Summary of the Meeting of the Strategic Advisory Group of Experts on immunization, 17-18 April 2018

The Strategic Advisory Group of Experts (SAGE) on Immunization met on 17–18 April 2018. This full report will be published on 8 June 2018 in the Weekly Epidemiological Record.

Malaria Vaccine Implementation Programme

SAGE was informed on the progress made on the implementation of the recommendation made by SAGE and the Malaria Policy Advisory Committee (MPAC) in October 2015 on pilot studies for the RTS,S/AS01 malaria vaccine. SAGE was provided an overview of the Malaria Vaccine Implementation Programme (MVIP) and given a status update of preparatory activities in the three pilot countries (Ghana, Kenya, Malawi).

The pilots consist of three components: 1) Sub-national introduction of the malaria vaccine, in areas with moderate to high malaria transmission led by country immunization programmes; 2) Rigorous evaluation, supported by country-based research institutions, to measure the programmatic feasibility of delivering RTS,S/AS01, the vaccine’s impact on mortality (overall and sex-specific) and the vaccine’s safety in the context of routine immunization, with an emphasis on meningitis and cerebral malaria; 3) the manufacturer-sponsored observational Phase 4 studies with hospital and active surveillance as part of the vaccine’s Risk Management Plan agreed between the manufacturer and the European Medicines Agency (EMA) taking place in a small sub-set of the pilot areas.

SAGE was reassured that uptake of the RTS,S/AS01 vaccine, as well as use of other vaccines and childhood health interventions will be monitored through countries’ routine data monitoring systems; three consecutive cross-sectional household surveys will provide representative community estimates of RTS,S/AS01 coverage, along with coverage estimates for other vaccines, for recommended malaria prevention and control measures, and for other childhood health interventions of interest. In addition, a qualitative research study will explore and document any changes in health-seeking behaviours and on health service provision that may occur upon RTS,S/AS01 introduction. SAGE re-emphasized the importance of communication and community engagement to ensure acceptance and understanding of the new vaccine in the context of other malaria control interventions. Experience from other efforts related to strengthening the second year of life (2YL) platform could prove useful.

SAGE was reassured that the evaluation has been sufficiently powered to assess whether the safety signals (i.e., meningitis and cerebral malaria) and the imbalance in mortality between males and females identified during the Phase 3 trial are causally related to RTS,S/AS01 vaccination.

SAGE agreed on the importance of having a framework to clarify how data collected through the MVIP might be used to answer identified questions and inform future policy recommendations for vaccine use beyond the pilots. SAGE specifically recommended the modelling inputs incorporate different scenarios and levels of uncertainty to enable interpretation of the MVIP results in the context of real world settings.

Polio eradication

SAGE acknowledged the ongoing efforts of the Global Polio Eradication Initiative (GPEI) and the progress achieved towards wild polio virus (WPV) eradication. SAGE shared concern over continuing WPV circulation in Pakistan and Afghanistan through the active corridors of transmission, as manifested through the continued detection of WPV1 in environmental samples during 2016 and 2017.

SAGE noted that the IPV supply is sufficient to introduce IPV in routine immunization globally in 2018, but not to conduct catch up campaigns for cohorts that did not receive IPV because of supply constraints. SAGE reviewed the available data on fractional IPV (fIPV) and emphasized that two doses of fIPV are superior to one full IPV dose. SAGE agreed that IPV should not be used routinely in outbreak response except in specific situations such as where there is co-circulation of WPV1 and cVDPV2 and in these instances fIPV should be used. In addition, SAGE recommended that instead of using term “fractional” for fIPV, GPEI should think of other term such as “intradermal” to avoid impression that fIPV is sub-standard. Studies to examine duration of immunity and protection following two doses of fIPV are in progress.

SAGE reviewed the Post Certification Strategy (PCS). This is a high-level working document which aims to guide Member States and stakeholders on the polio-essential functions required to sustain a polio-free world after WPV eradication and dissolution of GPEI. The PCS does not provide specific or detailed country level guidance. Its aim is to serve as a roadmap to ensure that the oversight, infrastructure and funding is in place to 1) contain polioviruses, 2) protect populations from polio, and 3) retain capacity to detect and respond to any poliovirus event. SAGE endorsed the content and approach of the PCS and agreed to submit it for discussion at the World Health Assembly in May 2018.

In order to align GAP III and SAGE recommendations on IPV schedules, SAGE reviewed recommendations on IPV schedules in countries with Poliovirus-Essential Facilities (PEFs). While the majority of the 29 countries hosting PEFs are located in Europe and North America, and have introduced exclusive or sequential IPV schedules, some countries are currently only using a single dose of IPV (together with bOPV) in their immunization schedule.

