

STRATEGIC OBJECTIVES

3.3 DEVELOPMENT OF PRODUCTS FOR POTENTIAL GLOBAL OPV CESSATION

The current risk posed by wild polioviruses remains far greater than the risk of vaccine-associated paralytic polio (VAPP) or circulating vaccine-derived polioviruses (cVDPVs). However, after interruption of wild poliovirus transmission, Sabin vaccine viruses could continue to cause individual paralysis or outbreaks. Consequently, as recommended by the ACPE, the Global Polio Eradication Initiative undertakes a programme of work for the identification, reduction and management of the potential risks associated with the cessation of OPV, whether the re-emergence of polio due to a cVDPV or re-introduction of either a wild or Sabin poliovirus. Progress on these strategies and related products are detailed in the section below.

■ MILESTONES 2006

MILESTONE 1: CESSATION OF OPV FOR ROUTINE IMMUNIZATION: CONSOLIDATE OPV CESSATION STRATEGY AND NATIONAL IPV DECISIONS.

STATUS: **PARTIALLY ACHIEVED** — Research is ongoing in a variety of settings to determine the scope and nature of the risks and risk mitigation options associated with OPV cessation and use of inactivated polio vaccine (IPV).

MILESTONE 2: DETECTION AND IMMEDIATE NOTIFICATION OF CIRCULATING POLIOVIRUSES: INCORPORATE POLIO SURVEILLANCE INTO INTERNATIONAL HEALTH REGULATIONS (2005) AND THE GLOBAL OUTBREAK AND ALERT RESPONSE NETWORK.

STATUS: **ACHIEVED.**

MILESTONE 3: POLIO VACCINE STOCKPILES AND EMERGENCY RESPONSE: LICENSURE OF AT LEAST TWO MOPV SUPPLIERS.

STATUS: **ACHIEVED.**

MILESTONE 4: LONG-TERM CONTAINMENT OF POLIOVIRUS STOCKS: FULLY ALIGN WITH SECURITY PROCESSES FOR SIMILAR PATHOGENS.

STATUS: **ACHIEVED** — Bio-risk management standard developed in consultation with those responsible for bio-containment of smallpox and experts in bio-safety and risk management.

IDENTIFICATION OF RISKS ASSOCIATED WITH OPV CESSATION

As the knowledge of VDPVs continues to evolve, a better understanding of the risks they pose to polio eradication has become a priority of the Global Polio Eradication Initiative. In terms of identifying and defining these risks, the focus is currently on: modelling of VDPV risk associated with OPV cessation; further defining VDPV prevalence among immuno-deficient persons (iVDPVs) in middle- and low-income countries; and analysing poliovirus isolates emanating from the global acute flaccid paralysis (AFP) surveillance system and other sources.

■ iVDPV STUDY SERIES

A known potential source of VDPVs are people suffering from primary immune deficiencies (PIDs) who excrete vaccine-derived polioviruses (iVDPV). It has been recognized that the risk of circulating VDPVs (cVDPVs) will eventually be reduced over time once OPV is no longer in use; however the risk of iVDPVs is likely to persist as long as there are persons excreting iVDPVs.

Thirty-two persons shedding iVDPVs have been reported to WHO since 1962. All of the iVDPVs identified to date have been reported from upper- or middle-income countries. Although most of the reported iVDPVs have spontaneously stopped poliovirus excretion or died, at least four have reported excretion for more than five years. Limited data are available on the prevalence and natural history of prolonged or chronic poliovirus excretion among persons with PIDs in middle- and low-income countries, and whether this population may serve as an important reservoir of VDPVs in these countries is unknown. To address the knowledge gaps associated with the incidence and behaviour of iVDPVs, as well as to increase local capacity for the surveillance and monitoring of iVDPVs, the Global Polio Eradication Initiative has begun planning a study series to generate information regarding the prevalence of PIDs with long-term poliovirus excretion in low- and middle-income countries currently using OPV.

■ LABORATORY ANALYSIS OF VDPVs

During 2006, the laboratory network detected VDPVs in a number of locations, including:

- Locations with evidence of person-to-person spread: Nigeria (type 2 VDPVs from 16 AFP cases in 4 different provinces), China (type 1 VDPV from 1 AFP case and 8 community contacts in Gaunxi), Myanmar (type 1 AFP case and 7 contacts); Cambodia (type 3 VDPV from 1 AFP case following isolation of a genetically related VDPV from an AFP case with onset in late 2005).
- VDPVs from AFP cases with follow up investigations pending: Syria (a single type 2 case)
- VDPVs detected in sewage waters without paralyzed persons found during follow up investigations: Czech Republic (10 type 1 VDPVs); Israel (2 type 2 VDPVs).
- VDPVs (type 2) in an immuno-deficient person from Tunisia, the case having been detected in France.

