

Candidate rotavirus vaccine recommendations for consideration by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization

1. *Overall recommendation*

WHO strongly recommends the inclusion of rotavirus vaccination into the national immunization programmes of all regions of the world.

In particular, countries where deaths among children due to diarrhoeal diseases account for $\geq 10\%$ of under-5 mortality rate should prioritize the introduction of rotavirus vaccination. Countries where deaths among children due to diarrhoeal diseases account for $< 10\%$ of under-5 mortality rate should also consider the introduction of rotavirus vaccination based on anticipated reduction in mortality and morbidity from diarrhoea, savings in health care costs, and the cost-effectiveness of vaccination.

Justification:

Rotavirus is a major cause of mortality in countries with high diarrhoeal disease mortality among children under five years of age. Every year, rotavirus gastroenteritis is estimated to cause approximately 527,000 (475,000-580,000) deaths globally among children < 5 years old. Most of these deaths occur in developing countries and 90% of the rotavirus-associated fatalities occur in Africa and Asia alone. Globally, > 2 million children are hospitalized each year for rotavirus infections. In a recent report of sentinel hospital-based rotavirus surveillance from 35 nations representing each of the six WHO regions between 2001 and 2008, an average of 40% (range= 34%-45%) of hospitalizations for diarrhea among children < 5 years old were attributable to rotavirus infection.

2. ***Detailed recommendation: Extrapolating efficacy data from a rotavirus vaccine study performed in one population to use of same rotavirus vaccine in other populations***

Efficacy/effectiveness data from a rotavirus vaccine study performed in a population from one of three under-5 mortality rate categories* can be extrapolated for use in populations in the same under-5 mortality rate category.

An oral live rotavirus vaccine rigorously evaluated for efficacy/effectiveness in a population in the high under-5 mortality rate category should be considered to have been assessed under the most challenging setting.

*Under-5 mortality rate is a key child health indicator compiled for all 193 of WHO Member States (see Table 1, Mortality and burden of disease http://www.who.int/whosis/whostat/EN_WHS08_Table1_Mort.pdf which comes from World Health Statistics 2008 available at http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf).

The 193 Member States may be ranked from highest to lowest according to under-5 mortality rate and divided into 4 quarters with the 4th quarter defined as the 25% of Member States with highest under-5 mortality; 3rd and 2nd quarters as the Member States with the subsequent under-5 mortality rates; and 1st quarter as the 25% of Member States with the lowest under-5 mortality. For the purpose of rotavirus vaccine recommendations, three categories of under-5 mortality rate have been defined as follows: high under-5 mortality rate = having mortality rates in the 4th quarter; intermediate under-5 mortality rate = having mortality rates in the 3rd quarter; and low under-5 mortality rate = having mortality rates in the 2nd or 1st quarters.

Justification:

Population and socio-economic parameters, as well as prevalence of other health conditions (e.g., malnutrition), that are likely to influence the performance of oral rotavirus vaccines are likely to be similar within the same under-5 mortality rate categories.

3. *Detailed recommendation: Need for bridging data to show noninferiority of new oral rotavirus vaccines*

Performing efficacy/effectiveness studies for oral rotavirus vaccines in each of the three under-5 mortality categories is encouraged since post-introduction vaccine studies suggest that different oral vaccines have variable effectiveness in different countries. Evidence of efficacy/ effectiveness in each of the three under-5 mortality categories could include bridging data (e.g., immunogenicity data), once appropriate criteria for such data have been developed.

Justification:

Oral rotavirus vaccines differ in antigenic composition, strain origin (human or animal), and presentation. Efficacy/effectiveness data may not be available for all oral rotavirus vaccines in all three under-5 mortality categories and performing such studies for each oral rotavirus vaccine in each under-5 mortality category may not be practical. Therefore, high priority should be placed on developing criteria for the nature and quality of bridging data (e.g., immunogenicity data) that are needed to demonstrate that new oral rotavirus vaccines are likely to lead to similar disease reduction which is non-inferior to already approved oral rotavirus vaccines without conducting efficacy/effectiveness evaluations of each new product in multiple settings.

