

Summary, SAGE meeting October 2018

## **Meeting of the Strategic Advisory Group of Experts on immunization, October 2018 – DRAFT conclusions and recommendations**

The Strategic Advisory Group of Experts (SAGE) on Immunization<sup>1</sup> met on 23–25 October 2018. This report summarizes the discussions, conclusions and recommendations.<sup>2</sup> **The full report will be published on 7 December in the WER.**

### **Global Vaccine Action Plan: 2018 review of progress and recommendations**

SAGE reviewed the draft assessment report and recommendations made by the Decade of Vaccines Working Group (DoV WG) and noted that in 2017, while progress was made towards the goals set out in the Global Vaccine Action Plan (GVAP)<sup>3</sup>, many targets are unlikely to be attained by the end of the decade. SAGE acknowledged the risk that hard-won gains are easily lost, the need to maintain gains, to do more and to do things better and differently. SAGE notes that outbreaks are a sobering reminder that no country can stop investing in immunization.

Looking towards the future and broader global health agenda imperatives, SAGE emphasized the critical importance of immunization as a central pillar of Universal Health Coverage and essential in attaining Sustainable Development Goals, as well as contributing to achieving global health security targets and winning the battle against antimicrobial resistance. SAGE also stressed that countries should be at the heart of a future global immunization agenda. Regions will have a key role to play in supporting the development of national immunization systems, while global immunization partners will continue working together to create an enabling environment for immunization.

In order to keep the momentum to address GVAP goals, including research and development targets, as well as to pave the way for the development of a post-2020 global immunization agenda, SAGE issued three broad recommendations:

- I. Countries, regions and global immunization partners should commit to developing an integrated post-2020 global immunization strategy.
  - A comprehensive review should be undertaken of progress, impact and implementation of the Global Vaccine Action Plan to inform a post-2020 strategy.
  - The monitoring and evaluation framework for the Global Vaccine Action Plan should be reviewed to inform the development of a revised framework for a post-2020 strategy.
  - A post-2020 strategy should build on the lessons learned during the Decade of Vaccines and draw upon the key themes identified in this 2018 Assessment Report.
- II. Global Vaccine Action Plan priorities, adapted to reflect changing contexts and lessons learned, should drive immunization activities until the end of the Decade of Vaccines.

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<sup>1</sup> See [www.who.int/immunization/sage/en/index.html](http://www.who.int/immunization/sage/en/index.html), accessed October 2018.

<sup>2</sup> Presentations and background materials used for the SAGE meeting together with the list of SAGE members and summarized declarations of interests are available at [www.who.int/immunization/sage/meetings/2018/october/en/](http://www.who.int/immunization/sage/meetings/2018/october/en/), accessed October 2018.

<sup>3</sup> See [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/GVAP\\_doc\\_2011\\_2020/en/](http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/)

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- A major focus should be tailored country support to build and sustain robust and effective national immunization systems aligned with national plans for achieving universal health coverage.
- A best practice framework should be developed to ensure equitable access to immunization services for migrant, displaced and disadvantaged populations, including those affected by humanitarian emergencies.
- Nurturing individual and community demand for immunization should be given high priority within countries.

### III. The contributions of research to immunization should be enhanced and expanded.

- Vaccine research and development (R&D): Connections between vaccine R&D and implementation communities should be further strengthened to ensure close collaboration in new product design, development and evaluation.
- Immunization systems: More use should be made of implementation, operational and other research to improve the performance of national immunization systems and to evaluate innovations in service delivery to reach underserved populations.
- Immunization research capacity in low- and middle-income countries should be developed across all these areas.

SAGE was presented with a concept note outlining the different components of a global immunization agenda for the next decade (2021-2030). SAGE took note of the tight timeline proposed for the elaboration and submission of the agenda to the World Health Assembly in May 2020 when this will be discussed, and underscored the need to draw all lessons learnt from the current Global Vaccine Action Plan to inform the development of the new agenda. SAGE urged WHO to work with all relevant partners from the immunization and the wider public health community, with particular attention to the bottom-up approach including the involvement of civil society organizations.

### **Report of activities from international immunization partners**

PREVENT<sup>4</sup> is an initiative committed to developing concrete, actionable, consensus-driven ethics guidance on how to equitably include the interests of pregnant women and their offspring (<5 years old) in vaccine R&D for priority pathogens and emerging epidemic threats.

PREVENT is composed of a multidisciplinary Expert Working Group specializing in bioethics, maternal immunization, maternal-fetal medicine, obstetrics, pediatrics, philosophy, public health, and vaccine research. It was established following recent epidemics of Zika virus, Lassa Fever, Ebola, and H1N1 influenza which put pregnant women and their offspring at significantly higher risk of serious disease and death or resulted in pregnancy loss or severe congenital harms.

