

Summary of the April 2016 meeting of the Strategic Advisory Group of Experts on immunization (SAGE)

The Strategic Advisory Group of Experts (SAGE) on immunization¹ met on 12-14 April 2016 in Geneva, Switzerland.

Dengue Vaccine

Worldwide, dengue is the most extensively spread mosquito-borne virus illness. It is caused by 4 related viruses (DENV 1-4). In the last 60 years, the incidence of clinical dengue cases reported to WHO has increased 30-fold, with a greatly increased geographic range and expansion from urban to rural settings. The objectives of the WHO Global Strategy for dengue prevention and control (2012-2020) are to reduce mortality and morbidity from dengue by 2020 by at least 50% and 25% respectively². The first dengue vaccine, CYD-TDV (Dengvaxia®), a live attenuated vaccine, has now been licensed by several dengue-endemic countries in Asia and Latin America for use in 9-45 or 9-60 year-olds, and is under regulatory review in several others.

SAGE reviewed the evidence generated from two large Phase 3 clinical trials, one conducted in 2-14 year-olds in 5 countries in Asia, the other in 9-16 year-olds in 5 countries in Latin America. Vaccine efficacy over 25 months from the first vaccine dose among 9-16 year-olds, using data pooled from both trials, was 65.6% (95%CI 60.7-69.9)³. The sub-group benefit profile is complex: vaccine efficacy varied by infecting virus (higher protection against DENV 3 and 4 than DENV 1 and 2), age (higher protection in older children), and disease severity (higher protection against hospitalized and severe dengue), and serostatus at the time of vaccination (higher protection in participants who had already been exposed to dengue virus). In those children first vaccinated at ages 2-5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose, though this dissipated in years 4 and 5. The biologic mechanism behind this increased risk is currently not understood but may be related to naïve vaccine serostatus and/ or age. A significant increase in hospitalizations was not seen in those older than 5 years. No other safety signal has been identified.

SAGE considered the results of a comparative mathematical modelling evaluation of the potential public health impact of CYD-TDV introduction done by 8 different groups. There was agreement across the different models that in high transmission settings, the introduction of routine CYD-TDV vaccination in early adolescence could reduce dengue hospitalizations by 10-30% over the period of 30 years, representing a substantial public health benefit. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, where the vaccine has less protective effect.

¹ See <http://www.who.int/immunization/sage/en/index.html>, accessed April 2016

² Using 2010 as a baseline

³ Post-hoc analysis

SAGE recommended countries consider introduction of CYD-TDV only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended when seroprevalence is below 50%. Dengue vaccine introduction should be a part of a comprehensive dengue control strategy together with a communication strategy, well-executed and sustained vector control, the best evidence-based clinical care for all patients with dengue, and robust dengue surveillance.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, affordability and budget impact. WHO and partners should provide further technical support to countries pre- and post-registration.

CYD-TDV should be administered as a 3-dose series given as a 0/ 6/ 12 month schedule. However, additional evidence is needed to understand whether simplified schedules may elicit equivalent or better protection. Because of the 12-month duration of the immunisation schedule and to enable better vaccine monitoring, countries should have systems in place for tracking vaccination.

Because of the safety signal of increased risk of hospitalized and severe dengue identified in the 2-5 year age group, CYD-TDV is not recommended for use in children under 9 years of age, consistent with current labelling.

The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular ages. For highly endemic settings (e.g. seroprevalence at 9 years of age of approximately 90% or greater), vaccination at 9 years of age is projected to maximize impact. In settings where seroprevalence at 9 years of age is below 90% (but above 50%), vaccination at 11-14 years of age is preferable.

Co-administration safety and immunogenicity data for age-relevant vaccines (in particular HPV and TT) in the adolescent age group are currently unavailable. Because the risk of immunological interference due to co-administration of live with non-live vaccines is considered small, co-administration is permissible with these and other non-live attenuated vaccines.

Polio eradication

SAGE reviewed the overall progress of the Global Polio Eradication Initiative (GPEI) and the implementation of oral polio vaccine type 2 (OPV2) withdrawal, and had initial discussions on future polio immunization policy. First, SAGE acknowledged the significant progress made towards eliminating wild poliovirus (WPV) in Afghanistan and Pakistan with improved access, coordination and operations. Lower performing areas in both countries are well-defined and specific plans are being implemented to take advantage of the low transmission season. There has also been progress in eliminating persistent

vaccine-derived poliovirus type 2 (VDPV2) in Pakistan and Nigeria with no case since May 2015. Over the last six months, there have been two VDPV2 outbreaks (Myanmar, Guinea) and one VDPV2 case (Democratic Republic of Congo). SAGE concluded that the response to the VDPV2 outbreak in Myanmar is adequate. However, SAGE was concerned about the situations in Guinea and DRC with evidence of inadequate surveillance. SAGE recommends that GPEI should ensure high quality Supplementary Immunisation Activities in Guinea and DRC, if necessary with monovalent OPV2 after April 2016, and to intensify programme surveillance in these countries as well as in Sierra Leone and Liberia, as they recover from Ebola.

