Immunisation – a global issue
Update from SAGE

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Te Whare Wānanga o Tāmaki Makaurau

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The World Health Organization (WHO) has a mandate to provide leadership on global policies, standards and norms and to support member countries in applying these to national programs to improve health.

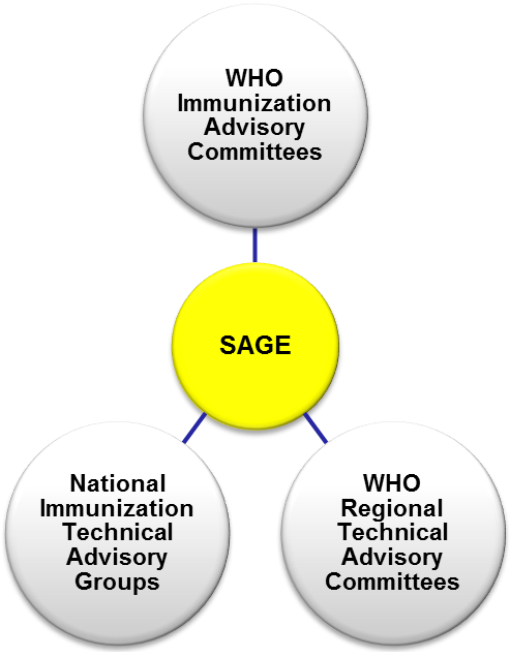
In alignment with this mandate, the Strategic Advisory Group of Experts (SAGE) on Immunization has been established in 1999 as the principal advisory group to the WHO for vaccines and immunization.

SAGE is comprised of 15 independent experts that meet twice a year to develop recommendations on global vaccine policies and strategies for vaccine-preventable diseases. Proceedings are open to partners as well as other observers and are preceded by a comprehensive review of current scientific evidence. The resulting evidence-based recommendations provide the basis for WHO vaccine position papers which inform country-level decision-making and program implementation. SAGE recommendations also assist partner organizations including the GAVI Alliance, non-profit organizations, and international professional associations.

WHO Advisory Bodies

- SAGE collaborates with global, regional and national advisory bodies

- **WHO Immunization Advisory Committees**
  Global safety, standards, practices, research
  - Global Advisory Committee on Vaccine Safety
  - Expert Committee on Biological Standardization
  - Initiative for Vaccine Research Advisory Committee
  - Immunization and Vaccines related Implementation Research Advisory Committee
  - Immunization Practices Advisory Committee
- **WHO Regional Technical Advisory Committees**
  Regional policies, strategies, priority-setting, monitoring
  6 WHO Regions: Africa, Americas Eastern Mediterranean, Europe, South-East Asia, Western Pacific
- **National Immunization Technical Advisory Groups**
  Country-level policies, strategies, priority-setting, program implementation, monitoring



World Health Organization

SAGE has made recent recommendations regarding target groups for seasonal influenza vaccination, rotavirus immunization schedules and use of single-dose inactivated hepatitis A vaccines. Planned vaccine-specific agenda items for include pandemic influenza vaccines, HPV vaccines, polio post-eradication IPV policies and varicella/herpes zoster vaccines. Thematic agenda items include optimizing immunization schedules, target product profiles, vaccine use for the immunocompromised and delayed and interrupted immunization schedules.

www.who.int/immunization/sage

Decision-making considerations

- Disease epidemiology
- Clinical characteristics
- Vaccine and immunization characteristics
- Economic considerations
- Health system opportunities and existence of, and interaction with, other intervention and control strategies
- Social, legal and ethical considerations

Quality of Evidence and Strength of Recommendations: GRADE

Quality of Evidence and Strength of Recommendations: GRADE

- Critical appraisal of scientific evidence is a necessary step in development of recommendations
- To assess the quality of evidence, SAGE uses broadly endorsed Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
- Rating method:
  - Quality of evidence – Levels of confidence in estimate of effect (very little confidence, limited confidence, moderately confident, very confident
  - Strength of recommendations – Strong (benefits do, or do not, outweigh risks and burdens) or Weak (benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks)

Global report: General updates Oct 2015

- Globally, 90% coverage with first dose of DTP containing vaccine but coverage with third dose only 86%.

- Vaccination coverage rates of newer vaccines, such as rotavirus and pneumococcal conjugate vaccine, remain very low (below 35% worldwide):
  - in addition to coverage issues this reflects the delayed vaccine introductions in particular in large countries.

Western Pacific Region (WPR)

- SAGE noted with concern, that although there is some progress towards elimination, the high incidence of measles was worrisome, with large-scale outbreaks ongoing in Vietnam, Malaysia, China and the Philippines

Global report

- Most unvaccinated infants in the world remain located in a few large underperforming countries. Data on missed opportunities, when provided to countries, could enhance country ownership and implementation of local solutions.

- 3 steps to close the immunization gaps:
  - Integrate immunization with other health services
  - Strengthen health systems so vaccination programmes can continue through crises
  - Ensure vaccines are accessible and affordable to all

Global report: General updates April 2016

- “WHO Vision and Mission” global report called for a stronger voice of the immunization community in communicating the benefits of vaccination to audiences beyond their primary focus, such as those dealing with reproductive, maternal, neonatal and child health, and health system strengthening.
- SAGE stressed the critical role of National Immunization Technical Advisory Groups(NITAGS) and applauded the reported progress. The importance of fostering exchanges between NITAGs was emphasized and SAGE requested a regular update on the number of established NITAGs.