SAGE endorsed the proposal to align the recommendations on future IPV schedule for countries hosting PEFs storing or manipulating WPVs and/or Sabin/OPV and recommends that those countries with PEFs using a single dose of IPV should adjust their IPV schedule, coverage targets and geographical scope as soon as possible but no later than at the time of all OPV cessation.

SAGE requested the program to explore the extent to which a legal instrument such as the International Health Regulation (IHR) could be used to ensure compliance with poliovirus containment requirements defined in GAP III and the Containment Certification Scheme.
SAGE recommendations on the use of the first licensed dengue vaccine

Dengue is a rapidly spreading mosquito-borne virus infection. The first dengue vaccine, CYD-TDV (Dengvaxia®) has been licensed in twenty countries. The key findings from two large Phase 3 trials involving over 30,000 participants aged 2 to 16 years indicated:

- Vaccine efficacy against virologically confirmed dengue, over 25 month period from the first dose of a three-dose immunization regimen among 9-16 year-olds was 65.6% and in this age-group, vaccination reduced severe dengue by 93% and dengue hospitalizations by 82%.
- An increased risk of hospitalized dengue was seen in the 2-5 year age group in year 3 of follow-up.
- At the time of SAGE April 2016, this increased risk was not observed in those aged 9 years and above.

The manufacturer had sought and obtained licensure as of 2015 with an indication of 9 years and older based on the above data and the absence of an observed increased risk of hospitalized dengue in older children.

WHO issued its position on the use of CYD-TDV in July 2016 based on recommendations provided by SAGE in April 2016, informed by clinical trial data and mathematical modelling which suggested that the public health benefits of vaccination could be maximized if dengue seropositivity in the age group targeted for vaccination was high. The position paper stated that countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings where epidemiological data indicate a high burden of disease. Seroprevalence should be approximately 70% or greater in order to maximize public health impact and the vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination. While no safety signal was evident at that time, SAGE noted the limited safety data in seronegative populations and recommended that safety studies should be conducted to monitor the occurrence over time of severe dengue illness in vaccinated persons, particularly among vaccinated seronegative persons.

On 29 November 2017, Sanofi Pasteur announced the results of additional studies to better describe the benefit-risk ratio in seronegative individuals. This was made possible through the use of a newly developed NS1-based antibody assay applied to blood samples taken 13 months after vaccination to retrospectively infer dengue serostatus at time of first vaccination.

The new analyses from the long-term follow-up of clinical trial participants indicated that:

- Overall population level benefit of vaccination remains favourable, but the vaccine performs differently in seropositive versus seronegative individuals;
- Vaccine efficacy (VE) against virologically confirmed symptomatic dengue was high among inferred baseline seropositive participants ≥9 years of age: 76% (95%CI: 63.9, to 84.0), but much lower among baseline seronegative participants: 38.8% (95%CI: – 0.9 to 62.9%) in the first 25 months after the first dose of vaccine;
- There is an increased risk of hospitalized and severe dengue in seronegative individuals from year 3 onwards throughout the observation time of 66 months;
In areas of 70% dengue seroprevalence, over a 5-year follow-up, for every 4 severe cases prevented in seropositives there would be one excess severe case in seronegatives per 1,000 vaccinees; for every 13 hospitalizations prevented in seropositive vaccinees, there would be 1 excess hospitalization in seronegative vaccinees.

Therefore, in high prevalence settings, the vaccine provides overall population benefit but an increased risk to seronegative individuals. SAGE carefully considered two vaccination strategies: Strategy 1 was using the vaccine only in populations with high seroprevalence; and Strategy 2 was screening individuals for seropositivity prior to vaccination. In the discussion of these two strategies, SAGE considered the feasibility of population seroprevalence studies and individual pre-vaccination screening, the heterogeneity of seroprevalence between and within countries, the number of people who could be eligible for vaccination under these scenarios, confidence in vaccination programmes, ethical considerations, and communication issues.

SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control program, a “pre-vaccination screening strategy,” in which only dengue-seropositive persons are vaccinated, is the preferred option.

Screening tests could be used to identify persons who have had a previous dengue infection. Two types of tests could be considered: serological assays such as dengue IgG ELISA which and rapid diagnostic tests. The disadvantage of serological assays is that they do not provide instant information on an individual’s serostatus. The disadvantage of currently available rapid diagnostic tests is that they have not yet been validated for the purpose of screening for previous dengue infection. Nevertheless, either could be considered in high prevalence settings until better tests are available.