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<sup>4</sup> The PREVENT Project is funded by the Wellcome Trust (203160/Z/16/Z)

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PREVENT is developing a roadmap for the ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens. The guidance aims to promote that:

- pregnant women and their offspring benefit from advances in vaccine technologies and are not left behind as new vaccine products are developed;
- pregnant women are not unjustifiably excluded from participating in vaccine studies because of their pregnancy status; and
- pregnant women have safe, effective, and accessible vaccines to protect them and their offspring against emerging and re-emerging pathogenic threats.

SAGE members welcomed the initiative, which is timely with regards to the R&D efforts for vaccines against emerging infectious diseases and projects aimed at standardizing the reporting of pregnancy outcomes. SAGE highlighted that aspects related to health care provider attitudes, vaccine hesitance and complexities related to pregnancy co-morbidities need consideration. The need for careful risk-benefit assessments when studying live vaccines in pregnant women was noted. Finally, SAGE members suggested that the guidance under development might be expanded to include other marginalized groups in vaccine and drug trials.

### **Polio**

SAGE noted the ongoing efforts of the Global Polio Eradication Initiative (GPEI) and the progress achieved in eradication efforts, including the current situation in the three countries that continue to have circulation of wild poliovirus (WPV), namely Afghanistan, Nigeria and Pakistan. SAGE was also briefed on the outbreaks of circulating vaccine-derived polioviruses (cVDPVs) in Nigeria, the Democratic Republic of Congo, Somalia and Papua New Guinea.

SAGE emphasized the need to continue reaching the unvaccinated children in countries in the most inaccessible areas around the globe and, especially, in the countries that continue to have transmission of WPV or are experiencing outbreaks of cVDPVs.

In addition, SAGE repeatedly stressed the need of the polio programme to work closely with the Expanded Programme for Immunization (EPI) with the objective of strengthening routine immunization and the health system in general. With cVDPV outbreaks, the known underlying problem is weak routine immunization, yet guidance for outbreak response only consists of well-developed standard operating procedures (SOPs) for polio supplementary immunization activities (SIAs) and does not address how to maintain, sustain, and strengthen routine immunization as an integral part of the outbreak response. SAGE called for deliberate efforts to integrate the polio response and routine immunization strengthening and to establish joint planning and joint implementation at country, regional, and global levels.

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SAGE was informed of the report from the external review of the polio programmes in the 3 remaining endemic countries by the chair of the Independent Monitoring Board. SAGE agreed that solutions to wild polio virus 1 (WPV1) eradication in Afghanistan and Pakistan must involve communities and local leaders as well as coordination and collaboration with other sectors and programs.

SAGE noted that the IPV supply is now sufficient to support routine IPV immunization globally. However, IPV supply is insufficient to meet needs for SIAs and for the catch-up activities to cover approximately 42 million children who never received IPV because of the supply constraints. SAGE emphasized that IPV catch-up vaccination activities are necessary and should be carried out as soon as the supply allows, and prioritized according to the risk criteria developed by the program.

SAGE welcomed the appraisal paper received from the Global Certification Commission (GCC) as a suitable exercise for reviewing the criteria for certification of eradication of polioviruses. SAGE highlighted the necessity of including eradication of cVDPVs in the criteria for certification of global eradication. SAGE recognized that WPV3 has not been detected since November 2012 and agreed with the GCC that certification of WPV3 eradication is therefore a possibility ahead of the certification of WPV1 eradication.

### **Measles and rubella**

SAGE was presented with a global update on the measles and rubella elimination efforts. SAGE noted the substantial progress in the reduction of global measles incidence and mortality since 2000 and the all-time low measles incidence in the Western Pacific Region in 2017. However, concerns were expressed around the loss of the measles elimination status for the American Region and in some countries in the European Region, and the resurgence of measles in 4 of the 6 WHO Regions compared to 2016. SAGE highlighted the fragility of gains made in measles elimination and the urgent need to prioritize measles in the global health agenda in order to achieve and sustain the global and regional goals.

At the 2017 WHA, the Director-General was requested to report through the Executive Board to the 2020 WHA “on the epidemiological aspects and feasibility of, and potential resource requirements for, measles and rubella eradication”. SAGE agreed with the proposed contents of the report but requested that given the slow progress with meeting the existing global and regional goals, it should also address the potential risks of proceeding with a global eradication goal. SAGE further recommended that the report include:

- an assessment of how capacity of countries’ health systems impact a measles eradication goal,
- the essential role of routine immunization with a life course approach and of health system strengthening to achieve measles eradication,
- a discussion on the financial sustainability of the strategies that are needed to achieve and sustain eradication, and
- how the eradication goal fits within the context of the SDG goals.

