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NEW POLIO 'ENDGAME' PLAN – SECURING A LASTING POLIO-FREE WORLD

The year 2012 marked the end-point of the Global Polio Eradication Initiative (GPEI) Strategic Plan 2010-2012. Over the past three years, new approaches, tailored tactics and new vaccines have revolutionised the global effort to eradicate polio. And although the end-2012 milestone of stopping all wild poliovirus (WPV) transmission was missed, the world now stands on the brink of eradication. This is the conclusion of the Independent Monitoring Board (IMB), set up to independently verify progress towards the achievement of a polio-free world.

With the prospect of eradicating WPV transmission realistically achievable in the near-term, in May 2012, the World Health Assembly (WHA) called for the development and finalization of a comprehensive polio eradication and endgame strategy. Since then, in broad consultation with polio-infected countries, stakeholders, donors, vaccine manufacturers, regulatory agencies and guided by national and international advisory bodies, the GPEI has been developing the Polio Eradication and Endgame Strategic Plan 2013-2018.

This new Plan aims to strike at the heart of the remaining endemic WPV transmission, by building on the lessons learnt since 2010 and introducing innovative approaches to overcome long-standing systemic challenges to success. At the same time, the Plan lays the groundwork for a lasting polio-free world, by addressing the long-term poliovirus risks, notably circulating vaccine-derived polioviruses (cVDPVs), even as the remaining strains of WPV transmission are being interrupted. In particular, the Plan outlines preparations needed for an eventual switch from trivalent oral polio vaccine (OPV) to bivalent OPV in routine immunization programmes (and the eventual cessation of all OPVs), including the universal introduction of at least one dose of inactivated polio vaccine (IPV).

The main elements of the Plan have been endorsed by the Strategic Advisory Group of Experts on immunization (SAGE) in November 2012, and the Executive Board of the World Health Organization (WHO) in January 2013. With the Plan expected to be finalized by the time of the WHA in May, this issue of Polio Pipeline examines the role research will play in ensuring the new Plan is fully implemented, and a lasting polio-free world can be secured.

Preparing the trivalent to bivalent OPV switch

Achieving significant public health benefits in a safe way

Since 1999 (when wild poliovirus type 2 - WPV2 - was eradicated globally), increasing scientific data have demonstrated that polio eradication will also require the eventual cessation of OPV in routine immunization programmes. Otherwise, the continued reintroduction of the attenuated polioviruses of OPV into a polio-free world will result in polio cases due to vaccine-associated paralytic polio (VAPP), and polio outbreaks due to circulating vaccine-derived polioviruses (cVDPVs), and could lead to re-establishment of endemic and epidemic transmission of poliovirus.

OPV cessation, it had been foreseen, would occur as soon as possible after the last case of WPV has been detected globally; at a time when immunity levels remain relatively high and disease surveillance sensitive. But with the majority of cVDPV cases caused by the type 2 serotype contained in trivalent

In this issue:

Upcoming meetings and events

- Regional Certification Commission of the Eastern Mediterranean. Cairo, Egypt. 26-27 March 2013.
- Strategic Advisory Group of Experts on immunization (SAGE). Geneva, Switzerland. 9-11 April 2013.
- Global Vaccine Summit. Abu Dhabi, United Arab Emirates. 24-25 April 2013.
- Independent Monitoring Board (IMB). London, United Kingdom (UK). 7-9 May 2013.
- 66th World Health Assembly (WHA). Geneva, Switzerland. 20-28 May 2013.
- 19th Informal Consultation of the Global Polio Laboratory Network (GPLN). Geneva, Switzerland. 27-28 June 2013.

OPV, and WPV2 transmission having already been successfully interrupted (since 1999), work is underway to prepare to remove all type 2-containing OPV at this time already - by switching from trivalent OPV to bivalent OPV in routine immunization programmes - even before the remaining strains of WPV1 and WPV3 transmission have been globally interrupted.

