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Management of long-term risks after wild poliovirus eradication

Once wild poliovirus (WPV) transmission has been interrupted globally, WPV stocks have been contained and eradication has been certified, the primary long-term risks of polio will derive from the continued re-introduction into the human population of the attenuated polioviruses contained in OPV, resulting in vaccine-associated

paralytic polio cases (VAPP) and outbreaks due to vaccine-derived polioviruses (VDPVs).

In 2007 – spurred by progress towards polio eradication – the Global Polio Eradication Initiative (GPEI) further intensified its programme of work to manage the long-term risks of polio following interruption of WPV transmission. This work fo-

cused on three areas, described in the following sections: the characterization of long-term polio risks, strategies to manage those risks and the international coordination of such strategies.

5.1 Characterization of long-term polio risks (VAPP and VDPVs)

Activities in 2007 significantly advanced the characterization of the long-term risks following polio eradication, helping to further formulate and refine risk management

strategies. Central to managing the risks of VAPP and VDPVs is to stop use of OPV in routine immunization, as endorsed by the Strategic Advisory Group of Experts (SAGE)

and the Advisory Committee on Poliomyelitis Eradication (ACPE), and presented in January 2008 to the Executive Board to the World Health Assembly (WHA).

Low population immunity remains the main known risk factor for the emergence and spread of cVDPVs. New molecular reagents and methods have enhanced the sensitivity of laboratory screening for all VDPVs.

Vaccine-associated paralytic polio (VAPP)

The risk of VAPP is already well-characterized. VAPP cases occur at a rate of approximately 1 in 2.5 million doses administered, almost exclusively at the first administered dose. At current usage-levels of OPV, an estimated 250-500 VAPP cases occur annually. In 2007, many low- and middle-income countries initiated processes to further investigate the burden of VAPP, particularly in EMR, SEAR and WPR.

Vaccine-derived polioviruses (VDPVs)

Circulating VDPVs (cVDPVs)

On rare occasions, in areas where polio immunization coverage has been low, VDPVs have regained the ability to circulate in a population and cause paralysis. Between 2000 and 2007, over 10 billion doses of

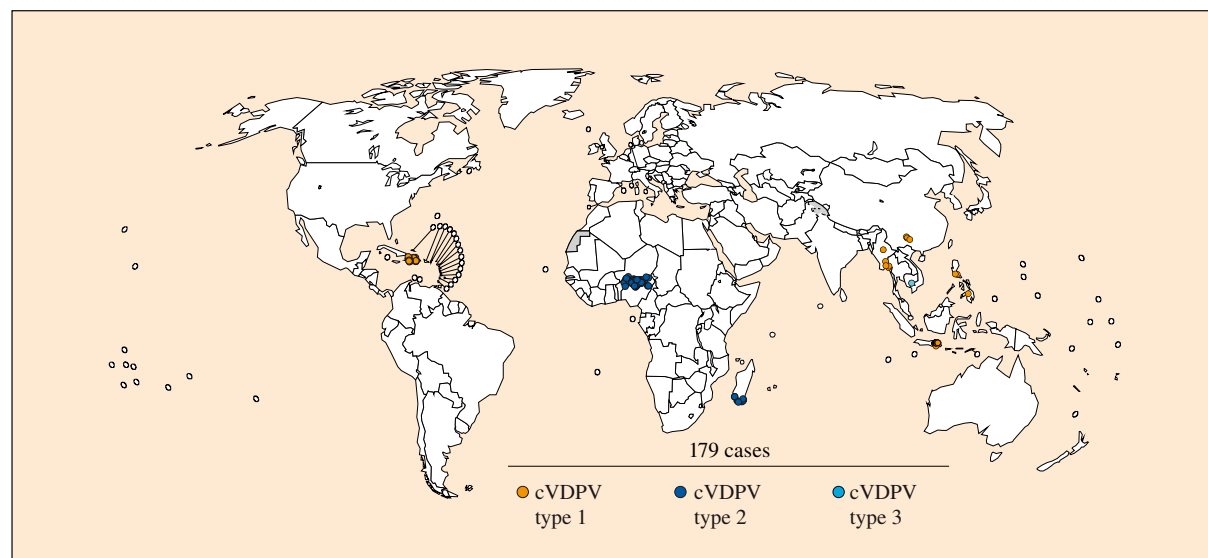
OPV were administered worldwide. In the same period, eleven cVDPV episodes in ten countries were confirmed, resulting in 179 polio cases, with a median of five cases per outbreak.