WHO's Vision and Mission in Immunization and Vaccines: core role

http://www.who.int/immunization/sage/meetings/2015/october/3_WHO_Vision_Final_Draft_WVAP_11Sept.pdf?ua=1

Global report: General updates April 2016

- Approval of a vaccination coverage indicator under the child mortality target of the Sustainable Development Goals (SDGs) has not yet been obtained. SAGE urged WHO and countries to request an aspirational immunization indicator under the SDGs.
- Ensuring and sustaining immunization services disrupted by humanitarian crises is an ongoing concern. Despite major challenges, successful activities had been implemented in crisis-affected countries in the Eastern Mediterranean Region (EMR). SAGE expressed appreciation of these activities and stressed the need for continuous efforts in strengthening vaccination in humanitarian crises including further updating of field vaccination guides.
- The ongoing yellow fever (YF) outbreak in Angola and current YF vaccine supply constraints were noted with concern. As from 11 July 2016 an amendment to the International Health Regulations (IHR) will change the validity of the YF vaccination certificate from 10 years to the life of the person vaccinated, and will be legally binding for all Member States.

Global report: Regional updates April 2016

- **Western Pacific Region**
  - Steady progress towards the 8 goals of the regional framework for implementation of the GVAP, notably through strengthening of NITAGs.
  - WPRO and RTAG focus on private sector provision of vaccines and strengthening of routine immunization.
  - Setbacks with re-importation of measles causing several outbreaks in the region.
  - The current outbreak of polio due to circulating vaccine-derived poliovirus (cVDPV) in the Lao People's Democratic Republic exemplifies the importance of enhancing the quality and equity of immunization services and addressing community demand as well as vaccine hesitancy issues.

April 2016 SAGE meeting - Global report: General updates

- The WHO Research& Development (R&D) Blueprint aims at developing and implementing a roadmap for R&D preparedness for priority pathogens, and enabling roll-out of efficient emergency R&D responses. In this context, WHO is developing product profiles for potential Zika virus vaccines.
- SAGE suggested that experience with Ebola vaccine development be used to guide the development of vaccines against other priority emerging pathogens.
- Promising data are emerging from the Ebola vaccine trials. Pending regulatory approval, WHO is developing a country-based “Expanded Access Brigade” to facilitate use until an Ebola vaccine is licensed.
- Following the October 2015 recommendations from SAGE and the Malaria Policy Advisory Committee, a public call for expression of interest triggered responses from 10 countries to serve as settings for pilot implementation of RTS,S malaria vaccine; selection of countries to host these pilot projects is currently ongoing.
- Developments in the field of vaccine administration via microarray patches were outlined.WHO is working with developers, regulators, manufacturers and funders to clarify product development strategies.

Topics of interest

- Vaccine Specific
  - Varicella and Zoster
  - HPV
  - Pertussis
  - Meningococcal A
  - Ebola
  - Measles and rubella
  - Polio eradication
  - Dengue vaccine

- Subcommittee feedback
  - Vaccine Safety (GACVS)
  - Product Development (PDVAC)

- Service Delivery issues
  - Vaccine hesitancy
  - Administration of multiple injections in one visit
  - Reducing pain and distress on vaccination

VACCINE SPECIFIC

2014 SAGE meeting recommendations

April 2014: Varicella and Herpes Zoster Vaccine

Recommendations

- Routine childhood immunization could be considered in countries where disease has an important public health impact, causes substantial socio-economic burden and resources are sufficient to ensure ≥80% vaccine coverage

- Countries deciding to introduce varicella immunization should administer vaccination at 12-18 months with dose dependent on goal of programme.
- Other risk groups to consider: HIV-infected children or adults, ALL patients, subjects with defects in antibody production, and health-care workers

April 2014: Human Papillomavirus Vaccine

- SAGE concluded that immunological evidence was sufficient to conclude that a 2 dose prime-boost schedule (with a minimal interval of 6 months) was non-inferior in girls to a 3-dose schedule
- SAGE reiterated the importance of targeting HPV immunization for girls aged 9-13 years, prior to sexual debut
- Recommendations for bivalent and quadrivalent vaccine
  - 2-dose schedule with ≥6 month interval between doses for girls <15 years
  - If interval between 1st and 2nd dose is < 5 months, a 3rd dose should be given at least 6 month after 1st dose
  - 3-dose schedule remains for girls >15 years of age and immunocompromised individuals

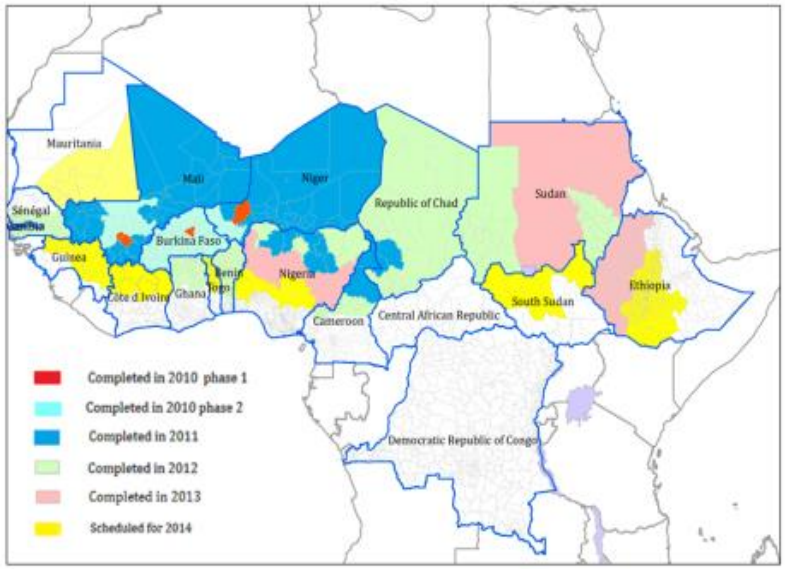
April 2014: Pertussis Vaccine

- The switch from wP to aP vaccines for primary infant immunization should only be considered if large numbers of doses can be included in national schedule
- Maternal immunization with aP during pregnancy is safe and highly effective in protecting infants; this does not extend to wP vaccines

