What are the implications of the new SAGE recommendations for rotavirus vaccines?

**Countries which are PLANNING TO INTRODUCE rotavirus vaccine**

As part of your vaccine introduction plan and together with your NITAG, SELECT the immunization schedule with the greatest potential for preventing rotavirus-related disease and deaths. This includes review of:
- the actual ages at which each dose of rotavirus vaccine is given;
- the peak age of rotavirus gastroenteritis cases and deaths;
- the possible risks and benefits of choosing a schedule without age limitation, in terms of potential additional intussusception deaths and additional rotavirus deaths prevented.

**Countries which have ALREADY INTRODUCED rotavirus vaccine**

Review progress of your introduction plan with your NITAG and ASSESS whether or not the removal of age restrictions would prevent additional rotavirus-related disease and deaths. This includes review of:
- the actual ages at which each dose of rotavirus vaccine is given;
- the peak age of rotavirus gastroenteritis cases and deaths;
- the possible risks and benefits of removing age limitations in the schedule in terms of potential additional intussusception deaths and additional rotavirus deaths prevented.

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**ROTAVIRUS VACCINE SCHEDULES**

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) reviewed new evidence that afforded an opportunity to avert additional deaths from rotavirus disease, including systematic reviews of rotavirus disease burden and effectiveness of different immunization schedules, improved estimates of the benefits in different epidemiological settings, and additional data on the risk of intussusception after rotavirus vaccination. SAGE was informed by separate reviews by both the Global Advisory Committee on Vaccine Safety and the Immunization Practice Advisory Committee.

The risk benefit analysis continues to favour early immunization but the current age restrictions for the first dose (<15 weeks) and last dose (<32 weeks) are preventing vaccination of many vulnerable children.

By removing the age restrictions, programmes will be able to immunize children who are currently excluded from the benefits of rotavirus vaccines and this is likely to include some of the children most vulnerable to severe rotavirus disease. Many thousands more deaths would be averted, but with the possibility of a small additional increase in intussusception cases.

SAGE also noted that in view of the age distribution of rotavirus disease, providing rotavirus vaccine to children older than 24 months of age will be of little benefit.

Considering the above, SAGE continues to recommend that the first dose of rotavirus vaccine be administered along with DTP, as soon as possible after 6 weeks of age as this maximizes protection.

SAGE recognized that countries have different burdens of disease and may or may not have introduced rotavirus vaccines. For this reason, countries should develop their own plans for how the removal of age restrictions on vaccine administration can be introduced in a manner that supports existing programmes.

SAGE encouraged all countries to establish or strengthen post-marketing surveillance which should focus on documenting any intussusception cases.

SAGE also stressed that vaccination is a dynamic field that will always be challenged by new data.

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**Plan to expand the benefits of rotavirus vaccines**

Enhance capacity to further assess danger signs that mean a sick baby should be brought to medical attention. This should focus on documenting any cases of intussusception.

Establish or strengthen post-marketing surveillance. This should focus on documenting any cases of intussusception.

Do most children receive their pentavalent or rotavirus vaccines doses by the recommended ages?

YES

- Deliver rotavirus vaccination at 6 weeks of age or soon after with pentavalent vaccine, even if delayed
- Monitor regularly to ensure vaccine doses are given on time and high vaccination coverage is achieved

NO

- Deliver rotavirus vaccine with pentavalent vaccine, even if delayed
- AND develop a plan to ensure vaccine doses are given on time and high vaccination coverage is achieved

Inform relevant health care staff that although the benefits outweigh the risks, a small potential risk of intussusception after rotavirus vaccination remains and ensure that caregivers are adequately counselled on how to recognize the danger signs that mean a sick baby should be brought to medical attention immediately.

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Immunizing children against rotavirus:
Making the most of every contact

To maximize its impact, rotavirus vaccine has to be given before Rotavirus Gastro-Enteritis (RVGE) occurs.

Protection of children through vaccination before RVGE cases occur depends on both the actual age at which each dose is given and on rotavirus vaccine coverage.

It is critical to administer each dose of vaccine at the recommended age.

Rotavirus vaccine coverage needs to be high, especially among children at higher risk of rotavirus death.

The expected benefits of rotavirus vaccine (in terms of rotavirus deaths averted) outweigh the potential risks (intussusception deaths associated with rotavirus vaccine).

### Albania

**ABOUT THIS LEAFLET**

Countries should develop their own plans on how rotavirus vaccine can be introduced in a manner that strengthens existing immunization programmes.

