

## Summary of the October 2017 meeting of the Strategic Advisory Group of Experts on Immunization

The Strategic Advisory Group of Experts (SAGE) on Immunization<sup>1</sup> met on 17-19 October 2017 in Geneva, Switzerland.

### Polio eradication initiative

SAGE reviewed the progress of the Global Polio Eradication Initiative (GPEI) against its four objectives: 1) polio virus detection and interruption; 2) oral polio virus vaccine (OPV) withdrawal and inactivated poliovirus vaccine (IPV) introduction; 3) containment and global certification; and 4) transition planning.

As of 17 October 2017, there had been 6 reported cases of poliomyelitis due to wild polioviruses (WPV) during the previous 6 months, 3 in Afghanistan and 3 in Pakistan, compared with 13 cases during the comparable 6 months period in 2016.

The quality of surveillance and immunization campaigns has improved overall, especially in high risk populations. However, surveillance gaps exist due to inaccessibility in some parts of Borno State, Nigeria where the last WPV type 1 case was detected. Since the trivalent OPV (tOPV)- bivalent OPV (bOPV) switch, the vaccine-derived viruses in most OPV-using countries have disappeared. Six post-switch circulating vaccine derived polio virus type 2 (cVDPV2) outbreaks occurred in 4 countries (i.e. Pakistan, Syria, Nigeria (2), and Democratic Republic of Congo (2)).

SAGE expressed its concern over the waning mucosal immunity against type 2 poliovirus, and reiterated its recommendation from April 2017 that, in case of future co-circulation of WPV and cVDPV2, a country should administer at least 2 doses of monovalent oral poliovirus type 2 (mOPV2) before the next bOPV round. Also, countries should maintain high polio immunization coverage ( $\geq 90\%$  national and  $\geq 80\%$  in every district) to sustain population immunity against types 1 and 3, especially in high risk countries and sub-national high risk populations.

The IPV supply situation is expected to improve in 2018; all countries are expected to have access to IPV for their routine immunization programmes from the end of the first quarter of 2018.

To date, 4 countries have decided to move to a fractional IPV dose (fIPV) schedule in their routine immunization programmes (India, Sri Lanka, Bangladesh and Nepal). The 2 dose fIPV schedule (e.g. 6 and 10 weeks) provides better seroconversion than 1 full dose IPV and in the post-cessation era, the 2 fIPV doses (the first dose at or after 14 weeks, and the second dose at least 4 months after the first dose) will provide sufficient (above 90%) seroconversion. SAGE agreed that low-risk bOPV-using countries may adopt this schedule prior to global OPV cessation. In such cases, countries should continue bOPV in their routine schedule.

SAGE recommended that countries, which delayed the introduction of IPV or had a vaccine stock-out, should provide 1 full dose or 2 fIPV doses to all children who were missed as soon as supply becomes available.

SAGE reinforced the need for protocols for biocontainment in view of the recent incidents of breach of containment in 2 manufacturing facilities.

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<sup>1</sup> WHO Strategic Advisory Group of Experts (SAGE) on Immunization, available at <http://www.who.int/immunization/sage/en/index.html>, accessed October 2017.

## **Typhoid vaccines**

SAGE noted the continued high burden of typhoid fever and the alarming increase in antimicrobial resistance of *Salmonella* Typhi (*S. Typhi*) in low- and middle-income countries. SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of the available data, SAGE recommended the introduction of typhoid conjugate vaccine (TCV) for infants and children over 6 months of age as a single dose in typhoid endemic countries. Introduction of TCV should first be prioritized to countries with the highest burden of disease or a high burden of antimicrobial resistant *S. Typhi*. SAGE also recommended catch-up vaccination wherever feasible, with priority for catch-up in the youngest age groups (up to 15 years of age), depending on local epidemiology.

Typhoid vaccination is recommended in response to confirmed outbreaks of typhoid fever. Typhoid vaccination may be considered in humanitarian emergencies depending on risk assessment in the local setting.

Decisions on the preferred immunization strategy should be based on an analysis of disease burden, availability and quality of surveillance data, affordability, and operational feasibility. The experiences and impact of different vaccination strategies, as well as integration with water, sanitation and hygiene (WASH) or other interventions, should be monitored and documented in order to support a learning agenda for typhoid control.