Pertussis vaccination schedules April 2015

- Pertussis vaccination the main driver behind considering different schedules
- Emphasis on early start of pertussis immunization (6wks) and high coverage with primary course
- Current 3 dose primary course preferred option
- aP schedules need booster doses at 1- 6 yrs

MenA Conjugate Vaccine Progress 2011-2014



- 153 million people immunized
  - 1-29 year olds
  - MenAfriVac Campaigns in 12/26 countries
  - Benin, Burkina Faso, Cameroon, Chad, Ethiopia, The Gambia, Ghana, Mali, Niger, Nigeria, Senegal, Sudan

October 2014 SAGE meeting
Meningococcal A conjugate vaccine

- SAGE recommendations for routine immunization:
  - **One dose schedule at 9-18 months of age** (based on local programmatic & epidemiologic considerations)
  - If a child misses immunization at recommended age, should still receive single vaccination as early as possible thereafter
  - If compelling reason to immunize < 9 months of age, 2 dose schedule starting at 3 months of age (doses >=8 weeks apart)
  - Can be co-administered with other vaccines
- Safety in Pregnancy
  - Vaccination of pregnant women is safe
  - Pregnant women should be included in mass campaigns if in the target age group

2015, 90, 57–68 No. 8

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

20 FEBRUARY 2015, 90th YEAR / 20 FÉVRIER 2015, 90e ANNÉE
No. 8, 2015, 90, 57–68
http://www.who.int/wer

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Meningococcal A conjugate vaccine: updated guidance, February 2015

Background

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. A position paper on meningococcal vaccines was published in 2011 and its recommendations remain valid.[1] This update adds to the previous recommendations specifically concerning routine immunization of infants and young children in the African meningitis belt with meningococcal A conjugate vaccine, following discussions at the October 2014 SAGE meeting. Evidence presented at that meeting can be accessed at http://www.who.int/immunization/sage/meetings/2014/october/presentations_background_docs/en/.

Since publication of the meningococcal vaccine position paper, preventive mass

Vaccin antiméningococcique conjugué contre le sérogroupe A: orientations actualisées, février 2015

Informations générales

Conformément à son mandat, qui est de fournir des orientations aux États Membres sur les questions relatives aux politiques de santé, l'OMS publie régulièrement des notes de synthèse actualisées sur les vaccins et les associations vaccinales contre les maladies ayant des répercussions internationales en santé publique. Une note de synthèse sur les vaccins antiméningococciques a été publiée en 2011 et ses recommandations restent valables.[1] La présente actualisation complète les recommandations antérieures, en particulier pour la vaccination systématique des nourrissons et des jeunes enfants par le vaccin antiméningococcique conjugué contre le sérogroupe A dans la ceinture africaine de la méningite, suite aux discussions qui ont eu lieu lors de la réunion du SAGE en octobre 2014. Les données factuelles présentées à cette réunion peuvent être consultées sur: http://www.who.int/immunization/sage/meetings/2014/october/presentations_background_docs/en/.

Depuis la publication de la note de synthèse sur les vaccins antiméningococciques, des

Ebola vaccines April 2015

- Epidemic appears to be on the decline
- Early detection and isolation was important
- Incidence highest in adults
- 4 vaccine candidates from phase one trials
  - Four phase 2/3 studies underway
  - Individ RCT, cluster randomized, ring-vaccination design
  - May not obtain efficacy estimates due to epidemic waning

October 2015 SAGE meeting - Measles and rubella

- Global measles control milestones as well as regional measles and rubella elimination goals are off-track (except for the Americas).
- SAGE supported conduct of a midterm review of the global measles and rubella strategic plan to better understand why targets are missed and to propose measures that can accelerate progress.
- Recent outbreaks of measles in countries achieving high level control, or near elimination, demonstrate a bimodal age distribution, involving infants below the recommended age for vaccination, adolescents and young adults.

October 2015 SAGE meeting - Measles and rubella

SAGE concluded that evidence supports use of MCV before 9 months of age and recommends that infants from 6 months of age receive a dose of measles containing vaccine in the following circumstances:

1) during a measles outbreak as part of intensified service delivery;

2) during SIAs in settings where risk of measles among infants remains high (e.g., endemic countries experiencing regular outbreaks);

3) refugees, and populations in conflict zones or internally displaced;

4) individual children at high risk of contracting measles (e.g., contacts of known cases or in settings with increased risk of exposure during outbreaks such as day care);

5) infants travelling to countries experiencing measles outbreaks;

6) infants known to be HIV positive.

Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age. Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formulations in children <1 year.