To stimulate and assist this process at national level, this leaflet contains information available at the global level together with estimates generated by various models. However, it is important that the information in this leaflet is enriched by and checked against other locally relevant data, and that NITAG members, decision makers at the national immunization programme and other key stakeholders review and discuss these data together with any other available evidence.

Additional information is available at:
- www.vaccine-schedules.com

These data do not constitute official WHO estimates. Estimates are correct as of: 3rd June 2013
1. To maximize its impact rotavirus vaccine has to be given before RVGE occurs.

Rotavirus vaccine helps to prevent a leading cause of severe diarrhoea in children (c. 40% of hospitalizations in children aged <5 years globally). It is estimated that nearly all children will be exposed to rotavirus before age 5, regardless of where they are born. Children in low-income countries may acquire the infection early during the first year of life. For Albania, this age distribution was based on a global literature review and regression analysis using data from United Kingdom, France, Israel, Italy, Kyrgyzstan, Russia, Armenia, Azerbaijan, Georgia, Moldova, Tajikistan, Ukraine, Uzbekistan. Source: Sanderson 2012

2. It is critical to administer each dose of vaccine at the recommended age and to achieve high coverage

Vaccination should be scheduled as early as possible. This is especially important for rotavirus vaccine as many children will be exposed during the first months of life. Thus it is very important to ensure that each dose is given at the recommended age. If delay is beyond the recommended age, the vaccine may not be as effective. Vaccine coverage was based on household surveys (DHS/MICS) or a regression analysis in countries without a survey. Timeliness of vaccination was scaled to the 2011 estimates of DTP coverage as reported by WHO. Countries with surveys in the relevant WHO sub-region were: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Tajikistan. Source: Sanderson 2012

3. It is important to use regionally appropriate estimates of vaccine efficacy

The efficacy of the rotavirus vaccine against severe disease and hospitalisation has been found to be lower in Africa and Asia than in other parts of the world, so it is important to consider whether efficacy assumptions are regionally appropriate. Clinical trials have reported vaccine efficacy during the first and second year of life. This allows the duration of clinical protection to be estimated over time. A sigmoid shape is assumed. In Albania, modelling studies have used 97% efficacy against severe rotavirus disease (as a proxy for rotavirus mortality) based on studies conducted in other countries with a similar mortality profile. Source: Linhares, Lancet (Latin America, RV1)

4. Maximizing the benefits of rotavirus vaccine requires that each dose is given on at the recommended age and high coverage is achieved

The number of RVGE (rotavirus gastroenteritis) deaths prevented by vaccination is determined by: the age at which cases occur, coverage, timeliness of each dose, and vaccine efficacy (taking time since vaccination into account). If rotavirus vaccine is given at the same visits as doses of DTP/pentavalent vaccine, a model estimates that the numbers of cases represented by the blue shaded area shown above could be prevented by the vaccine. Rotavirus vaccine will prevent many but not all cases and deaths of RVGE, partly because the vaccine is not 100% effective, but partly because some children will get RVGE before they are vaccinated. Provision of the vaccine is also an opportunity to remind caregivers about other things they can do to prevent diarrhoea deaths, such as breast feeding, ORS, zinc etc.

5. The benefits of rotavirus vaccine (rotavirus deaths averted) outweigh the risks (rotavirus vaccine-related intussusception deaths)

In some countries (Australia, Mexico, Brazil) post-licensure data on intussusception (blockage of the bowel) associated with rotavirus vaccine (RVIS) suggest a low-level risk of RVIS of approximately 1-2 cases per 100,000 vaccinees. In other countries such as the US no increased risk has been documented to date, but there are insufficient data to exclude the possibility. All data available on RVIS are from vaccinees who received the 1st dose by 15 weeks of age and the last dose by 32 weeks of age. Thus there is a very limited basis for estimating RVIS risk when the 1st dose is given after 15 weeks of age. Natural intussusception rarely occurs before 3 months of age but the incidence increases ten-fold between 3 and 6 months of age. Health care staff should be aware of the possibility of an increased although very small risk of RVIS, and must be encouraged to strengthen the detection, reporting and investigation of intussusception cases.

6. The benefits of rotavirus vaccination continue to outweigh the risks after accounting for uncertainty in the calculations

Each dot on the chart above represents a different combination of possible model parameter values. The chart shows the result of 1000 possible combinations. The orange dots are for ‘unrestricted’ vaccination and the blue are for ‘restricted’ vaccination. SAGE, the principal advisory group to WHO on vaccination, has recommended that age restrictions be removed in settings with high rotavirus mortality to increase the potential number of lives that could be saved by the vaccine. Note the different scales on the two axes.