A switch from trivalent OPV to bivalent OPV will be associated with significant public health benefits. Since 2000, more than 85% of all cVDPV cases were due to the type 2 component of trivalent OPV (552 of 642 cases, as at 16 January 2013). Of the estimated 250-500 annual VAPP cases, up to 38% are due to type 2. These case numbers would no longer occur. In addition to these significant humanitarian benefits, OPV type 2 cessation would boost immunity against the remaining two wild serotypes (WPV1 and WPV3), and provide the GPEI with a 'push' for global OPV cessation of all OPVs. Feasibility of OPV cessation would be underscored in practice, and would ensure a 'trial run' for all OPV cessation. Key lessons would be learnt to ensure that this process can be implemented in the safest and most efficient manner.

Managing the risks: implementing the prerequisites

In November 2012, the Strategic Advisory Group of Experts on immunization (SAGE) – with guidance from the SAGE Polio Working Group – endorsed the strategic approach of such a switch, and elucidated necessary prerequisites to manage any associated risks, including the introduction of at least one dose of IPV into routine immunization programmes prior to – or at the time of – an eventual switch.

The primary risk associated with such a switch will be the increase in susceptible populations to poliovirus type 2, which in turn would increase the risk of new cVDPV type 2 emergence in the immediate period following OPV type 2 cessation.

To maintain immunity levels to type 2 polio, all countries should introduce at least one dose of IPV into routine immunization programmes prior to – or at the time of – an eventual switch. IPV will at that point be the only vaccine with which to maintain immunity to type 2 polio. The GPEI is continuing to work with manufacturers, regulatory authorities, the GAVI Alliance and other stakeholders and partners to ensure the availability of affordable IPV options for all countries. This work includes a combination of volume purchasing of existing IPV products and the realization of low-cost IPV options (i.e. new intradermal, fractional dose, adjuvanted IPV formulations and Sabin IPV).

The other prerequisites include the formal validation of the global interruption of WPV2 transmission and that all persistent cVDPV type 2s have been stopped; the availability of a monovalent OPV type 2 stockpile to ensure outbreak response capacity; the implementation of containment activities; surveillance to rapidly detect any potential re-introduction or re-emergence of any type 2 poliovirus; and the availability of bivalent OPV for routine immunization programmes.

Eye on affordable IPV

At its November 2012 meeting, the Strategic Advisory Group of Experts on immunization (SAGE) recommended the universal introduction of at least one dose of inactivated polio vaccine (IPV) ahead of – or around the time of – a switch from trivalent oral polio vaccine (OPV) to bivalent OPV.

Recognizing that current costs of IPV are substantially higher than OPV (current cost: US$2.50 per dose), the Global Polio Eradication Initiative (GPEI) is studying a range of affordable IPV strategies. The aim is to attain an immunizing dose price of US$0.50.

The approaches to achieve an affordable IPV are focusing on the following approaches:

1. **schedule reduction** (fewer doses) for routine immunization;
2. **dose reduction** with fractional doses through intradermal delivery;
3. **antigen reduction** with addition of adjuvant; and,
4. **production cost reduction** (e.g. production in developing countries, process optimisation).

All approaches are currently yielding promising results, though the actual availability of products will require more time.

Schedule reduction approach:
Currently, standard routine immunization programmes call for either a three- or four-dose schedule (depending on start date of the primary series). However, two studies have now demonstrated that fewer doses can be effective. A study in Senegal[1] demonstrated that two doses of IPV, given approximately six months apart, resulted in a clinical efficacy against type 1 poliovirus of 89%. In Cuba[2], a study suggested that a single dose of IPV administered at four months (both intramuscular or intradermal) can seroconvert and prime more than 90% of infants, and an additional dose results in more than 90% of

[1]Robertson SE et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet 1988.
[2]Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. NEJM 2013.

infants seroconverting with high antibody titers against all three poliovirus serotypes. It is based on the results of these two studies that SAGE made its recommendation of universal introduction of at least one IPV dose around the time of a trivalent OPV to bivalent OPV switch.