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SAGE was presented with new data on the co-administration of rubella and measles containing vaccines and yellow fever (YF) vaccine. There is evidence of interference with the magnitude of antibody response against rubella, mumps, and YF when MR/MMR and YF vaccines are co-administered; however, although lower in magnitude, titers are robust (well above the cut-off points for seroconversion) in all groups. Co-administration of MR/MMR and YF vaccines does not interfere with measles seroconversion or the magnitude of antibody response against measles. There was no evidence of safety concerns in any of the studies. Conclusions from data presented were that the programmatic implications of delaying one of these vaccines to a later vaccination visit instead of co-administering them would likely have a far greater impact on population immunity than any potential reduction in the immune response due to co-administration. Based on this, SAGE recommended that WHO maintain its current guidance that MR/MMR and YF vaccines be administered at the same visit, or at least 4 weeks apart (according to the schedule that will maximize coverage for all antigens in the national immunization schedule) and that WHO remove all qualifications about co-administration. SAGE highlighted that additional research is needed to determine if the lower titers or antibody concentrations against rubella, mumps, and YF observed following co-administration will impact long-term immunity and cause secondary vaccine failures.

SAGE reviewed a new guidance document developed to support countries to identify and address measles and rubella immunity gaps in order to raise population immunity. SAGE endorsed the following guiding principles which are intended for immunization programs in all countries:

- (i) the use of a Continuous Quality Improvement (CQI) approach that entails following four steps with a regular ongoing cyclical review:
  - review all available national and subnational data to understand measles and rubella/CRS epidemiology and potential immunity gaps;
  - assess the general epidemiologic profile of the country;
  - identify, prioritize and implement interventions; and
  - assess outcomes resulting from interventions.
- (ii) strengthening RI is the primary strategy for increasing population immunity;
- (iii) campaigns are needed (as rescue measures) where RI for two doses of measles and rubella-containing vaccines is sub-optimal and to address specific immunity gaps, and
- (iv) during campaigns and the time period following campaigns, activities must be quickly prioritized to strengthen RI systems.

SAGE stressed that the vaccination campaigns are resource intensive and are not sustainable as a strategy and that countries should prioritize routine strengthening activities so that they become less reliant on campaigns. When campaigns are conducted, their primary goal should be reaching unvaccinated (also known as “zero dose”) and under-vaccinated children.

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The unvaccinated children should be identified, monitored and documented so that they can also be reached with other health interventions. In addition, campaigns should be used as opportunities to strengthen the immunization system and integrate other health interventions, to the extent that additional interventions or activities do not compromise the quality of the campaign.

### **Human papilloma virus (HPV)**

SAGE welcomed the WHO Director General's multi-stakeholder launch in May 2018 of a "*Call For Action: Toward Cervical Cancer Elimination*". Cervical cancer is the fourth most common cancer among women globally, with an estimated 570,000 new cases and 311,000 deaths annually for 2018.

Without urgent scale-up of services, this burden is projected to increase to almost 460,000 deaths by 2040, a nearly 50% increase from 2018. This increase will be uneven, with lower income countries having the greatest relative increase, further compounding the current wide variation in the rates of cervical cancer incidence and mortality across the world, with nearly 90% of deaths occurring in low- and middle-income countries.

Globally, 85 countries (44%) have introduced HPV vaccine into their national immunization programmes but progress in countries with the highest burden of cervical cancer is lagging. Currently it is estimated that only 25% of the world's population of 10-year-old girls live in countries with access to HPV vaccine. While HPV vaccine has been introduced in 84% of high-income countries, only 31% and 12% of middle- and low-income countries, respectively, have introduced the vaccine. Challenges related to affordability, hesitancy, supply, and decision-making are affecting the uptake of HPV vaccination.

SAGE reviewed updated evidence on the immunogenicity, efficacy and effectiveness of HPV vaccines, the schedules of their administration, including number of doses and intervals, as well as use in HIV-infected and in male populations. SAGE concluded that the WHO 2017 vaccine position paper remains valid. For the prevention of cervical cancer, HPV vaccination with a 2-dose schedule in the WHO-recommended target population, i.e., 9-14 year old girls, is the most effective strategy. A 3-dose schedule continues to be recommended for 9-14 year old girls who are immunocompromised and for girls and women  $\geq 15$  years of age. To accelerate impact, vaccination of multiple cohorts of girls aged 9-14 years is recommended when the vaccine is first introduced. SAGE noted that although the use of a 1-dose schedule appears attractive, there is insufficient evidence at this time to recommend it.