4. *Detailed recommendation: Rotarix[®] immunization schedule*

When Rotarix[®] vaccine is used, a 3-dose schedule should be implemented for countries that have EPI visits scheduled at 6, 10, and 14 weeks of age while a 2-dose schedule may be used for countries that have EPI visits scheduled at 2 months and 4 months of age. A 3-dose rotavirus vaccine schedule is essential in any setting where RotaTeq[®] and Rotarix[®] vaccines are interchanged.

Justification:

Use of a 3-dose schedule is recommended because administering only 2 doses at EPI visits 1 and 2 (6 and 10 weeks of age) has not been demonstrated to be sufficiently immunogenic and efficacy data are not available. Administering 2 doses at EPI visits 2 and 3 (10 and 14 weeks of age) is not a desired option because this may result in incompletely vaccinated or unvaccinated children as a result of the vaccine's age restrictions and delayed presentation of children for vaccination. Furthermore, most countries with high rotavirus disease incidence or which have high under-5 mortality and thus which would particularly benefit from robust protection from rotavirus infection have 6, 10, 14 week EPI schedules. In addition to offering immunogenicity advantages, a 3-dose schedule is practical from a programmatic perspective as it matches the dosing of other EPI vaccines so staff training is straightforward.

5. Detailed recommendation: Maximum ages of first and last rotavirus vaccine doses

Data from the major efficacy trials of Rotarix[®] or RotaTeq[®] and from post-licensure monitoring should be used to recommend that the first dose of RotaTeq[®] or Rotarix[®] vaccine may be administered during the period of 6 weeks to 15 weeks of the child's age while the maximum age for administering the last dose of either vaccine may be at 8 months or 32 weeks of age. This recommendation should be made pending review and concurrence by the Global Advisory Committee on Vaccine Safety. High priority should be given to evaluating the benefit and safety of further expanding the recommended ages of vaccine administration in order to increase vaccine coverage and realize the full potential of rotavirus vaccination.

Justification:

Harmonization of the maximum ages for doses of the two vaccines would be unlikely to affect the safety and efficacy of the vaccines and would be programmatically advantageous. The maximum age for dose 1 in the major efficacy trials of RotaTeq[®] and Rotarix[®] differed by approximately 3 weeks (the RotaTeq[®] study used 6-12 weeks 0 days and the Rotarix[®] studies used 6-12 weeks 6 days or 6-14 weeks 6 days). In addition, because the Rotarix[®] series has only 2 doses of vaccine whereas the RotaTeq[®] series has 3 doses, the maximum age for the last dose for the Rotarix[®] was younger than that for the RotaTeq[®] trial (the RotaTeq[®] study administered the final dose at ≤ 32 weeks 0 days and the Rotarix[®] study administered the final dose at ≤24 weeks 6 days). When developing recommendations for the maximum ages for doses, the vaccine safety and efficacy data for each vaccine need to be considered as well as the effect that having the same or different maximum ages for the products would have on the ability of health care staff to follow the recommendations.

6. Detailed recommendation: Encouragement of sentinel surveillance for severe rotavirus gastroenteritis and of postmarketing surveillance for adverse events

Sentinel surveillance for severe rotavirus gastroenteritis should be in place prior to vaccine introduction in order to monitor vaccine impact but absence of such surveillance should not be an obstacle to introducing the vaccine. These sentinel surveillance platforms could also be used to evaluate postmarketing effectiveness of vaccine through case-control methods. In addition, as rotavirus vaccines are introduced in developing countries, postmarketing surveillance systems should be set up monitor possible vaccine adverse effects, including intussusception.

Justification:

Rotavirus disease surveillance programs are important to a) assess the incidence of severe rotavirus disease over time, b) to measure the effectiveness and impact of vaccination in reducing rotavirus morbidity and mortality, and c) to assess potential changes in rotavirus epidemiology and serotype distribution.

To ensure vaccine safety, postmarketing surveillance to monitor potential adverse events is encouraged. In December 2008, the Global Advisory Committee on Vaccine Safety (GACVS) reviewed additional new post-marketing safety data and stated that intussusception risk of the order of that which had been associated with Rotashield[®] can be ruled out with confidence but the available post-marketing surveillance data are still too few to rule out, with confidence, a risk of substantially lower magnitude. GACVS noted that it remains important to continue to accumulate postmarketing surveillance data, particularly as rotavirus vaccines are introduced into more countries.

Absence of disease or adverse event surveillance, however, should not be an obstacle to introducing rotavirus vaccine.