

## SAGE CONFIRMS GLOBAL VACCINE SWITCH DATE AS APRIL 2016

Convening in Geneva, Switzerland, on 20-22 October 2015, the Strategic Advisory Group of Experts on immunization (SAGE) re-affirmed that the globally coordinated switch from trivalent oral poliovirus vaccine (tOPV) to bivalent (bOPV) should occur in April 2016. Countries should further intensify their preparatory efforts, including by fully implementing containment activities of wild poliovirus type 2 (WPV2) ahead of the switch.

SAGE's landmark decision had previously been endorsed by the World Health Assembly (WHA) in May 2015, when Ministers of Health from 194 member states adopted a historic resolution on the global effort to eradicate polio, paving the way once and for all for a lasting world free of both wild and vaccine-derived polioviruses.

Both SAGE and delegates at the WHA had noted the strong progress being achieved in eradicating polio and the impact of national emergency action plans, as more and more children in the remaining two endemic countries – Pakistan and Afghanistan - are now fully protected from lifelong polio-paralysis.

Withdrawing type 2 OPV is a crucial part of the polio endgame strategy, in order to combat the very rare cases of vaccine associated paralytic polio (VAPP) or circulating vaccine derived polioviruses (cVDPVs). The type 2 component of OPV accounts for 40% of VAPP cases, and more than 90% of cVDPV cases. By contrast, wild poliovirus type 2 has not been detected anywhere since 1999 and the Global

Commission for the Certification of Poliomyelitis Eradication (GCC) declared this strain globally eradicated at its meeting in September 2015.

SAGE cautioned, however, that more work needs to be done ahead of the April 2016 switch date. It is critical that countries meet established deadlines to destroy or appropriately contain WPV2 materials in facilities that have a reason to retain it, so the virus is not released to again cause paralysis and death in the population. Ongoing cVDPV2 outbreaks in Nigeria and the Guinea/Mali border area needed to be fully stopped. And a global supply constraint of inactivated poliovirus vaccine (IPV) needed to be carefully managed in the lead-up to the switch. The level of commitment from countries to meet the deadline to introduce IPV ahead of the switch has been exceptional, however due to technical challenges in scaling up manufacturing, short term supply constraints mean that some low risk countries may experience slight delays in deliveries. The available supply must be prioritized to highest risk areas in the most equitable manner possible.

The withdrawal of type 2 OPV will not only minimise the risk of the emergence of new cVDPV2s in the future, but will also prevent upwards of 200 cases of VAPP that currently occur each year as a result of the type 2 component in trivalent OPV. This globally synchronised switch will therefore be of great significance for the polio eradication programme with tremendous public health benefits.

### In this issue:

- Switching from tOPV to bOPV: overcoming remaining challenges
- Research agenda critical to successful switch

### Lancet publishes landmark study on new routine immunization polio vaccination schedule

In advance of April 2016 switch from trivalent OPV to bivalent OPV, a new study published in the prestigious science journal The Lancet confirms the efficacy of the new routine schedule with bivalent OPV and IPV. The study, coordinated by Sutter et al through a grant from Rotary International, assessed immunogenicity in 900 newborns, receiving 4 doses of bivalent OPV and one dose of IPV. Results clearly demonstrated that the new routine immunization schedule improves immunogenicity against all polioviruses, and especially against poliovirus type 3.

The results of the study are a further critical building block in preparing for next year's switch from trivalent OPV to bivalent OPV, to ensure the new routine immunization schedule will continue to protect children against polioviruses. The study is available online at the below link. "Immunogenicity of a new routine vaccination schedule for global poliomyelitis prevention: an open-label, randomized controlled trial." Sutter, R et al. The Lancet Online, 18 September 2015.

[http://www.thelancet.com/journals/lanet/article/PIIS0140-6736\(15\)00237-8/abstract](http://www.thelancet.com/journals/lanet/article/PIIS0140-6736(15)00237-8/abstract)

## Trivalent OPV to bivalent OPV switch – overcoming remaining challenges

Success in achieving polio eradication requires eventual withdrawal of all oral poliovirus vaccine (OPV), starting with the withdrawal of the type 2 component in April 2016.

As the world prepares for the global switch of trivalent OPV to bivalent OPV, a number of remaining challenges must be overcome.

### **Introducing IPV**

As part of the global preparations for the switch, all OPV-using countries have committed to introducing inactivated poliovirus vaccine (IPV) into their routine immunization schedules.

The level of commitment from countries to introduce IPV has been extraordinary. However, due to technical challenges in scaling up manufacturing, short term supply constraints mean that some low risk countries may experience slight delays in deliveries. The available supply must be prioritized to highest risk areas in the most equitable manner possible.