Results of a comparative modelling collaboration using optimistic assumptions, including long-term duration (>20 years) of vaccine protection, demonstrated the impact and effectiveness of various HPV vaccination and screening strategies and the potential for cervical cancer elimination at proposed incidence thresholds. The three models produced consistent findings. Girls-only vaccination with coverage >80% could lead to elimination in most countries/regions without changes to current screening practices. With the same vaccination scenario, adding one or two lifetime screenings would lead to the achievement of lower cervical cancer incidence levels sooner. Because of the high population-level effectiveness and strong herd effects, girls-only vaccination was highly cost-effective, irrespective of the vaccine used. In all income levels, increasing coverage in girls provides greater impact on disease than expanding vaccination to boys (gender-neutral strategy).

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With optimistic assumptions and depending on the strategy and threshold, elimination could be achieved in all countries between 2085-2105. Number of screenings and multi-age cohort vaccination accelerates elimination by 5-15 years.

SAGE agreed that the modelling exercise was robust, helpful and informative, and affirmed that HPV vaccination was the most critical intervention required to achieve cervical cancer elimination. With respect to immunization, the following interim goals were proposed: by 2030, all countries should have introduced HPV vaccination to at least a single cohort of girls in their national immunization programme and achieved at least 80% final dose coverage. The countries with the highest cervical cancer rates should prioritize HPV vaccine introduction.

SAGE proposed monitoring indicators that should be further reviewed by a multi-sectoral group, the rationale for indicator selection elaborated, and quantifiable targets set.

SAGE noted the need for research and further evidence review of the following: alternative vaccination schedules including guidance on possible extension of the timing of the second dose; vaccine effectiveness in HIV-infected and in malnourished populations; comparative effectiveness and cost-effectiveness of 9-valent HPV vaccine; and burden of HPV disease besides cervical cancer.

Concerned about the impact of an HPV vaccine supply which is forecasted to be constrained until at least 2024, SAGE urged that a globally equitable distribution of available doses be encouraged to facilitate optimal global public health access to the vaccine.

## **Ebola**

SAGE was presented with a review of data submitted by the candidate vaccine developers and the published data. Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical trial evaluation. SAGE recognized the significant progress made in the development and evaluation of several vaccine candidates against Ebola and other filoviruses. SAGE also reviewed Ebola Virus Disease (EVD) epidemiology and the progress with the implementation of the Expanded Access/Compassionate Use protocol in the Democratic Republic of Congo (DRC) where over 20,000 individuals at risk have received the rVSV-ZEBOV vaccine. SAGE acknowledged the massive efforts made by the Government and partners on the ground in DRC to fight the epidemic.

SAGE discussed the results from modelling the impact of various preventive and reactive vaccination strategies. For reactive vaccination, model results suggest that ring vaccination would work best in reducing the duration of outbreak and the number of cases if implemented in conjunction with reactive vaccination of health-care and front-line workers and together with full implementation of other non-vaccine outbreak control measures. Comprehensive contact tracing is essential for effective ring vaccination since missed infected contacts can seed an outbreak to new areas. For preventive strategies, vaccination of health care workers has significant potential of reducing scale and duration of outbreaks.

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Based on these reviews, SAGE reiterated that should an EVD outbreak due to the Zaire strain occur before a candidate vaccine is licensed, rVSVΔG-ZEBOV-GP vaccine should be promptly deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practice. 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:

- contacts and contacts of contacts;
- local and international health-care and front-line workers in the affected areas; and
- health-care and front-line workers in areas at risk of expansion of the outbreak.

A geographically targeted vaccination strategy may be considered in settings where it is not possible to identify the individuals making up the ring vaccination cohorts due to serious security, social or epidemiological issues.

In this case, the geographic area immediately around an Ebola case, such as a village or a neighbourhood, is most likely to include those individuals who were the contacts or contacts-of-contacts of the index case.

If the outbreak is caused by an Ebola virus strain other than Zaire, consideration should be given to the use of other candidate vaccines that target the respective viral strain. Currently one multivalent vaccine (Ad26.ZEBOV/MVA-BN-Filo) is in Phase II of clinical development. SAGE noted the importance of seeking opportunities to assess the efficacy of other candidate Ebola vaccines.