After interruption of wild poliovirus transmission, Sabin vaccine viruses could continue to cause individual paralysis or outbreaks.

REDUCTION OF RISKS ASSOCIATED WITH OPV CESSATION

Reducing the potential risks of OPV cessation involves the preparation for containment of all polioviruses in a post-eradication world and the demonstration of the scientific and logistic feasibility of producing inactivated vaccine based on Sabin rather than wild poliovirus. Additional projects include the development of products such as rapid diagnostics and antiviral compounds against polioviruses.

■ CONTAINMENT OF POLIOVIRUSES

In 2006, the plan for long-term containment of poliovirus was completed with the development of the draft *WHO Global Action Plan to minimize poliovirus facility associated risk in the post-eradication/post-OPV era (GAP III)*. The development of *GAP III* provides the Global Polio Eradication Initiative with a long-term vision and rational plan to ensure that polioviruses are not reintroduced to human populations once circulation has been interrupted.

A key recommendation of *GAP III* is to reduce to fewer than 20 the number of research or production facilities retaining polioviruses worldwide that serve essential functions and meet defined primary and secondary safeguards against transmission. *GAP III* outlines a two-pronged strategy of risk elimination and risk management implemented in four phases, each linked to achievement of milestones in global polio eradication. The first three phases of the plan focus on eliminating and managing the risk of wild polioviruses in facilities after eradication is achieved.

In countries retaining wild poliovirus materials, primary and secondary safeguards are described based on findings from risk assessment and risk consequence models. Primary safeguards were developed in consultation with the WHO department responsible for bio-containment of smallpox along with experts in biosafety and risk management. The resulting *Biorisk management standard (BSL 3/polio) for essential poliovirus facilities in the post-eradication/post-OPV era* establishes a new international benchmark for managing the risk of an eradicated pathogen. This document outlines goals to be achieved by each facility in 16 broad areas, based on the principles of a quality management system. It places the responsibility of risk management squarely on the facility and its management and requires that appropriate controls and systems for managing the risk be not only developed but also demonstrated during periodic national and international accreditation procedures.

Beyond these primary safeguards, secondary safeguards are necessary in order to minimize the consequences in the unlikely event of a poliovirus release. These include the location of essential poliovirus facilities in areas with high routine national population coverage with IPV (more than 90%) and high quality closed sewage systems with secondary or greater effluent treatment.

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■ SABIN IPV

A critical element of risk-reduction in the post-eradication era is the effort to replace wild poliovirus in vaccines with Sabin virus, which is less neuro-virulent and therefore safer. A vaccine manufacturer has been contracted to establish the feasibility of inactivated vaccine production from Sabin strains. Once this “proof-of-principle” is established through the production of what is known as a pharmaceutical batch, the Global Polio Eradication Initiative will sponsor the clinical development of Sabin IPV. In addition, work has begun to establish standards for Sabin IPV through the United Kingdom’s National Institute for Biological Standardization and Control. The goal of both these lines of work is a potent vaccine based on the least neuro-virulent strain of virus, reducing the potential risks of manufacturing, handling and taking vaccine.

MANAGEMENT OF RESIDUAL RISKS ASSOCIATED WITH OPV CESSATION

While research and policy activities are focused on identifying and reducing the risks associated with OPV cessation, the residual risk must be managed. The scientific guidance for national immunization policies, the preparation of a vaccine stockpile and the development of monovalent oral polio vaccine type 3 (mOPV3) are all integral to both reduction and management of these risks. Ensuring long-term surveillance of polioviruses must be planned for as well.

■ IPV INTRODUCTION AND FRACTIONAL DOSE STUDIES

Scientific research helps form national policy decisions on maintaining population immunity in a post-eradication world: this is the goal of fractional IPV dose trials in Cuba and Oman and an IPV project in a tropical country.

A series of natural disasters in Indonesia and the importation and a large outbreak of poliomyelitis led to substantial delays in the introduction of IPV in the province of Yogyakarta. This project continues to be a high priority for the Global Polio Eradication Initiative and will answer key scientific questions, including whether IPV-induced immunity will prevent the emergence of VDPVs in a tropical setting, which will potentially influence a future recommendation for an IPV-only schedule for tropical developing countries. While environmental surveillance in the context of this project is ongoing, a policy switch from OPV to IPV is expected in 2007.