As many as 29 countries may experience delays in deliveries until no later than September 2016 (additionally, Indonesia is expected to secure nationally-produced supply by July 2016), expected to affect a 3-month birth cohort of less than 4 million infants worldwide, in areas of high immunity against type 2 poliovirus, and no history of cVDPV emergence or wild poliovirus importations.

### **Withdrawing and destroying trivalent OPV stock**

When the switch from trivalent OPV to bivalent OPV has occurred, any remaining stocks of trivalent OPV must be withdrawn

from the cold chain and disposed of according to existing national procedures. This will help to prevent the continued introduction of type 2 virus into populations (which could lead to the emergence of new cVDPV2s). Trivalent OPV will be destroyed following safe disposal procedures, and use up excess quantities in vaccination campaigns or catch-up rounds. To help boost immunity and optimize residual trivalent OPV stocks, countries are encouraged to calculate their inventories as soon as possible to minimise the quantity of trivalent OPV disposed and assess availability for any trivalent OPV SIAs.

To validate the switch to bivalent OPV and certify that trivalent OPV has been withdrawn from the cold chain within two weeks of the National Switch Date, countries are encouraged to identify or establish an independent validation committee, separate from switch implementation activities. All trivalent OPV stocks should subsequently be destroyed within three months of the National Switch Date with the process reviewed by the countries' own immunization program supervisors who would review disposal data and disposal sites and validate the country free of trivalent OPV within three months of the National Switch Date.

### **Facilitating outbreak response to type 2 polioviruses**

To enable outbreak response capacity to potential re-emergence or reintroduction of type 2 poliovirus, a global stockpile of monovalent OPV type 2 (mOPV2) has been established. While the Strategic Advisory Group of Experts on immunization (SAGE) has recommended maintaining a global stockpile of mOPV2, in its

Resolution, the WHA stipulated that while a global stockpile should be the primary goal, individual member states deciding to establish national stockpiles should be able to do so, on the condition that containment be verified by Regional Certification Commissions, and that any release of such national stockpiles be authorized by the Director-General of WHO.

### **Containing type 2 polioviruses**

In 2014, the strategic approach and plan for fully aligning the containment of polioviruses with the milestones and timelines of the Polio Eradication and Endgame Strategic Plan 2013–2018 were finalized and endorsed by SAGE. The *WHO global action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of OPV use* (GAPIII) establishes specific requirements for the appropriate containment of all polioviruses, starting with type 2, and sets timelines and parameters for designating and certifying poliovirus-essential facilities retaining specific poliovirus materials. GAPIII was endorsed by the World Health Assembly in May 2015.

In September 2015, the Global Commission for the Certification of Poliomyelitis Eradication (GCC) declared that wild poliovirus type 2 has been eradicated. The last detected wild poliovirus type 2 case dates to 1999, from India. The GCC arrived at this conclusion after reviewing formal documentation submitted by Regional and National Certification Commissions, the Global Polio Laboratory Network and surveillance systems.

## “And then there were two...” – the Beginning of the Endgame

September 2015 was a historic month for the global polio eradication effort, as ‘three became two’. Nigeria was officially removed from the list of remaining endemic countries, leaving only two countries – Pakistan and Afghanistan – in the world. It is the lowest number of endemic countries in history.

And on 20 September, the Global Commission for the Certification of Poliomyelitis Eradication (GCC) concluded that wild poliovirus type 2 (WPV2) has been eradicated worldwide. The last detected indigenous WPV2 dates to 1999, from Aligarh, northern India. This announcement marks a major landmark in the global efforts to eradicate all three wild poliovirus serotypes: WPV1, WPV2 and WPV3. WPV3 has not been detected globally since November 2012 (in Nigeria); the only remaining WPV1 strains are now restricted to Pakistan and Afghanistan.

With the world closer than ever to eradicating polio, and one strain officially eradicated from the world, preparations for the phased removal of OPVs are being intensified, beginning with the planned switch from trivalent OPV to bivalent OPV in OPV-using countries in April 2016.

September 2015 may well be remembered in the global eradication effort as a historic month, which truly launched the ‘beginning of the endgame’.



## Research agenda critical to ensuring successful trivalent OPV to bivalent OPV switch

The polio research agenda is playing an integral part in both preparing for the planned switch from trivalent OPV to bivalent OPV, and in helping to monitor and evaluate its implementation.

### ***Assessing a new polio immunization schedule***

With IPV being globally introduced, and the phased removal of OPVs, it will be critical to ensure that the most effective immunization schedule can be implemented to protect children, and to ensure that different outbreak response mechanisms are in place should this be necessary in a post-eradication, post-OPV world.

To this effect, a joint collaboration between the Global Polio

Eradication Initiative and Aga Khan University in Karachi, Pakistan, is underway to generate important data for the full implementation of the Polio Endgame Plan.