In 2007, the emergence of cVDPVs in Myanmar and Nigeria and their detection by the Global Polio Laboratory Network (GPLN) further increased the understanding of cVDPVs. In Myanmar, four cases of polio associated with a type 1 cVDPV were identified. In response, three SIA rounds were conducted with mOPV1. In Nigeria, 68 cases associated with a type 2 cVDPV were identified in northern states. In response, SIAs were conducted throughout the year, using different vaccines (mOPV1, mOPV3 and trivalent OPV, to address circulation of WPV1, WPV3 and type 2 VDPV). In particular, the temporal

and geographical clustering of vaccine-related type 2 poliovirus isolates in northern Nigeria prompted the further laboratory investigations which led to the eventual confirmation of the cVDPV. To close the gap in laboratory detection of VDPVs, new molecular reagents and methods have been developed, with the goal of substantially increasing the sensitivity of laboratory screening for all VDPVs, especially those of type 2.

In November 2007, the ACPE was presented with a detailed review of the epidemiology of cVDPV outbreaks, the impact of control measures and the risks of cVDPVs. Low population immunity remains the main known risk factor for the emergence and spread of cVDPVs. Although cVDPVs result on average in fewer polio cases and respond more rapidly to SIAs than WPV

Figure 8: Circulating vaccine-derived polioviruses, 2000-2007



outbreaks, reviewing all available data, the ACPE concluded that cVDPVs should be subject to the same control measures as WPVs. Collaboration continues between the GPEI and Harvard University/Massachusetts Institute of Technology to conduct mathematical modelling of cVDPVs and outbreak response following interruption of WPV transmission.

Immunodeficiency-associated VDPVs (iVDPVs)

Immunodeficiency-associated excretion of VDPVs (iVDPVs) is currently the least characterized risk. Such extended intestinal replication of OPV viruses has been observed in 33 individuals with rare immune deficiency disorders, who are classified into two separate categories: those with 'prolonged' excretion

(individuals excreting virus for a period >6 months); and, chronic excretion (individuals excreting virus for a period of >5 years).

Five of the 33 individuals – from industrialized countries – were categorized as 'chronic' excretors; two continue to excrete. In no instance has this been associated with secondary cases. In 2007, a review was conducted of all known iVDPVs to date. Subsequently, to more accurately estimate the scale of this risk following interruption of WPV transmission, a protocol has been established and studies set up for 2008 in six low- to middle-income countries: Bangladesh, China, Russian Federation, Senegal, Sri Lanka and Tunisia.

Ambiguous VDPVs (aVDPVs)

Ambiguous VDPVs (aVDPVs) are VDPVs with a currently unclassifiable source (either an iVDPV or another source). In 2007, further molecular study and genetic sequencing of numerous aVDPVs isolated (through environmental sampling or from an individual without diagnosed immune deficiency disorders) provided further insight, suggesting biological links of isolated aVDPVs to either iVDPVs or VDPVs from another source. Further review is ongoing to determine if a clear epidemiological connection exists, to allow a precise classification. As understanding of VDPVs grows, a clearer characterization of aVDPVs should become possible.

5.2 Management of VAPP and VDPV risks: role of eventual OPV cessation

Eliminating the long-term risks of VAPP and VDPVs following interruption of WPV transmission would require the eventual cessation of the use of OPV in routine immunization, as endorsed by the SAGE and the ACPE and presented in January 2008 to the Executive Board to the WHA.

Over the past ten years and following numerous expert consultations, the ACPE has elucidated the follow-

ing six prerequisites to prepare for the cessation of OPV use in routine immunization programme, and to ensure that the risks associated with OPV cessation are minimized:

Prerequisite 1: Wild poliovirus certification and containment

Before the cessation of OPV, the interruption of WPV transmission must be confirmed and certified globally, and all WPVs must be under appropriate, final bio-contain-

ment, to minimize the risk of WPV re-introduction. Meeting this prerequisite begins with identification of facilities with wild poliovirus-infectious and potentially infectious materials, through the implementation of national laboratory surveys in all countries. By the end of 2007, over 80% of WHO Member States had completed the survey and inventory activity¹².

¹² See also section 4.3

Prerequisite 2: Global surveillance and notification

Highly sensitive disease surveillance is required before and after OPV cessation, to rapidly detect the potential reintroduction of any poliovirus and/or emergence of a cVDPV.

To maintain disease surveillance worldwide, active surveillance for acute flaccid paralysis (AFP) is increasingly aligned with long-term roadmaps for surveillance, notably with the Global Framework for Immunization Monitoring and Surveillance (GFIMS) and the International Health Regulations (IHR 2005). Since mid-2007, cases due to wild poliovirus in polio-free areas have already been notified successfully through the IHR (2005) framework, which came into force only in June 2007, re-affirming the important role this mechanism may have for rapid detection of circulating polioviruses, should they occur after OPV cessation.