October 2015 SAGE/MPAC meeting - RTS,S/AS01 malaria vaccine

- Estimated 214 million new episodes of clinical malaria will have occurred during 2015, with 438 000 deaths. Most cases and deaths occur in Sub-Saharan Africa.
- Substantial reduction in the last 15 years (over 50% for global malaria mortality in children under 5 years of age) mainly due to improved investments in malaria control that have facilitated access to insecticides-treated nets, effective anti-malaria medicines and other tools.
- Given increasing problem of multi-drug resistance and insecticide resistance, new tools to combat malaria are needed
- Malaria vaccine RTS,S (Mosquirix) = recombinant vaccine, engineered using genes from the outer protein of the Plasmodium falciparum malaria parasite and a portion of a hepatitis B virus (adjuvanted)

October 2015 SAGE/MPAC meeting - RTS,S/AS01 malaria vaccine

- A pivotal Phase 3 clinical trial of RTS,S/AS01 has been completed involving approximately 15,000 infants and young children in 7 sub-Saharan African countries with a range of low to high malaria transmission settings.
- The trial showed that there was moderate but important protection against clinical malaria after 3 doses that waned substantially by 18 months. Protection was partially restored by a fourth RTS,S dose, given 18 months after the third dose.
- The group receiving 4 doses of malaria vaccine experienced less clinical and severe malaria than those receiving 3 doses.

Vaccine efficacy against severe malaria by time interval

5-17 months	3-dose schedule	4-dose schedule
Study End	**-2.2** (-31.3, 20.4)	**31.5** (9.3, 48.3)

6-12 weeks	3-dose schedule	4-dose schedule
Study End	**16.0** (-14.5, 38.4)	**20.5** (-9.8, 42.5)

October 2015 SAGE/MPAC meeting - RTS,S/AS01 malaria vaccine

- To address how best to ensure that 4 doses of malaria vaccine can be given between 5 to 27 months of age, SAGE/MPAC recommend evaluation of RTS,S in staged pilot implementations, taking in to consideration various knowledge gaps before wider country level introduction can be considered.

- Other questions that should be addressed as part of the pilot implementation include:
  - The extent to which RTS,S vaccination impacts mortality. This could not be adequately assessed in the Phase 3 trial due to the very low overall mortality in the trial setting;
  - Whether the excess cases of meningitis and cerebral malaria, identified during the Phase 3 trial are causally related to RTS,S vaccination.

April 2016 SAGE meeting - Polio eradication

- Withdrawal of type 2 oral polio vaccine (OPV2) should proceed in April 2016 through a globally synchronised switch from trivalent to bivalent OPV).
- SAGE confirmed that the switch should proceed, despite IPV supply constraints, because IPV will be primarily a risk mitigation tool to reduce the risk of paralysis if a type 2 vaccine-derived poliovirus (VDPV2) emerges post-switch.
  - However, use of IPV does not reduce the risk of VDPV emergence.
  - Furthermore, should a VDPV2 emerge post-switch, stockpiles of monovalent OPV2 (mOPV2) and IPV are available to be distributed to countries in need.
- To promote dose-sparing, SAGE encouraged countries to evaluate the cost-benefits, trade-offs and programmatic feasibility associated with providing IPV in a 2-dose fractional intra-dermal dose schedule, e.g. at 6 and 14 weeks, in lieu of a single intramuscular dose at 14 weeks.

April 2016 SAGE meeting - Polio eradication

- SAGE reiterated its concern over the global IPV supply shortage, which will likely persist into 2017/18.
  - SAGE urged that IPV suppliers make best efforts to fulfil their commitment to supply IPV, accommodate the needs of the programme (e.g. supplying more vaccine in 1-dose or 5-dose vials to reduce wastage).
  - SAGE requested that WHO address concerns of countries affected by the IPV supply situation via frequent and clear communications and providing technical support.
  - It also requested the Working Group to evaluate options for catch-up vaccination for cohorts born after 1 May 2016 in countries where IPV introduction will be delayed or regular supply disrupted.

April 2016 SAGE meeting - Polio eradication

- Significant progress has been made towards eliminating wild poliovirus (WPV) in Afghanistan and Pakistan with improved access, coordination and operations. SAGE noted the importance of the environmental sampling efforts in these countries.

- There has been progress in eliminating persistent VDPV2 in Pakistan and Nigeria with no case since May 2015. Over the last six months there have been VDPV2 outbreaks in Myanmar and Guinea and one VDPV2 case in the Democratic Republic of Congo (DRC). SAGE recommended that GPEI should ensure high quality supplementary immunization activities (SIAs) in Guinea and DRC and to intensify programme surveillance in these countries, and in Sierra Leone and Liberia as they recover from the Ebola epidemic.

April 2016 SAGE meeting - Dengue vaccine

- Worldwide, dengue is the most extensively spread mosquito-borne viral infection. In the last 60 years, the incidence of clinical dengue cases has increased 30-fold. 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% respectively.

- It is caused by 4 related viruses (DENV 1-4).

- The first dengue vaccine, CYD-TDV (Dengvaxia®), has been licensed by several dengue-endemic countries in Asia and Latin America for use in persons aged 9–45 or 9–60 years.

April 2016 SAGE meeting - Dengue vaccine

- 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 dose among 9–16 year-olds, using data pooled from both trials, was 65.6% (95% CI 60.7–69.9).
  - The sub-group benefit profile is complex: vaccine efficacy varied by infecting serotype (higher protection against serotypes 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 notably serostatus at the time of vaccination (higher protection in participants who had already been exposed to dengue virus).
  - Some level of protection was seen even after the first dose.
- In children 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. No other safety signal has been identified
  - The biologic mechanism behind this increased risk is currently not understood but may be related to naïve vaccine serostatus and/or age.
- Comparative mathematical modelling evaluations of the potential public health impact of CYD-TDV introduction:
  - In high transmission settings, the introduction of routine CYD-TDV vaccination in early adolescence could reduce dengue hospitalizations by 10%-30% over a 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 limited protective effect.

