

## **Executive Summary**

### **Regarding Rotavirus Vaccines for April 2009 SAGE Meeting**

#### **Purpose of the document**

This document summarizes data available through March 2009, including unpublished data, which were reviewed by the Ad-hoc Group of Experts on Rotavirus Vaccines during January-March 2009. This summary includes the key points and evidence available that are most relevant and that provide the basis for the Ad-hoc Group's candidate recommendations on rotavirus vaccines for consideration by SAGE.

#### **Rotavirus epidemiology and rationale for rotavirus vaccines**

- Rotavirus is a major cause of severe gastroenteritis among young children. In developing countries, it is a major cause of under-5 year old mortality, accounting for up to 20% of all childhood deaths in countries with high diarrheal disease burden.
- In developing countries, first rotavirus infections usually occur between 6-9 months of age, and 80% occur among infants <1 year old.
- Developing countries often have year-round transmission, intense rotavirus exposure, and a diversity of circulating rotavirus strains.
- Each year, rotavirus causes >500,000 deaths worldwide among infants and very young children, with 90% of these deaths occurring in Africa and Asia alone.
- Worldwide, around 40% of all pediatric hospitalizations for diarrhea are attributable to rotavirus infections.
- Rotavirus vaccination mimics the protective first infection without causing illness, thus inducing strong and broad heterotypic immunity after repeated doses against future severe rotavirus infections.
- Rotavirus vaccines are considered to be the optimal strategy to decrease the morbidity and mortality due to rotavirus diarrhea.

#### **Rotavirus vaccine characteristics and efficacy**

- Rotarix<sup>®</sup> is a live vaccine containing the attenuated monovalent G1, P[8] human rotavirus strain, and is presently recommended to be orally administered in 2 doses beginning at 6 to 12 weeks of age, with an interval of at least 4 weeks between the first and second dose, and with series completion by 24 weeks of age.
- RotaTeq<sup>®</sup> is a live attenuated, bovine-human reassortant rotavirus vaccine containing the most common rotavirus antigens seen in humans (G1, G2, G3, G4, and P[8]), and is presently recommended to be orally administered in 3 doses, starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals, and the third dose administered before 32 weeks of age.
- Both vaccines have been demonstrated in clinical trials using European, North American, and South American populations to be 90-100% effective in preventing severe rotavirus gastroenteritis and 74-85%

effective in preventing rotavirus infection of any severity. Clinical trial data have shown both vaccines to have acceptable safety profiles.

- In a large randomized, placebo-controlled clinical trial conducted in Malawi (a high under-5 mortality rate country) and in South Africa (an intermediate under-5 mortality rate country), the efficacy of Rotarix<sup>®</sup> in preventing severe rotavirus gastroenteritis was 61% in the combined study populations (77% in South Africa and 50% in Malawi). However, despite the lower vaccine efficacy in Malawi, the number of severe rotavirus gastroenteritis episodes prevented by vaccination was found to be higher in Malawi (3.9 per 100 vaccinees) compared with South Africa (2.5 per 100 vaccinees).
- The seroconversion rates of serum IgA in immunogenicity studies conducted in Bangladesh and India with Rotarix<sup>®</sup> were observed to be higher than that seen in South Africa or Malawi.
- In clinical trials in several low or intermediate under-5 mortality rate Asian populations (Hong Kong, Taiwan, Singapore), Rotarix<sup>®</sup> was 96.5% in protecting against severe rotavirus gastroenteritis.
- In Nicaragua, an intermediate under-5 mortality rate South American country, RotaTeq<sup>®</sup> was 60% effective in preventing severe rotavirus gastroenteritis and was 78% effective against very severe rotavirus gastroenteritis in a post-licensure case-control study.
- Post-licensure impact evaluation studies of RotaTeq<sup>®</sup> have been performed in the United States. U.S. surveillance data demonstrate 80-90% declines in severe rotavirus gastroenteritis cases and in rotavirus positive laboratory tests during the 2008 post-licensure year compared with the pre-licensure period. In addition, a case-control study showed that vaccine effectiveness of 3 doses of RotaTeq<sup>®</sup> against rotavirus-related emergency department visits was 85-89% at a single, large US medical center.