Dose reduction approach:

Antigen-sparing through intradermal administration of IPV has been evaluated extensively over the years. There is much evidence demonstrating that fractional dose IPV (1/5th of the full dose) can yield similar immunogenicity as a full dose. The above-reference study in Cuba further demonstrated that a fractional dose of IPV can induce an immune response in over 90% of subjects, yielding similar results to the full dose arm.

IPV can be administered intradermally by BCG needle and syringe, or by needle-free devices which would facilitate its delivery, primarily in mass vaccination campaign use. Several devices are currently tested in clinical trials. A licensing trial is currently planned to facilitate a label change for regulatory approval of IPV intradermal administration (current indication is for intramuscular administration only).

The GPEI is also supporting the development of micro-needle patches with IPV, containing one hundred microscopic needles that dissolve into the skin.

Antigen reduction approach:

Several research evaluations in animals have demonstrated that a three- to five-fold reduction in antigen content in IPV could be achieved, including through an oil-in-water adjuvant or aluminium hydroxide. Adjuvants could be used for both IPV standalone and/or combination vaccines. For example, the current IPV combination already contain adjuvants in its DTP component, so antigen reduction of IPV components in combination vaccines is theoretically feasible. The GPEI is working with several manufacturers to develop an aluminium-adjuvanted IPV over the next three to five years. And viral replicon particles (VRPs) were shown to boost not only systemic responses, but also to induce mucosal responses after a non-mucosal delivery with different antigens.

Production cost reduction approach:

Production costs of IPV could be further reduced if the vaccine were produced in low-cost settings. Given that current IPVs, produced from a wild-type seed strain, is not suitable for manufacture in developing countries where population immunity and sanitation infrastructure may not be sufficiently high to prevent the spread of these strains in the event of an inadvertent containment failure, development of IPV from less virulent strains is a key priority.

Manufacturers in China, India, Indonesia, Japan and the Republic of Korea are already developing IPV using Sabin poliovirus seed strains (S-IPV), and in 2012, the first two manufacturers obtained a license to market S-IPV in Japan, confirming the feasibility of this approach. See text box for more.

In addition, the GPEI is working with different institutions to develop IPV from alternate further-attenuated strains, which may also require lower bio-containment requirements. These approaches include increased replication fidelity to reduce neurovirulence; alteration of nucleotide sequence to use a different codon set to reduce virus fitness; modification of internal ribosome entry site of the viral genome to reduce neurovirulence; and, developing IPV through non-infectious production methods which could eliminate the need for containment altogether.

With all approaches showing encouraging signs of feasibility, efforts are continuing to ensure the availability of affordable IPV for all countries around the time of a trivalent OPV to bivalent OPV switch.

WHO facilitates new polio vaccine technology transfer

As part of efforts to prepare for the polio post-eradication era, the World Health Organization (WHO) and its partners are facilitating the development of a new polio vaccine technology to transfer this technology to vaccine production facilities in China, India, Mexico and the Republic of Korea.

In collaboration with Intravacc (formerly part of the National Institute for Public Health and the Environment - RIVM) in the Netherlands, clinical lots of inactivated polio vaccine (IPV) produced from Sabin poliovirus seed strains (S-IPV) have been prepared. Traditional IPV is manufactured using wild poliovirus seed strains, and in such a case a bio-containment failure could lead to serious consequences in some areas of the world in the post-eradication era (i.e. areas with high population density, inadequate sanitation infrastructure and low population immunity levels). Therefore, the use of S-IPV has the advantage over wild polioviruses that they are attenuated, and hence are safer for handling and IPV production in developing country settings.

The development, manufacture and distribution of a safe, effective and affordable S-IPV that can be produced securely in developing country settings is a key landmark in this programme of work. This technology transfer will also help to boost more broadly the domestic production capacity for vaccines and strengthening public health systems to ensure more equitable access to vaccines. A fractional dose formulation could be available within two years, and an adjuvanted formulation within three to five years.

The development of S-IPV and the related technology transfer preparations is being generously supported by the Bill & Melinda Gates Foundation.