April 2016 SAGE meeting - Dengue vaccine

- SAGE recommended that 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 where seroprevalence is below 50% in the targeted age group.
- 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.
- When CYD-TDV is introduced it should be administered as a 3-dose series given as a 0/6/12 month schedule. Because of the prolonged duration of the immunization schedule and to enable better outcome monitoring, countries should have systems in place for tracking vaccination.
  - additional evidence is needed to identify minimal and maximal intervals between doses and determine whether simplified schedules may elicit equivalent or better protection. In particular, 1 or 2 dose initial schedules with or without later boosting should be evaluated.

April 2016 SAGE meeting - Dengue vaccine

- Because of the safety signal of increased risk of hospitalized and severe dengue identified in the 2–5 year age group, CYD-TDV not recommended for use in children <9 years of age, consistent with current labelling.
- Target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular age groups. For highly endemic settings (e.g. seroprevalence at 9 years of age of approximately 90% or greater), 9 years of age is projected to maximize impact. In settings with seroprevalence at 9 years below 90% (but above 50%), 11–14 years of age may be preferable.
- CYD-TDV has not been studied as an intervention for dengue outbreak control. Vaccination is not expected to impact the course of an ongoing outbreak. Any use of the vaccine during an outbreak should only be done in areas that meet the recommended criteria for routine vaccine introduction.

April 2016 SAGE meeting - Dengue vaccine

- Important research and implementation questions remain.
  - Research to better understand options for reduced or condensed dosing schedules, and safety in pregnant women are high priorities.
  - Epidemiologic metrics based on high-quality age-stratified surveillance are needed to infer likely seroprevalence by age in order to target vaccination efforts.
  - Phase 4 studies on vaccine effectiveness by dose, duration of protection, and long-term impact are also priorities.
  - SAGE noted that using surveillance data to monitor population impact of a vaccination programme may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact.
  - Long-term monitoring for severe dengue, in particular in seronegative vaccinated subjects, should be done in selected areas.

- Surveillance should be strengthened, particularly for emerging infections with clinical similarities to dengue, such as Zika virus, arising in areas of the world where data are scarce or absent. Use of harmonized case definitions is encouraged to enhance data sharing and comparability across regions.

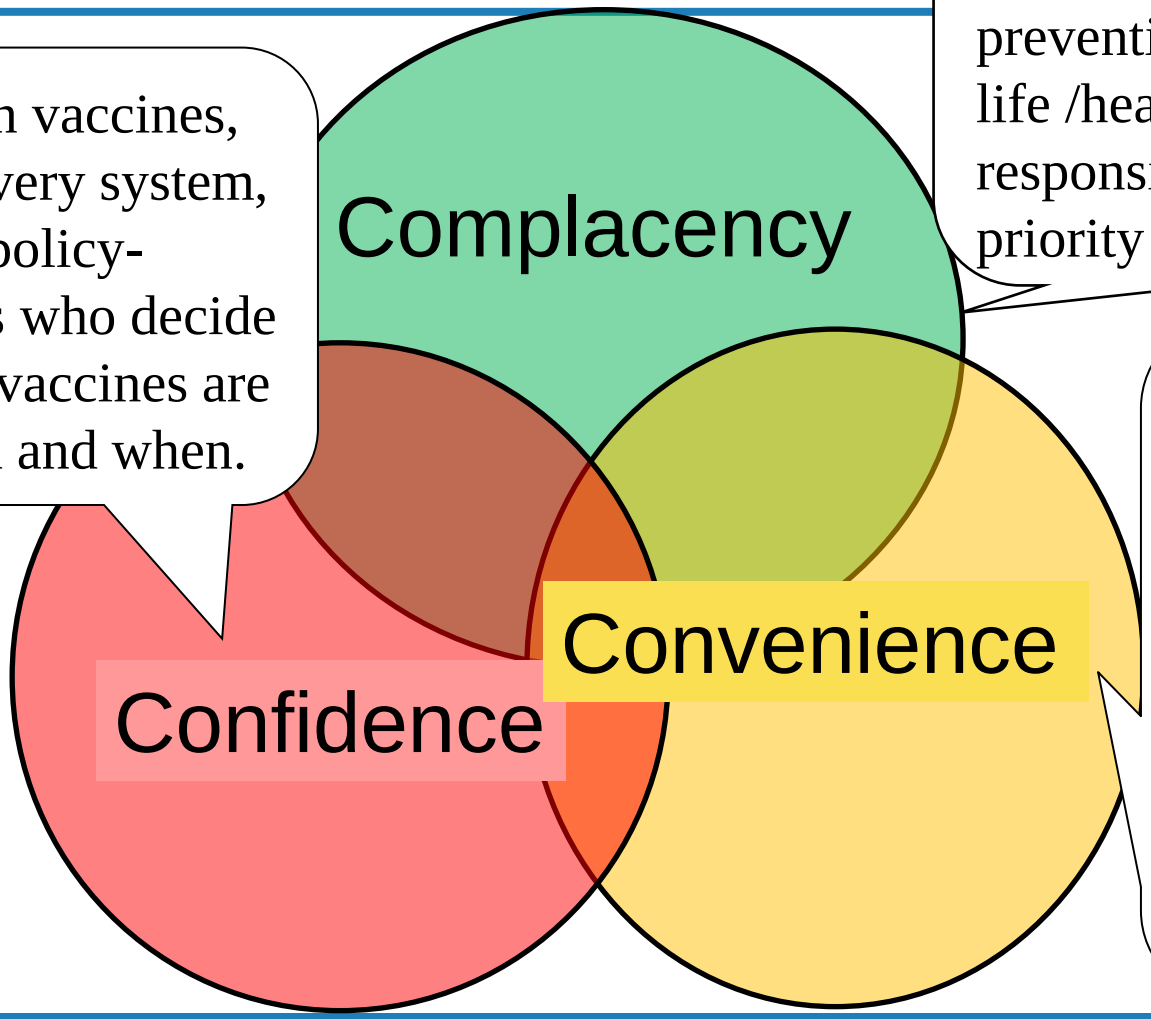
SERVICE DELIVERY ISSUES

October 2014 SAGE meeting
Vaccine Hesitancy Definition

- SAGE endorsed the working group definition of hesitancy:
  - Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccination services
  - Vaccine hesitancy is complex and context specific varying across time, place and vaccines
  - Includes factors such as complacency, convenience and confidence