Given that no test will be 100% specific, some seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Hence, the limitations of CYD-TDV will need to be clearly communicated to those offered vaccination.

Vaccination should be considered as part of an integrated dengue prevention and control strategy together with well-executed and sustained vector control and the best evidence-based clinical care.

SAGE highlighted that important research and implementation questions remain for CYD-TDV, in particular the development of a highly sensitive and specific rapid diagnostic test to determine serostatus, simplified immunization schedules, and assessment of the need for boosters. An updated dengue vaccine WHO position paper on dengue vaccine will be published on 7 September 2018.
**Measles and Rubella**

SAGE noted the substantial progress in the reduction of global measles incidence and mortality since 2000. However, concerns were expressed around resurgence of measles in some areas, particularly in the European region, and the measles outbreak in Venezuela that has put the elimination status of the American Region at risk.

SAGE reviewed preliminary modelled scenarios, designed to approach an investment case (IC) for measles and rubella eradication. The investment case in development is planned as part of the response to the GVAP 2017 resolution at the World Health Assembly (WHA) to provide a report to the 73rd WHA in 2020 on the epidemiology, resource requirements, and feasibility of measles and rubella eradication.

SAGE recommended that the Measles Rubella (MR) Working Group (WG) should revise the key scenarios to include a baseline scenario that reflects current vaccination efforts and disease in the countries and a separate mortality reduction scenario, besides the “eradication as soon as possible” scenario. The MR WG was requested to develop additional eradication scenarios with different timelines and with different levels of achievements (for example, elimination in all but a few countries and including the costs of reaching inaccessible pockets and hard-to-reach populations). SAGE also highlighted the importance of the inclusion of total cost when a decision regarding a global eradication target is considered, as well as the cost of elimination-standard surveillance. Furthermore, the IC should consider including the contribution of measles and rubella eradication effort towards the prevention of other vaccine preventable diseases. This IC model is currently under review by IVIR-AC and a revised version will be presented to SAGE for recommendations.

SAGE also reviewed the guidance tool for endemic countries on prioritizing measles and rubella control/elimination activities in order to increase population immunity, prevent outbreaks and achieve elimination. The approach proposed four country categories that take into consideration the disease epidemiology, population immunity and capacity to carry out elimination strategies. Guidance was then provided within each category on how to best prioritize the control or elimination interventions/activities. SAGE agreed with the overall approach and highlighted the need to include sub-national and sub-groups within countries when assessing and addressing immunity gaps and the importance of including civil society organizations (CSOs) and community participation as important elements for successful interventions.

**Full Public Health Value Propositions for Vaccines (FPHVPs)**

The remit of IVB includes accelerating development of vaccines against priority pathogens, identified through its Product Development for Vaccines Advisory Committee (PDVAC), and supporting countries with policy decisions to introduce vaccines once they become available. In addition, many of the vaccines currently in development are expected to be targeted towards specific populations, depending on the burden of disease and context-specific epidemiology. In resource-poor settings, increasingly robust evidence will be needed to justify the inclusion of new vaccines in the context of other disease interventions over and
above many other public health priorities. With this in mind, key stakeholders are advocating that there is a need to broaden the evaluation of vaccine value beyond the demonstration of individual, direct health benefits and related costs that support licensure to the evaluation of broader economic, societal and indirect impacts of vaccination at a population level. Consideration of these data and evidence requirements that inform policy decisions, prior to undertaking phase III pivotal clinical studies, could help to prioritize the vaccines that would have the greatest impact, and reduce delays between licensure and introduction encountered by vaccines such as the RTS,S malaria vaccine.  

A conceptual framework of pathways between immunisation and its proposed broader economic and social benefits has been developed, leading to publications on ‘Estimating the full public health value of vaccination’ and proposed methodology and measures to quantify the economic elements. This novel global health paradigm considers the population impact of vaccination and encompasses measures of community benefits against a range of outcomes, such as improvements in health inequity, financial risk protection, reduction in long-term/ongoing disability and a decrease in the development of antibiotic resistance. IVB, under the auspices of PDVAC and IVIR-AC, is building on these efforts, to develop an approach for describing the Full (i.e. articulating both the individual and population benefits) Public Health Value Proposition for vaccines where there is a clear public health need for, but a lack of investment in, developing vaccines for LMIC markets. This FPHVP approach was presented to SAGE for information and discussion.

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