Strengthening operations in the 'Polio Endgame'

An intensified research agenda has underpinned many of the approaches outlined in the Polio Eradication and Endgame Strategic Plan 2013-2018, and will be critical in its implementation. Strategically guided by the Polio Research Committee (PRC) and the Strategic Advisory Group of Experts on immunization (SAGE), the core elements of the partner-coordinated research work are designed not only to ensure the necessary strategies and products are in place to manage the long-term poliovirus risks associated with the Polio Endgame, but also to accelerate eradication of remaining wild poliovirus transmission.

Therefore, ongoing and new research projects are evaluating innovative ways to improve operations, particularly to help address persistent supplementary immunization activity (SIA) coverage gaps and surveillance gaps. A specifically-established cross-partner Inter-Agency Innovation Working Group is coordinating this work to ensure innovative solutions help address identified systemic challenges to improve operations.

A broad operational research agenda aims to address three **key questions**:

1. **What is the problem?**
2. **Why is the problem occurring?**
3. **How can the problem be solved?**

The problem of missing certain locations in SIAs is being addressed through an increased use of technology: in Nigeria, new micro-planning templates, supplemented by new global information systems (GIS) maps are helping to identify these areas. Special population strategies, as for nomadic populations, prove these important groups can now be reached and it will be crucial to employ these templates effectively in the worst-performing LGAs and districts. Global positioning systems (GPS) technology, meanwhile, is being used in Nigeria to monitor SIAs, identify gaps and missed areas and assist vaccination teams navigate hard-to-reach areas.

Once the immunization teams have reached the local populations, new communications strategies are being employed to reduce the rejection rate. A Nomadic Children's Festival in Pakistan and a Volunteer Community Mobilizer Network in Nigeria are increasing community participation and building trust among parents to vaccinate their children against polio. In Afghanistan, a greater effort is being made to train women vaccinators. This is because male vaccinators cannot enter homes, which can lead to misinformation such as the belief that newborn, sick or sleeping children can be exempted from an immunization campaign. Women work in only a small percentage of vaccination teams in the country, but efforts to change the composition of vaccination teams have yielded some progress in urban areas at least.

The outbreak response approach is also being altered based on research during previous responses in China and the Republic of Congo, for example. The target age group for the first two OPV response rounds is now being extended to 15 years of age after previous experiments appeared to have value in rapidly increasing overall population immunity where there were significant immunity gaps in older children and adults. Targeting an expanded age group is now the gold-standard approach for any new outbreak response. Research into vaccines has also found that new vaccine solutions, including combinations of bivalent OPV and fractional dose IPV can enhance the vaccines' impact.

Surveillance is also being enhanced by technology. Mobile phone SMS prompting to help encourage reporting for acute flaccid paralysis (AFP) cases will be piloted in hard-to-reach areas of high-risk countries, with a view to wider scale-up. This is part of a wider strengthening of surveillance, which incorporates research into expanding environmental surveillance.

In Pakistan, mobile phones are also used to collect pre-SIA performance indicators from Union-Councils nationwide, to help assess the level of preparedness ahead of the next respective SIA.

Finally, statistical research is being deployed to help evaluate operations more effectively. Lot Quality Assurance Sampling (LQAS) has become the gold-standard for evaluating SIA quality in a timely manner. To further enhance its reliability, use of mobile phone technology to collect and analyse data is being explored. Initially evaluated in Pakistan, mobile phone technology use has now been fully adopted in Nigeria to support LQAS activities.

In addition, most users found the technology easy to use and reliable. In Pakistan, the error rate of data entry on children's finger-marking status was less than 1%. With improvements of mobile network connection in most polio-affected areas and availability of an inexpensive smart phone, the GPEI is expanding the application of this technology in other operational areas (e.g. field checklist) and countries.