SAGE reviewed the currently available data on risk and safety of vaccinating pregnant women with the replicating live virus vaccine, rVSV-ZEBOV-GP. Preliminary results of a risk-benefit analysis aimed at comparing the safety of rVSV-ZEBOV-GP vaccination in pregnancy with the risk of acquiring EVD in the setting of ring vaccination were examined. The risk of acquiring EVD among unvaccinated pregnant women and all unvaccinated persons in vaccination rings is very low (0.12%, CI 0.02 -0.28) at vaccination coverage levels of eligible persons of 50% or more, likely as a result of herd immunity. Safety data on rVSV-ZEBOV-GP vaccination in pregnancy are quite limited. A single randomized control trial (RCT) indicates that the risk of pregnancy loss is 1.35 (0.73, 2.52) for those becoming pregnant within 60 days of vaccination and is 1.33 (0.56, 3.20) for those becoming pregnant within 14 days of vaccination. However, the very small number of pregnant women in the RCT limits interpretation of the data. Furthermore, data are lacking on other pregnancy outcomes, on gestational age relative to timing of vaccination, and on long-term follow up.

In summary, SAGE noted that what is known is that:

- EVD in pregnancy results in a very high risk of maternal and fetal loss;
- in an outbreak setting with no vaccination, risk of EVD to contacts and contacts of contacts of Ebola case-patients is moderately high; and
- the risk of EVD is low among unvaccinated persons of a ring vaccination cohort with vaccination coverage levels of 50% or more.

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SAGE furthermore noted that the risk of adverse effects from administering the live virus vaccine, rVSVΔG-ZEBOV-GP, to pregnant women remains largely unknown given the limited amount of data. SAGE recognized that the decision on whether to offer rVSVΔG-ZEBOV-GP to pregnant women is a complex matter and that inclusion of pregnant women in a research protocol depends on the local National Regulatory Authority and local Ethics Review Committee and more importantly, on informed consent of the pregnant woman. SAGE therefore encourages researchers to seek opportunities to gather more data on the benefits and risks of administering this replicating live virus vaccine to pregnant women, particularly under conditions permitting close and sufficiently long follow-up of vaccinees to completely document outcomes. Additionally, the development of non-replicating Ebola vaccine candidates should proceed with priority, as they represent fewer safety concerns for use in pregnancy.

SAGE reiterated that WHO should support National Regulatory Authorities of Ebola endemic countries with developing consensus on the pathways for the evaluation and potential market authorization of candidate Ebola vaccines. Licensure of candidate Ebola vaccines remains a high and urgent priority.

### **Lessons learned from diphtheria outbreaks: opportunities for early warning and preventive action**

Outbreaks of vaccine-preventable diseases (VPDs) continue to occur despite the availability of effective vaccines. Reasons for outbreaks are multifactorial and may include migration or internal displacement of populations, humanitarian crises, weak health infrastructures, inadequate policy implementation, and vaccine hesitancy. The cost of outbreak responses can be large and increase quite quickly, which reinforces the importance of preventive vaccination strategies. Using the 2017 diphtheria outbreak in Bangladesh among the Rohingya people in Cox's Bazar as a case study, SAGE reviewed the availability of global immunization programme data and its potential for identifying populations at-risk for VPDs in order to be able to better anticipate or prevent outbreaks.

To identify at-risk populations and geographic areas, it is essential to have data on vaccination coverage, equity, and disease surveillance at national and sub-national levels. Together with the existence of appropriate immunization policies, the analysis of granular, timely, good quality data on coverage and surveillance can help guide programmatic action. Since 2017, district level data are being reported to the global level by 141 member states. The collation and reporting of these data is time-consuming, and the quality is variable. Many countries do not have surveillance for diphtheria and for countries that do conduct surveillance, many countries lack laboratory capacity to diagnose diphtheria and therefore rely upon a clinical case definition. While WHO recommends a total of 6 doses of diphtheria-containing vaccine, 178 of 194 countries have not implemented booster doses which are required to combat waning immunity. Therefore, population immunity against diphtheria can be low despite good DTP3 coverage.

Opportunities to improve globally available data through a project called the WHO Immunization Information System (WIISE) was discussed. Understanding both numerators and denominators of populations, including potentially hidden and mobile populations, is necessary.

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There was discussion of expanding collaborations with other stakeholders and UN agencies such as the International Office of Migration for a multi-sectoral approach that could make use of ongoing population mobility mapping exercises. SAGE noted that using the data locally, in the country, is the first step, since that underlines the utility of data and results in improving the data quality. At local levels, the issue is often not the lack of data, but the lack of data analysis and use. Examples were provided on efforts to combine existing datasets and opportunities to use country data for risk prediction. VPD outbreaks expose gaps in vaccination coverage, surveillance, and policy implementation. Opportunities to improve immunization and to pre-empt outbreaks require data, investment in data, and broad collaborations from countries, regions, and the global level.