SAGE highlighted the need for countries to strengthen the surveillance of typhoid fever, and to monitor the occurrence of antimicrobial resistant strains of *S. Typhi* in endemic and epidemic disease, before and after programmatic use of TCV.

Introduction of TCV should include post-licensure monitoring of effectiveness and robust monitoring of vaccine safety, including any potential risks in special population groups.

Priority should be given to further research to support TCV policy and introduction decisions. In particular, data will be needed on co-administration of TCV with routine childhood vaccines in typhoid-endemic countries, including yellow fever vaccine, meningococcal A conjugate vaccine, pneumococcal conjugate vaccine and Japanese encephalitis vaccine.

## **Pneumococcal conjugate vaccines (PCV)**

SAGE data on the optimal use of PCV with respect to dosing schedules (3p+0 and 2p+1), product differences (10-valent, PCV10, and 13-valent, PCV13 formulations), and use of catch up immunization. SAGE reviewed primary data reporting PCV impact on serotype specific immunogenicity, impact on nasopharyngeal (NP) carriage and on invasive pneumococcal disease (IPD), and modelled evidence on the incremental impact of catch up immunization.

### *Schedule Choice Recommendations*

Based on the evidence provided, SAGE concluded that both 2p+1 and 3p+0 schedules have a substantial impact on overall vaccine type disease. SAGE also concluded that 2p+1 has a desirable impact on serotype 1 (ST1) disease; more limited data on 3p+0 suggest an impact on ST1 disease from this schedule. Therefore, SAGE recommended administration of PCV in either a 2p+1 or a 3p+0 schedule starting as early as 6 weeks of age. SAGE recommended a minimum of 4 weeks and a maximum of 8 weeks intervals in the primary series for the 2p+1 schedule with a booster dose 9-18 months thereafter.

### *Product Choice Recommendations*

SAGE considered the latest evidence on serotype specific immunogenicity, and impact on nasopharyngeal carriage and disease endpoints for the two available PCV products. SAGE found that both vaccines have substantial impact against pneumonia, vaccine-type invasive disease and carriage. PCV13 may have additional benefit in settings where disease attributable to serotype 19A (ST19A) or serotype 6C (ST6C) is significant. Product switching for individual children is only acceptable if it is not possible to complete the primary series or booster with the original product.

### *Catch Up Recommendations*

Modelled data indicate that catch up in those <5 years of age will accelerate PCV impact on disease burden regardless of transmission intensity, however the efficiency of catch-up (cases prevented per doses delivered) varies by age strata, and that variation depends on the transmission intensity of the setting. Catch-up vaccination in those <5 years of age should also be considered in humanitarian emergency settings, for possible control of outbreaks, and for improved disease control in low PCV coverage settings. Vaccination in children >5 years may be useful for outbreaks that include older children and adults.

### *Surveillance and Research Recommendations*

Based on current evidence gaps, SAGE highlighted surveillance and research priorities to guide future policy revisions, which included the following: sustained high quality, sentinel and population-based surveillance for pneumococcal disease and carriage, ideally indefinitely but no shorter than 5 years following full PCV introduction in order to quantify long term impact and monitor serotype changes; establishment of serotype-specific immune correlates of protection against IPD; assessment of duration of protection; further assessment of dosing schedules and pneumococcal outbreak epidemiology, particularly epidemics of ST1 disease; PCV impact on antimicrobial resistance and on antibiotic use; and, a systematic analysis comparing 1 versus 2 dose catch up schedules.

## **Rabies vaccines**

SAGE systematically reviewed new evidence and programmatic experiences available on rabies immunization in humans and issued recommendations on pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) and rabies immunoglobulin (RIG) administration.

Using fractionated intradermal doses of the vaccine is a cost- saving, safe and effective in settings where intradermal vaccination allows for better use of dose vials. Shortened schedules for both PEP and PrEP were recommended.

PrEP makes administration of rabies immunoglobulin unnecessary after a bite. Accelerated PrEP regimens for all age groups of healthy individuals of the general population are either a 2-site (0.1 ml per site) ID regimen on days 0 and 7, or a 1-site (1 vial per site) intramuscular (IM) regimen on days 0 and 7. Special regimen apply to immunocompromised subjects.

