Summary of the April 2017 meeting of the Strategic Advisory Group of Experts on Immunization

The Strategic Advisory Group of Experts (SAGE) on Immunization[1] met on 25-27 April 2017 in Geneva, Switzerland.

Polio eradication

SAGE acknowledged the progress towards eliminating wild poliovirus (WPV) transmission. There were 8 WPV cases reported over the last six months (as of 18 April 2017) in Afghanistan and Pakistan, versus 32 cases during the comparable 6 month period, 1 year ago. The overall situation in Afghanistan and Pakistan has significantly improved in common corridors of transmission. A recent serosurvey in Pakistan among 6-11 month-old children indicated more than 95% seroprotection in all districts, except for Pishin and Quetta. The programme is addressing the remaining risks (e.g. potential outbreak outside high-risk areas and among high-risk mobile populations). Nigeria has not reported any WPV case since August 2016. However, significant areas in Borno remain inaccessible and up to half a million children under 5 years old remain unreached.

After the type 2 poliovirus withdrawal (through the synchronized global switch from trivalent to bivalent oral polio vaccine (bOPV) in April 2016), Sabin type 2 appears to have disappeared from the environmental/Acute Flaccid Paralysis (AFP) samples outside countries using monovalent OPV2 (mOPV2). However, Nigeria detected several vaccine-derived poliovirus type 2 (VDPV2) from the environment in Bauchi, Gombe and Sokoto in 2017. SAGE expressed concern over the ongoing circulation of VDPV2 in Nigeria. Given that the risk of a significant outbreak increases with waning immunity levels, SAGE recommended that countries with co-circulation of wild polio virus (WPV) and cVDPV2 should give priority to stopping cVDPV2 outbreaks over WPV elimination (i.e. at least 2 mOPV2 given before the next bOPV round).

In recognition of the ongoing global inactivated polio vaccine (IPV) supply constraint, SAGE discussed the evidence on the role of IPV. While IPV may offer primarily a complementary benefit in stopping WPV/circulating vaccine-derived poliovirus type 2 (cVDPV2) transmission , the primary vaccine of choice to eliminate WPVs and respond to cVDPVs is OPV (bOPV and mOPV2). On the other hand, IPV has a significant role in routine immunization in protecting children against poliomyelitis caused by cVDPV2 in countries using bOPV for routine immunization. This use of IPV in routine immunization is especially important as population immunity for type 2 continues to decrease since the time of the switch.

Therefore, in the short-term, given the ongoing global IPV shortage, SAGE recommends that:

[1] http://www.who.int/imunization/sage/en/index.html

1. Regional and national immunization technical advisory groups should recommend 2 fractional IPV doses in national routine immunization schedule, where practical, provided that countries have access to appropriate IPV presentations (e.g. single dose or 5 dose-vials), the capacity to administer intradermal injections, and a good advocacy and communication plan for parents and healthcare providers;

2. IPV supply should be prioritized for use in routine immunization (especially in Tier 1 and 2 countries);

3. SAGE also requests that WHO reviews its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection and the recent type 2 VDPV events.

Lastly, SAGE discussed polio immunization policy after global OPV withdrawal. Studies indicated that 2 fractional or 2 full IPV doses (for prime and boost) are required to achieve 90% or more seroconversion (individual protection), with the first dose after 14 weeks and an interval ≥ 4 months between the first and second doses. SAGE also reviewed the risk of reintroduction of polioviruses after global OPV cessation. The modelling and epidemiology suggest that VDPV may emerge 0-4 years after the global cessation of OPV. WHO immunodeficiency-associated vaccine-derived poliovirus (iVDPV) registry indicated that iVDPVs could be excreted for up to 5 years in middle income countries and for more than 10 years in high income countries. In addition, the risk of containment failure and deliberate release of poliovirus may continue even after 10 years.

With available evidence, SAGE recommends that after global OPV withdrawal:

1. Countries should include at least two doses of IPV in their routine immunization schedule, the first at or after 14 weeks (e.g. with the 2nd or 3rd dose of DTP-containing vaccine) and the second dose ≥4 months after the first dose, administered either as full or fractional doses;

2. Countries without Poliovirus Essential Facilities (PEFs) should maintain IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, to address: immediate (VDPVs), intermediate (iVDPV) and longer-term (e.g. containment failure) risks;

3. Countries with PEFs should continue to use IPV as long as mandated by the Global Action Plan to minimize poliovirus facility-associated risk (GAP III).

SAGE noted the progress in the implementation of biocontainment of poliovirus and the development of post-certification strategy, which aims at defining the essential functions that need to be sustained to maintain a polio free world post certification; these include containment, detection and response to outbreaks, protection of population (e.g. administration of bOPV, management and monitoring of the essential functions).

Cholera

Cholera continues to be a threat for the world's poorest and most vulnerable populations and the disease remains endemic in many settings across Africa, Asia and Haiti in the Americas. There are between 1.3 and 4 million cases every year worldwide, and between 21,000 and 143,000 deaths. With increased urbanization and climate change, this figure is expected to increase over the next decade.