A first study will provide data on serological protection achieved with different combinations of OPV and IPV. This study will also assess whether a potential outbreak of circulating vaccine-derived poliovirus could be effectively stopped with the available tools and evaluate new tools such as monovalent OPV type 2 (mOPV2) and a high-potency monovalent IPV type 2 (hpIPV2). The study started in early 2015 and results are anticipated in the first half of 2016.

A second study will provide information on serological response and usability of novel techniques for intradermal fractional dose IPV (1/5<sup>th</sup> of a dose) administration in supplementary immunization activities (SIAs). This data may be of importance if IPV supply is limited and rapid SIAs with IPV are needed in high risk areas. The study started in the end of September 2015 and results are expected to be available by the end of the year.

### ***Access to bivalent OPV licensed for routine immunization***

Ensuring access to a bivalent OPV licensed for routine immunization will be a critical factor to a successful switch. Previously,

bivalent OPV was licensed for use in supplementary immunization activities (SIAs) only. Manufacturers of bivalent OPV supplying the global market have applied for an appropriate label change: GlaxoSmithkline (approval granted in June 2015), Sanofi Pasteur (approval granted August 2014), Bio Farma (approval granted August 2015), Serum Institute of India (approval granted July 2015), Haffkine (approval expected Q4 2015) and Bharat (approval expected Q4 2015).

In addition, the World Health Assembly in its Resolution adopted in May 2015 urged all countries to authorize use of bivalent OPV in routine immunization exceptionally on the basis of prequalification granted by WHO should it be required (ie if national registration is pending at the time of the switch), as: a) the vaccine is identical to trivalent OPV (except that the type 2 component is removed); b) the history of successful and safe large-scale use since 2009 (>5 billion doses used); and, the short life-cycle of this product until all OPV will be withdrawn (anticipated in 2019-2020).

### **New IPV formulations**

#### **a) Intradermal IPV**

Different studies have shown that intradermal (ID) IPV is almost as immunogenic as full dose delivered intramuscularly, if it is given as primary series, provided there is less interference with maternal antibodies. However, as a booster dose, fractional ID IPV seems to have less ability to increase antibody titers (especially when the baseline titers are high). Therefore, the Dutch National Regulatory Agency (NRA) proposed that WHO should conduct a non-inferiority trial of a single fractional IPV dose (administered intradermally) compared with a single full IPV dose (administered intramuscularly), with adults who previously

received OPV doses as children. The study was implemented in Cuba, and the results confirm the non-inferiority of fractional dose IPV in a booster indication. This would potentially mitigate the IPV supply issue and expand the possibility of IPV use in vaccination campaign settings. Conventional ID IPV administration, with BCG needle and syringe, is time consuming and requires specific training for health workers; using needle and syringe also carries the risk of needle-stick related injury, and the need for specific waste disposal systems to be in place. Multiple ID IPV administration devices are being developed, which would optimize safety and consistency in ID delivery. In addition, multiple studies have indicated the feasibility of ID device use, as well as health worker preference when compared to needle and syringe. To accelerate the development and adoption of these devices, the possibility of maintaining a stockpile of these devices for vaccination campaign use is being explored.

#### **b) Sabin IPV**

After a decade-long development process, Sabin IPV was licensed in 2012 in Japan and in 2015 in China. Additionally, Sabin IPV technology transfer has already been initiated through agreements signed with Intravacc by Korea (LG), India (Panacea and SII), China (Sinovac and Minhai) and negotiations are currently proceeding with Mexico (Birmex), with ongoing consideration for technology transfer for national suppliers in India, Iran, and in the future, the Russian Federation.

Results from clinical trials conducted in Cuba and Japan on the decay of antibody titers induced by IPV demonstrate similar trends in median antibody titers at 21-22 months after vaccination, between Salk IPV, Sabin IPV and adjuvanted Sabin IPV.

The next steps in Sabin IPV include the provision of support for the technology transfer of Sabin IPV and the development of optimised production processes using Animal component free (ACF) media which are expected to be cost-competitive in the long-term.

A cost of goods (COGs) analysis of ACF Sabin IPV based on preliminary experiments indicated that the ACF-based production process may improve the upstream production yield. In addition, downstream production yield of type 2 D-antigen may improve from 11% to 22% with the overall cost of goods reduced by up to double.

During the sixth meeting of the Advisory Panel for Sabin IPV development and technology transfer, the panel endorsed the ACF project proposal. Subsequently, WHO and Intravacc initiated the development of new Sabin IPV production technology with ACF and anticipated that this technology would likely become available for the technology transfer to partners in 2017.

If these options become available, they are expected to contribute to creating a more affordable supply of IPV more as well as mitigating the current IPV shortage due to the universal introduction of IPV expected in 2015-16.