PEP regimens administered intradermally (ID) are cost and dose-sparing, even in clinics with low patient throughput. Three PEP regimens have proven effective and are recommended depending on health service and patient needs. The IPC regimen: 2-site (0.1 ml per site) ID on days 0, 3 and 7; the Essen regimen: 1-site (1 vial per site) IM on days 0, 3, 7 and 14-28, unrestricted for all populations,

and Zagreb regimen: on 2-sites IM on day 0 and 1-site IM on days 7 and 21. Patients with documented immunodeficiency should be evaluated on a case-by-case basis.

There is no contraindication for use of PrEP and PEP, including for children, pregnant women, immunocompromised individuals and those receiving chloroquine or hydroxychloroquine. PrEP is indicated for individuals exposed by virtue of occupation, place of residence or travel. PrEP can be considered in populations with very high bite incidence above 5% annually and should be based on assessment of the local context and epidemiology.

New evidence from Cambodia and Tanzania shows that when thorough wound washing and prompt administration of vaccine is provided to category III bite victims, 99% survive. Trials and programmatic experience indicate that infiltration of RIG in and around the wound neutralizes rabies virus within hours and RIG administered intramuscularly distant to the wound is of limited value. These recommendations will allow RIG dose sparing by calculating the maximum dose based on body weight, but injecting only the volume needed to infiltrate the wound(s). Guidance for aseptic use of remaining RIG will need to be developed. Equine RIG (eRIG) is clinically equivalent to human RIG (hRIG) and skin testing prior to its administration should be abandoned.

In summary, SAGE recommended these updates that allow a more efficient, prudent and equitable use of human rabies biologics, particularly in endemic settings.

### **Bacille Calmette-Guérin (BCG)**

SAGE was presented with epidemiological data, currently used schedules, safety and efficacy of BCG vaccines against tuberculosis (TB) and leprosy.

SAGE reaffirmed the current recommendation of universal birth dose vaccination with BCG in high incidence TB settings and expanded this to include high burden leprosy settings regardless of the TB incidence. SAGE further stressed that BCG vaccination together with hepatitis B vaccination should be administered as soon as possible after birth, ideally within 24 hours and that it is safe to do so.

SAGE recommended that countries with a low incidence of TB and leprosy may choose to selectively vaccinate neonates in recognized groups at high risk of developing disease. SAGE reiterated that BCG re-vaccination is of little additional benefit and is, therefore, not recommended.

SAGE further stressed that BCG vaccination is contraindicated for human immunodeficiency virus (HIV)-infected persons and those with congenital cell-mediated or severe combined immunodeficiency, acquired immunodeficiency diseases syndrome and for patients or infants born to mothers receiving immunosuppressive therapy. However, SAGE considered that administration of BCG can be recommended if HIV-infected individuals have started anti-retroviral therapy (ART), are clinically well and immunologically stable (CD4% > 25% for children under 5 years or CD4 count ≥200 if age > 5 years), especially for those living in high incidence TB settings.

SAGE identified several topics for further research needs and emphasized the need for new vaccines against TB and leprosy for all age groups.

### **Global Vaccine Action Plan (GVAP): Progress report**

SAGE reviewed the draft assessment report and recommendations made by its Decade of Vaccines Working Group and noted that in 2016, while some progress was made towards the goals set out in the Global Vaccine Action Plan, multiple issues at all various levels threaten progress, and have the

potential to reverse hard-won gains, such as global economic uncertainty, conflicts and natural disasters, displacement and migration, and infectious disease outbreaks. Moreover, SAGE noted with concerning signs of the complacency and inadequate political commitment to immunization – as well as an insufficient appreciation of its power to achieve wider health and development objectives. Additional risks identified include growing levels of vaccine hesitancy, the worrying rise in vaccine stock outs disrupting access to vaccines and the continued underperformance of certain countries (the “outlier countries”) relative to others within their region. The full assessment report and recommendations are available at:

[http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/sage\\_assessment\\_reports/en/](http://www.who.int/immunization/global_vaccine_action_plan/sage_assessment_reports/en/)

The full meeting report will be published in the WHO Weekly Epidemiological Record on 1 December 2017. The meeting documents — including presentations and background readings — can be found at <http://www.who.int/immunization/sage/meetings/2017/october/en/>