Cholera is often predictable, preventable and can ultimately be eliminated where access to clean water and sanitation facilities, and satisfactory hygiene conditions are ensured and sustained for the whole population.

Although the mainstay for cholera control remains access to safe water, hygiene promotion and sanitation, there is mounting evidence that high coverage with oral cholera vaccines (OCV) results in significant reduction of cholera transmission in various settings.

Three whole cells killed OCVs are currently pre-qualified by WHO and all 3 vaccines have good safely profiles and provide sustained protection of >60% for at least 3 years after 2 doses.

SAGE recommended that given the current availability of pre-qualified whole-cell killed OCV and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crisis with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies.

Appropriate case management, Water, Sanitation, and Hygiene (WaSH) interventions, surveillance and community mobilization remain cornerstones for cholera control. Vaccination is synergistic with these activities.

Mass vaccination campaigns are usually the most practical option for delivering OCV. Based on available evidence, there are considerable benefits and very few risks for including pregnant women in OCV vaccination campaigns.

Ebola Vaccines

Ebola outbreaks can be controlled through well defined interventions: (i) early isolation of patients to prevent transmission at home and in the community; (ii) early detection of new Ebola cases through close monitoring of contacts and isolation of contacts when they show symptoms and; (iii) safe burial of the deceased to reduce transmission through contact with dead bodies. In the 2013-2016 outbreak these measures were initially not fully implemented resulting in an unprecedented geographical spread, a large number of reported cases and high mortality.

Twelve candidate vaccines (including monovalent, bivalent or multivalent candidates) have undergone or are actively undergoing clinical development at different trial phases. The Phase 3 trial for an rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP) was undertaken

in Guinea and is the only study that has reported clinical efficacy and effectiveness for any candidate Ebola vaccine.

Should an Ebola virus disease outbreak occur before any candidate vaccine is licensed, SAGE recommends that the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practice. If the emerging outbreak is caused by an Ebola virus species other than *Zaire*, consideration should be given to the use of other candidate vaccines that target the putative viral species. Ring vaccination, as used in the Phase 3 study in Guinea, is the recommended delivery strategy. This should be adapted to the social and geographic conditions of the outbreak areas and include people at risk including, but not limited to: (i) contacts and contacts of contacts; (ii) local and international health care and front line workers in the affected areas and (iii) health care and front line workers in areas at risk of expansion of the outbreak.

The Expanded Access study protocol—that is being discussed with Member States by Médecins Sans Frontières, the vaccine developer, and partners—should be implemented promptly after the confirmation of a case of Ebola virus disease in coordination with the current control interventions. It should be used as an opportunity to accumulate additional information on vaccine safety, efficacy and effectiveness.

SAGE considers that available evidence on candidate Ebola vaccines is insufficient to formulate conclusive recommendations regarding mass immunization of the general population or regarding immunisation of health care workers in the absence of an outbreak. The existence of effective control interventions when outbreaks are detected and responded to in a timely and decisive fashion is also a consideration.

Diphtheria

SAGE stressed that diphtheria is a forgotten disease in large parts of the world and that it needs global attention.

The analysis of data reported through the WHO-UNICEF Joint Reporting Form (JRF) revealed that progress in decreasing diphtheria incidence has stalled in the last five years, with approximately 5,000 cases reported per year.

Analysis of data from other sources indicates that cases with known vaccination status occurred mostly in unvaccinated individuals, and to a lesser degree in individuals with incomplete vaccination status underlining the need for administration of the full primary immunization series plus booster doses.

SAGE highlighted the need for strengthening surveillance systems to enhance their capacity to detect and investigate diphtheria cases to generate better data to inform recommendations on optimal vaccination schedules to prevent outbreaks and respond promptly to outbreaks when they occur. Countries should be encouraged to report diphtheria cases caused by *C. diphtheria* and *C. ulcerans,* where laboratory capacity for confirmation is available.

SAGE also concluded that vaccination coverage with diphtheria-containing vaccines in the paediatric immunization programmes must increase and harmonization of immunization schedules between diphtheria, tetanus and, when appropriate, pertussis vaccination should occur. Available data from non-endemic countries and the findings from the systematic review on the duration of protection currently do not support the need for a decennial booster dose.

SAGE expressed its grave concerns in regard to the limited and often expired diphtheria antitoxin (DAT) supplies worldwide and highlighted that DAT is urgently needed for administration already upon suspicion of diphtheria disease to improve survival. SAGE therefore advised that WHO collaborates closely with partners to establish and manage a global procurement mechanism and a physical or virtual stockpile. SAGE further urged that regulatory pathways be put in place to ensure the rapid deployment of DAT. In the long term, SAGE advised WHO to identify mechanisms for support to development of a monoclonal antibody as an alternative to DAT.

In the context of the need for acceleration of the implementation of the Global Vaccination Action Plan SAGE also discussed i) National immunization programme management: functions and competencies and ii) the strengthening of national immunization technical advisory groups and the engagement of private providers with the national immunization programme.
The full meeting report will be published in the WHO Weekly Epidemiological Record on 2 June 2017. The meeting documents — including presentations and background readings — can be found at http://www.who.int/immunization/sage/meetings/2017/April/en/