Prerequisite 3: Monovalent OPV stockpile and response

To optimize the response to cVDPV events immediately following synchronized OPV cessation, an international stockpile of monovalent OPVs (mOPVs) must be maintained and managed. By end-2007, five mOPV1s and three mOPV3s were licensed and used in more than 20 countries and four countries respectively. In close collaboration with the Imperial College of London, studies were undertaken to better estimate the efficacy of mOPV 1 & 3 in different field settings (India, Nigeria and Pakistan). In addition, two manufac-

turers took steps towards the licensing of mOPV type 2 (mOPV2), with licensing applications submitted in India and Belgium. UNICEF issued a request for commercial indication in 2007 for mOPV stockpiles of type 1, 2 and 3 for the post-eradication era, with four manufacturers expressing interest in producing the stockpile of mOPV following interruption of WPV transmission. To examine the assumptions underpinning current planning for the mOPV stockpile, a Harvard University/Massachusetts Institute of Technology collaboration continues to conduct mathematical modelling of outbreak response activities for polioviruses following OPV cessation.

Prerequisite 4: Appropriate IPV coverage in all countries retaining polioviruses and affordable IPV options for any country desiring to continue polio immunization

While the full role of inactivated polio vaccine (IPV) following OPV cessation is still being evaluated, at a minimum IPV will be needed in all countries that store poliovirus stocks¹³. For countries which are not storing poliovirus, but perceive that the long-term poliovirus risks warrant continued routine immunization, IPV will be the only option with which to do this. Recognizing that current costs of IPV are substantially higher than OPV, the Global Polio Eradication Initiative is studying a range of approaches to establish 'affordable' strategies for IPV-use (i.e., to achieve immunity at a cost similar to that achieved through OPV) in low-income settings, following OPV cessation.

In 2007, research focused on:

- fractional dosing, to evaluate the serologic response to 1/5th of a standard dose of IPV (two ongoing studies in Cuba and Oman);
- reduced dosing, to determine if fewer doses administered at different ages could result in the same serological response as with the current routine EPI schedule (a literature review has been completed and a study will be initiated in 2009);
- safer IPV production processes, using less neuro-virulent seed strains (such as a Sabin poliovirus seed strain), to facilitate manufacturing at low-cost production sites (three ongoing studies);
- IPV adjuvants, to evaluate the feasibility of reducing the viral content in IPV through the use of adjuvants;
- process optimization in IPV manufacturing to improve viral yields.

Initial results of this ongoing research suggest that low- and middle-income countries that want to maintain population immunity with IPV after OPV cessation may be able to do so at a cost similar to that of OPV.

Prerequisite 5: Synchronization of OPV cessation

To minimize the risk of a country being inadvertently put at risk of importing a cVDPV from a country that continues to use OPV, all countries should simultaneously stop the use of OPV in routine immunization. This prerequisite requires international coordination. An IPV

13 IPV following OPV cessation, Weekly Epidemiological Record, 14 April 2006, Vol. 81, 15 (pp 137-144).

introduction project was launched in 2007 in Yogyakarta province, Indonesia, to ascertain the technical and operational challenges of stopping OPV and introducing IPV and to determine the effect of IPV-induced immunity in preventing emergence of cVDPVs in tropical settings. The ongoing evaluation of this project is expected to help develop appropriate strategy for eventual global, synchronized OPV cessation.

Prerequisite 6: Containment of Sabin polioviruses

Following OPV cessation, all countries will need to implement appropriate 'interim' conditions for the storage and handling of Sabin polioviruses (as the absence of VAPP and VDPVs is verified), followed eventually by the 'final and full' containment of Sabin polioviruses. In 2008, the 3rd edition of the *Global Action Plan to*

minimize post eradication poliovirus facility-associated risk (GAPIII) will be finalized, to integrate projections of programmatic needs for polioviruses, risk assessment findings, risk consequence models and new risk management strategies. *GAP III* will reflect Sabin poliovirus strains in phases that correspond to the changing risk profile.

5.3 International coordination of strategies for the management of long-term polio risks

Minimizing long-term polio risks requires international cooperation and coordination of three particular aspects of the overall strategy: the synchronized cessation of OPV; the containment of wild and Sabin polioviruses; and internationally-

agreed processes for the use of OPV in response to new outbreaks of polio.

In January 2008, the Executive Board to the WHA was presented with potential mechanisms for establishing international consensus

on strategies to manage the long-term polio risks.

Discussions will continue at the WHA in May 2008 on the most appropriate mechanisms for the international coordination of these three areas of risk management.