- Vaccine can be described by a matrix of contextual influences, individual/social influences, and vaccine and vaccination-specific issues

Vaccine Hesitancy Model



Perceived risk of VPD low; vaccination not deemed a necessary preventive action. Other life /health responsibilities higher priority at time

Trust in vaccines, in delivery system, in the policy-makers who decide which vaccines are needed and when.

Physical access-availability, affordability, willingness to pay; geographical access, ability to understand (language, health literacy); appeal of immunization services

World Health Organization

http://www.who.int/immunization/sage/meetings/2014/october/3_SAGE_WG_Strategies_addressing_vaccine_hesitancy_2014.pdf

Administration of multiple injections in a single visit. April 2015

- Generally well tolerated
- No increase in reactogencity
- Positive provider recommendation very important

Recommendations to support:

- Administer IM where at all possible, better tolerability that SC
- Two in one limb – separated by approx. 2.5 cm

Reducing pain and distress at the time of vaccination April 2015

- Very common – 30 – 70% across all settings
- Can lead to vaccine hesitancy and needle phobias

Recommendations:

1. All ages: no aspiration, administer in order of increasing painfulness, proper positioning (holding < 3 yrs, sitting > 3 yrs), use of neutral words, avoid language that increases anxiety and/or promotes distrust
2. Infants/young children: breastfeeding during(or just before) vaccination, use rotavirus vaccine first,
3. Children < 6 yrs caregiver presence and distraction eg music
4. Adults; distraction with coughing or breath-holding

Priority research areas: studies on impact on acceptance and hesitancy, interventions for adolescents, in mass campaigns and school-base settings, documentation of which vaccines are more painful on injection

April 2016 SAGE meeting - Implementation of immunization in the context of Health Systems Strengthening and Universal Health Coverage

- A systems perspective remains the best way for immunization programmes to take forward their goals in a sustainable manner. The need to include a clear aspirational indicator for immunization within the SDG monitoring was discussed.
- Many new vaccines require special service delivery approaches due to their nature. HSS initiatives need to recognize such situations, which are becoming more common.
- Emergencies and crises are becoming common and complex in many countries. This requires a more in depth understanding of resilience of systems at national and subnational levels to ensure countries are able to absorb disruptions, or adapt/respond to changing needs on a continuous basis.

April 2016 SAGE meeting - Implementation of immunization in the context of Health Systems Strengthening and Universal Health Coverage

- The need to embed health systems thinking in every initiative and action, without losing goals so far attained, was appreciated by SAGE as a way forward.
- SAGE emphasized the importance of ensuring the visibility of immunization goals in planning HSS efforts. A system to generate data for evidence-based decision-making, with a focus on implementation research, is a route to achieving this.
- It was proposed that implementation research take up specific challenges that lead to strengthening of health systems.
- Improvement of immunization services within the broader health services should be a third dimension of vaccine programmes alongside safety and effectiveness, and this will need appropriate long term funding.
- SAGE recommended that WHO more actively promote further progress in this arena and that a preparatory team continue the dialogue and develop a more targeted agenda.

April 2016 SAGE meeting - Pre-empting and responding to vaccine supply shortages

- Various countries across regions and income groups have reported shortages of vaccines, sometimes causing critical disruptions of services. This has been reported for multiple vaccines, including yellow fever, BCG, DTP, acellular pertussis containing vaccines and IPV. Various essential medicines have also been in short supply in recent years.
- Countries have expressed their concerns to WHO and are requesting more information and solutions in order to mitigate the effects of current vaccine and drug shortages and prevent them in future.
- Access to timely and affordable supplies of vaccines is an integrated component of the Middle Income Countries (MIC) strategy, presented at SAGE in April 2015, and of Resolution 68.6 on the GVAP, adopted in May 2015 by the WHA. A resolution is currently being prepared for consideration at this year's WHA on "Addressing the global shortages of medicines".
- Reasons behind shortages are multiple and vary for different vaccines and markets. Several partners are active on these causes at global level, but most have a restrictive focus area, leaving some countries more at risk of shortages, notably self-procuring countries and particularly the self-procuring MICs.
- The lack of a global mechanism to capture information or provide guidance for all countries and all products limits the possibility to identify, assess and manage shortages.

April 2016 SAGE meeting - Pre-empting and responding to vaccine supply shortages

- The session generated extensive discussion; following are the main points:
  - Information collection and sharing was recognized as a major area for potential further investment.
  - The importance of taking into account and acting upon the multiple causes and dimension of shortages was emphasized.
  - The need to rationalize product and regulatory requirements was particularly stressed. It was suggested that regulators should meet to discuss how regulatory processes can become more coherent and flexible.
  - It was noted that in addition to new activities, long term strategies targeting vaccine supply security are important and should be continued.

