccines were used extensively in 2005 (>500 million doses) and proved to be an important additional tool to the polio eradication initiative. Most importantly, these vaccines may be responsible for eliminating wild poliovirus transmission in Egypt and Mumbai as well as significantly decreasing the incidence of poliovirus in the polio-endemic reservoirs of South Asia and Africa (outside Nigeria). mOPV3 was licensed by one manufacturer and approximately 10 million doses were used in a large campaign in Western Uttar Pradesh, India in December 2005.



A stockpile of monovalent vaccines for outbreak response in the post-OPV era.

Monovalent OPVs are now the ‘workhorses’ of the final polio eradication effort, and also play a crucial role in the post-eradication era.

An internationally-managed global stockpile of mOPVs (types 1, 2 and 3) is being developed for use in the event of a polio outbreak after the cessation of OPV. Such a stockpile will allow a type-specific response which will not only ensure a greater impact of the outbreak response, but also prevent the reintroduction of other polioviruses. As a major development in 2005, the up-front financing of the stockpile which includes development, licensing, procurement, operational and storage costs was secured through the International Finance Facility (IFF) for Immunization, in the amount of US\$ 226.4 million.

IPV: Supplement to the WHO position paper on IPV following OPV cessation

As part of the preparations for a polio-free world, it will be essential that all countries currently using OPV develop a well-defined immunization policy for the post-OPV cessation era. Each country must determine the most appropriate national immunization policy: whether to discontinue all polio vaccination or switch to IPV routine use. During 2005, the Global Polio Eradication Initiative worked on the preparation of a “Supplement to the WHO position paper on IPV following OPV cessation”, published on 14 April 2006. The supplement provides guidance for countries that elect to retain poliovirus after OPV cessation for vaccine production, polio diagnostics or research in laboratories. Specifically, it articulates the concept of secondary safeguards and lays out the requirements for high population immunity against polio for countries that retain polioviruses. In addition, for countries that do not elect to retain poliovirus, but perceive themselves at risk of intentional use or because a neighbouring country retains poliovirus, it introduces the concept of a 2-dose IPV schedule to provide adequate population immunity.

The supplement also outlines a research agenda which includes the development of new vaccines such as IPV produced from Sabin strains, which may allow additional options for protection against polio.

Antiviral compounds against poliovirus

The Global Polio Eradication Initiative continues to evaluate the potential role of antivirals in the post-OPV era for both outbreak response and the management of rare long-term shedders of poliovirus (iVDPVs). A special meeting was convened by the National Academy of Sciences (NAS) in Washington (at the request of CDC and WHO) in the beginning of November 2005 to deliberate the rationale and programmatic needs for and the development of antiviral compounds against polio. The NAS committee identified promising approaches, including capsid-binding inhibitors, and protease inhibitors. A detailed report by the NAS committee was published in late February 2006.