SAGE noted the strong and sustained progress toward addressing the readiness criteria for the OPV2 withdrawal. To date, 94/ 126 OPV countries have introduced the inactivated poliovirus vaccine (IPV) into their routine immunization. However, SAGE reiterated its concern over the global IPV supply shortage, which will likely persist into 2017/ 18. SAGE urged that IPV suppliers should make their best effort to fulfil their commitment to supply IPV, accommodate the needs of the program (e.g. supplying more vaccine in one-dose or five-dose vials), and immediately inform the SAGE Polio Working Group of any further change in the IPV supply situation. To help mitigate the IPV supply situation, SAGE encouraged countries to evaluate the cost-benefits, trade-offs and programmatic feasibility associated with providing IPV in a two dose fractional dose schedule, e.g. at 6 weeks and 14 weeks, in lieu of administering 1 intramuscular dose at 14 weeks. SAGE requested that WHO address concerns of countries affected by the IPV supply situation and provide technical support. It also requested the Polio Working Group to evaluate options for catch-up vaccination for those cohorts born after 1 May 2016 in countries where IPV introduction will be delayed or continued supply disrupted.

SAGE noted that a small number (one to two) of type 2 circulating vaccine-derived poliovirus (cVDPV2) outbreaks are expected within 12 months after the switch. It recommended that GPEI should enhance surveillance in countries with high risk of VDPV emergence and in countries without IPV, and respond to any type 2 VDPV emergence after April 2016 as an emergency, as per the updated response protocol. WHO should also amend the surveillance case definition to include type 2 Sabin so that all type 2 polioviruses will be notified under the International Health Regulations.

SAGE acknowledged the progress made in completing containment phase I (i.e. reducing the number of facilities containing poliovirus) for WPV2/ VDPV2 in most countries, under the Global Action Plan for Containment (GAP III). SAGE urges all countries to ensure completion of phase I for all type 2 polioviruses, including Sabin 2, and to strengthen national intersectoral collaboration to comply with phase II of GAP III (i.e. reduce risk in facilities containing poliovirus).

Pre-empting and responding to vaccine supply shortages

Over the past couple of years, various countries across regions and income groups have reported shortages of vaccines, sometimes causing critical disruptions of immunization programmes. Countries have expressed their concerns to WHO and are asking for more information and solutions in order to mitigate the effects of current vaccine shortages and

prevent future ones. Many partners are active in this area and are implementing solutions in a collaborative manner. However, a comprehensive and global view of vaccine shortages is missing, particularly for vaccines not supported by external development assistance. SAGE noted that information collection and sharing was a major area for potential further investment to pre-empt and manage vaccine shortages. This is also aligned with the draft resolution on “Addressing the global shortages of medicines” to be presented at the WHA in May 2016. The discussion emphasised the importance of taking into account and acting upon the multiple causes and dimension of shortages and the need to streamline product and regulatory requirements was particularly stressed.

SAGE particularly recommended that WHO plays a key role in setting up an “Exchange Forum”, helping to collect demand information from all member states and to enhance dialogue between countries and manufacturers on supply availability and threats to vaccine supply. requested that effective communication with countries be undertaken on the causes of shortages and current mitigation and long term activities.

Missed opportunities for vaccination

SAGE strongly and unanimously endorsed the updated strategy to deal with missed opportunities for vaccination as a simple and concrete strategy for improving coverage, equity and timeliness of vaccination. The proposed strategy was seen as a “substantial move forward” with great potential impact, immediately actionable and to be promoted widely.

SAGE stressed the importance of giving attention to implementation research as part of vaccine development in addition to looking at vaccine safety and efficacy.

To allow better follow-up of immunization globally SAGE stressed the critical importance of an immunization specific indicator to assess progress toward the under five mortality target of the Sustainable Development Goals.

SAGE also discussed the respiratory syncytial virus vaccine pipeline, implementation of immunization in the context of health systems strengthening and universal health coverage, and guidance on the establishment of a platform for immunization and other health interventions in the second year of life.

The full meeting report will be published in the WHO Weekly Epidemiological Record on 27 May 2016. The meeting documents — including presentations and background readings — can be found at <http://www.who.int/immunization/sage/meetings/2016/april/en/>