- SAGE recommended that WHO could play a key role in setting up an “Exchange Forum”, helping to collect demand information from all Member States and to enhance dialogue between countries’ demand (including anticipation of schedule evolution and new introductions) and manufacturers’ supply availability and risks.

- SAGE proposed as immediate action to communicate effectively to countries on causes of shortages and current mitigation and long term activities. This would provide a necessary level of confidence in countries that the topic is not being overlooked, given the recognized impact of shortages on community level trust in immunization programmes.

April 2016 SAGE meeting - Missed opportunities for vaccination

- **A MOV occurs when a person eligible for vaccination, and with no valid contraindication, visits a health service facility and does not receive all of the recommended vaccines.**
- The number of MOV in some countries is huge, and globally the pooled prevalence of MOV was estimated at round 32% for children. With little effort or cost (compared with reaching children who have no access to the health system), ensuring that all visitors to health centres are vaccinated can have a major impact on the coverage of national immunization programmes.
- WHO has recently updated the protocol and tools for conducting MOV assessments, as well as the guidance for follow-up interventions. These components comprise: a Planning Guide outlining a 10-step process; a detailed MOV Assessment Protocol; an Interventions Handbook; and a Partner Coordination Framework to support the scale-up of the MOV strategy and amplify its impact.

April 2016 SAGE meeting - Missed opportunities for vaccination

- SAGE was presented with the MOV experiences from two regions (AFR and AMR)
- Reasons for MOV were mostly attributed to health-care workers (>60%), caregivers (27%) and health services (11%).
- Lack of integration of services was illustrated by the very high proportion of children attending for treatment who were not referred for vaccination. Related to this is the importance of vaccination records.
- A key feature of the MOV strategy is that data collection is designed to lead to action through the identification of locally appropriate solutions and the development of work plans to reduce MOV. To ensure sustainability these are accompanied by supervision and long-term impact monitoring of the use and impact of these tools.

April 2016 SAGE meeting - Missed opportunities for vaccination

- SAGE encouraged countries and partners to include interventions to reduce MOV in every HSS funding application and plan.
- SAGE recommended increasing the pace of development of electronic immunization registry/recall/reminder systems given the widespread adoption of mobile phones and evolution of mHealth technologies even in resource-limited settings, ensuring highest level of data protection.
- A key change in mind-set to address MOV could be to vaccinate children as a default response, and to treat every clinical presentation as a vaccination opportunity. Without a specific reason *not* to vaccinate (noting that lack of documentation is not a valid reason for not vaccinating), every child should be vaccinated.

References: Meeting of the Strategic Advisory Group of Experts on immunization, October 2014 – conclusions and recommendations. Weekly epidemiological record, 2014;50 (89):561-579. Available at http://www.who.int/wer and Sridhar, et al. A systematic literature review of missed opportunities for immunization in low- and middle-income countries. Vaccine 2014; 32:6870–6879

April 2016 SAGE meeting - Second-Year-of-Life immunization platform

- Information was presented to SAGE on creating guidance for national programmes to establish routine healthy child visits during the second year of life (2YL).
- There are multiple benefits to establishing a strong platform for immunization and other interventions in the 2YL:
  - It provides an additional routine contact to deliver primary vaccination doses, booster doses (e.g. DTP) and second doses (e.g. measles-containing vaccine (MCV2) For some newer vaccines some schedule options include a routine dose in the 2YL.
  - A strong platform in the 2YL provides an important opportunity for children to complete their vaccination schedule and to improve overall coverage.
  - A routine visit creates opportunities to integrate multiple other evidence-based health interventions, and reinforces good Primary Health Care (PHC) practice.

April 2016 SAGE meeting - Second-Year-of-Life immunization platform

- The global landscape analysis and literature review :
  - While many countries have introduced a 2YL visit, there is a large vaccination drop-out for doses given in the first year of life.
  - Missed opportunities for catch-up are a major cause of lower 2YL coverage.
  - Frequently vaccines are given at different times during the 2YL, and other health interventions are poorly integrated with the vaccination visit
  - SAGE emphasised that measures should be taken to ensure that health-care services were also developed to accommodate catch-up doses at other ages when opportunities arose through health-care contact.
- SAGE endorsed the development of this guidance, noting that this work is strongly supportive of a comprehensive PHC approach with continuum of care, ensuring that the immunization service requirements are firmly embedded into a broader delivery of health services appropriate for this age group.
  - The increasing complexity of the schedule requires better guidance to health workers on how to decide on eligibility for vaccines, especially for children who missed earlier doses.
  - Countries should be supported to develop easy-to-understand job-aids or decision flow-charts to deal with such events, helping the health worker to make appropriate decisions.

SAGE SUBCOMMITTEES

Global Advisory Committee on Vaccine Safety (GACVS) April 2015

- Safety monitoring is frequently the weakest piece of immunization programs
- Global Vaccine Safety Blueprint being implemented
  - Increased capacity for vaccine pharmacovigilance in several Asian and Latin American countries, priority effort starting in Africa
- Criteria for assessing websites with vaccine safety info wrt credibility, content , accessibility and design
- Preparedness for safety monitoring of new vaccines: malaria, dengue and Ebola virus

April 2016 SAGE meeting – Report of the Global Advisory Committee on Vaccine Safety (GACVS)

- SAGE noted the continuing attention to safety concerns related to human papilloma virus (HPV) vaccines and was reassured that none of the new issues altered the GACVS assessment of the safety of HPV vaccines.
  - Given the substantial amount of accumulated experience and ongoing pharmacovigilance efforts that GACVS continues to stress, the main challenge is communicating the excellent safety profile of HPV.