Technology is also facilitating a more comprehensive approach to data analysis. A large project to develop a standard global polio data platform has been underway at WHO headquarters since mid-2012. The main objectives of this 'POLIS' project are to facilitate the access to - and use of - polio eradication data, including data on surveillance quality and SIAs. POLIS converts previous polio databases, which consist of databases with different formats and analysis requirements, into

Data collection with mobile phones has several **key advantages**, including:

- real-time data transmission and analysis;
- no risk of mistake/falsification during manual transmission; and,
- GPS functions allow validation of surveyor's location.

one unified web-based system. The new system will then bring all polio data together into a central data store ('data mart'), with common dimensions (geography, time, virus, vaccine type, etc.), utilizing state-of-the-art, standardized data storage based on SEQUEL server technology. Multiple web-based outputs and options will enable the visual analysis of results and generate pre-defined online reports, as well as interactive online reports linked directly to the central database (reflecting the most up-to-date data). This new platform will greatly facilitate data analysis requirements for both routine reporting and special reports, such as research studies. As a web-based system, the platform will be accessible by users outside of WHO headquarters (i.e. WHO polio teams at regional and country levels).

In these and other ways, research is playing an integral part in maximising operations, to help ensure that no child is missed and the remaining chains of wild poliovirus transmission are rapidly and successfully interrupted.

Looking to the future: securing the GPEI 'legacy'

Full financing and implementation of the Polio Eradication and Endgame Strategic Plan 2013-2018 will secure a lasting polio-free world. It will ensure that no child will ever again be affected by lifelong polio-paralysis, be it due to a wild- or vaccine-derived poliovirus.

At the same time, the GPEI's 'legacy' will need to be secured to ensure that the vast infrastructure, knowledge, capacities and assets created over the past 25 years will continue to be of broader benefit to other public health programmes, even after a lasting polio-free world has been secured.

During 25 years of operations, the GPEI has mobilized and trained millions of volunteers, social mobilizers and health workers; reached into households untouched by other initiatives; mapped and brought health interventions to communities previously unreached; and, established a standardized, real-time global surveillance and response capacity. All these activities have brought the world to the brink of polio eradication, however they have also been able to benefit other public health work, principally through its surveillance and response capability for other vaccine-preventable diseases and the delivery of basic health services by vaccination teams. The GPEI has reached and learned lessons in accessing the chronically unreached, marginalized and most vulnerable populations in the world. This has enabled the delivery of other health services, and a global surveillance and response capacity for both health and humanitarian emergencies.

In 2013, an extensive consultation process on legacy planning will begin with governments, stakeholders, donors and implementing partners, and outcomes of these consultations will be brought to the World Health Assembly through the Regional Committees. Focus will be on mainstreaming the long-term polio functions into existing national and international public health mechanisms.

Available and upcoming publications

- Progress report of the GPEI to the 132nd Session of the Executive Board.
- Polio Eradication and Endgame Strategic Plan 2013-2018 (working draft).
- Independent Monitoring Board (IMB) January 2013 statement.
- Resik S et al. Priming after a fractional dose of inactivated polio vaccine. NEJM 2013; 368(5):416-424. 31 January 2013

Published in Weekly Epidemiological Record (WER)

- Meeting of the Strategic Advisory Group of Experts on immunization (SAGE), November 2012 – conclusions and recommendations. WER 4 January 2013, vol 88 (pp 1-16)
- Performance of acute flaccid paralysis (AFP) surveillance and incidence of poliomyelitis, 2012. WER 7 December 2012, vol 87, 49/50 (pp 493-508)
- Progress towards poliomyelitis eradication, Nigeria, January 2011–September 2012. WER 9 November 2012, vol 87, 45 (pp 437-448)
- Progress towards poliomyelitis eradication in Chad, January 2011–August 2012. WER 26 October 2012, vol 87, 43 (pp 413-420)
- Progress towards eradicating poliomyelitis: Afghanistan and Pakistan, January 2011–August 2012. WER 5 October 2012, vol 87, 40 (pp 381-388)
- Update on vaccine-derived polioviruses detected worldwide, April 2011– June 2012. WER 21 September 2012, vol 87, 38 (pp 357-368)