Above and beyond the various scientific, programmatic and operational issues affecting IPV use in the developing world, the cost of IPV vaccination is a major decision factor (especially when weighted against limited resources and the opportunity costs). For the past year, AMRO, EMRO and WHO HQ have collaborated in promoting research to evaluate fractional doses of IPV administered intra-dermally by needle-free devices. Such an approach could lead to substantial cost-saving for an IPV schedule.

The implementation of a study series to compare the immunogenicity of fractional doses of IPV administered by needle-free device versus full doses of IPV administered by intramuscular injection began in September 2006, with an initial study set in Cuba, while another set in Oman is expected to begin enrolment in early 2007. The data generated by this study series are intended to facilitate the regulatory approval of fractional doses of IPV.

■ VACCINE STOCKPILE SOPs AND TENDER PROCESS

The Standard Operating Procedures for an mOPV stockpile were drafted and presented to the ACPE in October 2006. This document sets forth the basis for emergency response in the post-eradication world. Furthermore, it outlines the triggering events for such an emergency response as well as a decision-making mechanism in case mOPV has to be released in an emergency situation. This work represents a major step forward for the Global Polio Eradication Initiative in terms of tools and products to manage a post-eradication response to the re-introduction or re-emergence of poliovirus.

In 2006, mOPV1 was licensed by four different producers: GSK (in Indonesia, Belgium and Nigeria), Panacea and Bio Farma (in Indonesia) and Sanofi Pasteur (in Pakistan). GSK also licensed its mOPV3 in Belgium. Several more applications for licensure of mOPV products are pending with national regulatory authorities.

Another significant achievement in the preparedness for emergency response in a post-eradication world was the UNICEF Request for Commercial Indication (RCI). In December 2006, UNICEF issued its RCI to four manufacturers – all of which are WHO pre-qualified for trivalent OPV products – to provide them with basic information on stockpile requirements for suppliers, such as presentation of the vaccine, the number of doses per serotype, storage and security, etc.

The Standard Operating Procedures for the vaccine stockpile set forth the concepts for emergency response in the post-eradication world.

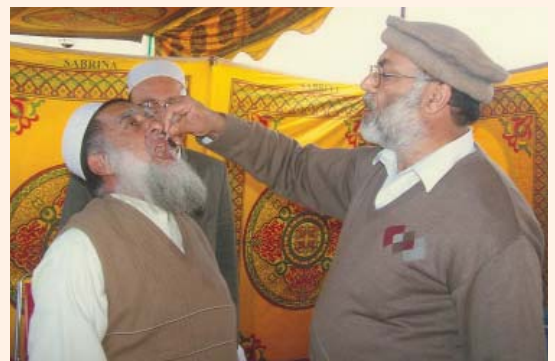
CURBING THE RISK OF INTERNATIONAL SPREAD OF POLIO

The poliovirus has repeatedly shown its ability to travel great distances, causing importations by land, sea or air travel. To minimize the risk and consequences of potential future importations, countries are protecting themselves with immunization measures.

Full vaccination of all travellers from any polio-affected area may be necessary in the near future. The Executive Board of the World Health Organization, convening

in January 2007 in Geneva, Switzerland, called for an appropriate standing recommendation under the International Health Regulations (2005), after their entry into force in June 2007.

Individual countries are already enforcing similar policies at national level. Saudi Arabia, for example, requires all Hajj travellers from Afghanistan, India, Nigeria and Pakistan to be immunized against polio.



Pilgrims from Peshawar, Pakistan, are immunized prior to their departure. Such polio immunization requirements may be instituted by other countries.

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Plans to finance the necessary preparations for a post-eradication world were aided by the launching of the innovative financial issuer, the International Finance Facility for Immunization. The Executive Committee of the GAVI Fund in September 2006 approved the use of US\$ 191 million from this issue to help build the stockpile of OPV for the post-eradication era.

■ POLIO SURVEILLANCE UNDER THE INTERNATIONAL HEALTH REGULATIONS (2005)

With the global reduction and eventual interruption of wild poliovirus, and in a post-eradication world, long-term surveillance for polioviruses takes on a new role. Circulating wild polioviruses will become one of the four diseases specifically mentioned in and “notifiable” under the International Health Regulations 2005 (IHR 2005), which come into effect in June 2007. The evolving relationship between IHR and vaccine-preventable disease control and polio eradication activities, especially at regional and country level, is expected to increase in importance as the Initiative approaches the global interruption of wild poliovirus circulation.

Event-based reporting for polio cases will need to be fully incorporated into existing mechanisms for dealing with events of international public health importance, such as the IHR. Integration of polio into the IHR will further help to prevent, protect, and control the international spread of the disease in the event of an outbreak. As the IHR comes into force, countries will be assessing their capacity to identify, verify, and control potential polio outbreaks.

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