- SAGE was particularly interested in anxiety-related clusters, especially the body of evidence emerging on their occurrence and potential severe impact on related immunization programmes.
  - GACVS has established a working group to further develop evidence-based prevention and intervention strategies. Systematic reviews are in progress to examine anxiety clusters and their handling.

- SAGE commented on the safety signal detection from passive surveillance data as conducted by the Uppsala Monitoring Centre (UMC). SAGE was concerned that these signals are not undergoing peer review and concurred on the need to increase collaboration in a strong review process.
  - Since most of the vaccine-related data in the UMC database come from a smaller group of high income countries, SAGE urged that efforts be pursued to enhance AEFI reporting worldwide.

Product Development for Vaccine Advisory Committee (PDVAC) April 2015

- Jordan report : 110 pathogens with ongoing vaccine research and development as of 2012
- Prioritised: unmet public health need, changes of a product emerging within 5-10 yrs, role for WHO in advancing produce development for low and middle income countries
  - RSV
  - Gp A and B streptococcal (GAS, GBS)
  - E coli, shigella and norovirus
- Early stage vaccine development eg
  - Ebola
  - Monovalent oral polio vaccine
  - Forward looking framework on emergency vaccine development

April 2016 SAGE meeting - Respiratory syncytial virus vaccine development pipeline

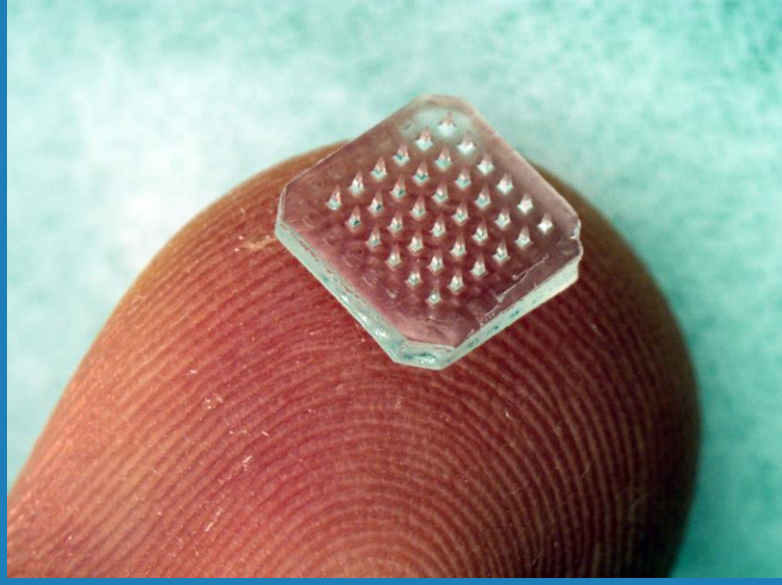
- Estimated 33.8 (95% CI 19.3–46.2) million episodes of respiratory syncytial virus (RSV)-associated acute lower respiratory infections (ALRI) occur annually in children aged <5 years (22% of ALRI episodes), with approximately 3.4 (2.8–4.3) million episodes representing severe RSV-associated ALRI necessitating hospital admission. An estimated 66 000–199 000 children aged <5 years died from RSV-associated ALRI in 2005. 99% of these deaths occur in developing countries.

- The RSV vaccine and immunization pipeline consists of 3 main classes of products:
  - subunit vaccines mainly in development for maternal immunization;
  - live attenuated or recombinant viral vaccines for active paediatric vaccination;
  - long-acting monoclonal antibodies targeted for seasonal or birth dosing using a one-dose regimen.

- >60 candidate vaccines, mostly in pre-clinical development and 16 currently in clinical trials. Of these, one recombinant protein approach is undergoing clinical trial Phase 3 evaluation in pregnant women, and one long-acting monoclonal antibody (mAb) is now in Phase 2 testing.

April 2016 SAGE meeting -
Respiratory syncytial virus vaccine development pipeline

- SAGE asked for preparations to be made to support global policy-making for RSV maternal immunization as well as passive immunization with long-acting mAb and encouraged determination of prequalification pathways. SAGE emphasized the need to link maternal immunization platform strengthening with other vaccines along with preparations for potential country introductions of RSV vaccine. SAGE encouraged initiation of early discussions with financing bodies.
- SAGE confirmed that the generation of cost-effectiveness and impact data was a priority.
- SAGE recommended that the current critical 4–5 year interval should be used to systematically identify and fill gaps in evidence required from regulatory, prequalification and policy recommendation perspectives for RSV preventive interventions, including maternal immunization, passive immunization with long-acting mAb and paediatric immunization.
- SAGE recommended that WHO endorse the importance and ethical imperative of clinical trials in pregnant women for potentially life-saving interventions such as RSV vaccine (and future vaccines against other targets now in development, such as group B streptococcal disease).



Drugdelivery.chbe.gatech.edu

Microneedle patch for measles vaccination: cdc.gov

SAGE 2017-2018 meetings

Selected topics on the horizons

Cross-cutting

- GVAP monitoring of progress
- Use of vaccines in immunocompromised populations
- Strategies to reach older age groups
- Involvement of the private sector
- Strengthening NITAGs
- Maternal vaccination
- Emergency vaccine development
- Implementation policies

Vaccine specific

- Polio eradication
- Measles and rubella elimination
- Ebola
- Oral cholera vaccines
- Typhoid
- BCG
- Pneumococcal conjugate
- Rabies
- HPV
- Rotavirus
- RSV


THANK YOU!