### **Important considerations for recommendations regarding use of rotavirus vaccines**

- When evaluating rotavirus vaccines, important vaccine data include
  - public health impact against severe rotavirus gastroenteritis (i.e., episodes of severe rotavirus gastroenteritis prevented)
  - vaccine efficacy against severe rotavirus gastroenteritis
  - estimated number of deaths prevented.
- In developing countries with high rotavirus disease incidence, even moderate to low vaccine efficacy translates into a significant number of severe rotavirus gastroenteritis episodes prevented and into significant public health impact.
- 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. As a result, efficacy/effectiveness data from a rotavirus vaccine study performed in a population in one of three child under-5 mortality rate categories can be extrapolated for use in populations in the same under-5 mortality rate category.

- Countries where deaths among children due to diarrheal diseases account for  $\geq 10\%$  of under-5 mortality rate should prioritize the introduction of rotavirus vaccine into their routine immunization programs

#### **Cost-effectiveness of rotavirus vaccines**

- A cost-effectiveness study by Rheingans, et al. has shown that at a vaccine price of 5 USD per dose (range, 2-15 USD for a 2-dose Rotarix<sup>®</sup> vaccine series), rotavirus vaccine is very cost-effective across all income groups.
- A model by Atherly, et al. has shown that rotavirus vaccine health benefits would be greatest in Africa (180 DALYs averted per 1,000 vaccinated) and Southeast Asia (102 DALYs averted per 1,000 vaccinated). Rotavirus vaccine would prevent 2.4 million deaths among children in low-income countries, primarily in Southeast Asian and African countries during 2007-2025. In Africa and Asia alone, a vaccine with approximately 60% efficacy has the potential to save more than 1.5 million lives in the period from 2010 to 2025.

#### **Rotavirus vaccine safety, co-administration, and special populations**

- In December 2008, the Global Advisory Committee on Vaccine Safety (GACVS) reviewed additional new post-marketing safety data from the Rotarix<sup>®</sup> and RotaTeq<sup>®</sup> manufacturers, the Immunization Safety Office of the United States Centers for Disease Control and Prevention using data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD) surveillance systems, from the Australian National Immunization Program, and from the PAHO Network for Rotavirus Vaccines. Based on this data review, GACVS stated that intussusception risk of the order of that which had been associated with Rotashield<sup>®</sup> 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.
- Co-administration of either of these live, oral rotavirus vaccines with OPV and other routine childhood vaccinations has been shown to not interfere with the immunogenicity or safety of the routine EPI vaccines, including OPV. Seroconversion rates and antibody geometric mean concentrations to each of the polio serotypes were similar when co-administered with rotavirus vaccines. Although OPV does have an inhibitory effect on the rotavirus vaccine immune response for the first dose, the immune response to subsequent rotavirus vaccine doses are not affected by OPV co-administration.
- Rotarix<sup>®</sup> was demonstrated to be well-tolerated and immunogenic in a South Africa study of HIV-infected infants and infants born to HIV-infected women. Receipt of the rotavirus vaccine did not affect HIV clinical status of the infants.

- No difference in vaccine efficacy has been demonstrated between breastfed and non-breastfed infants.

### **Vaccine schedules and age restrictions**

- 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.
- The lower immune response when rotavirus vaccine dose 1 is administered at 6 weeks of age may be due to the impact of concomitant OPV administration and/or the presence of maternal antibodies.
- Most countries with high rotavirus disease incidence or which have high under-5 mortality rates (where children 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 Rotarix<sup>®</sup> schedule is practical from a programmatic perspective as it matches the dosing of other EPI vaccines, so staff training is straightforward.
- A 3-dose rotavirus vaccine schedule is essential in any setting where RotaTeq<sup>®</sup> and Rotarix<sup>®</sup> vaccines may be interchanged.
- The full potential of rotavirus vaccines can not be realized without expanding the maximum age of first and last vaccine dose administration. Pending review and concurrence by the Global Advisory Committee on Vaccine Safety, data from the major efficacy trials of Rotarix<sup>®</sup> or RotaTeq<sup>®</sup> and from post-licensure monitoring should be used to recommend that the first dose of RotaTeq<sup>®</sup> or Rotarix<sup>®</sup> vaccine may be administered during the period of 6 weeks to 15 weeks of the child's age while the maximum age for administration of the last dose of either vaccine is at 8 months or 32 weeks of age. 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.
- In the major efficacy trials of RotaTeq<sup>®</sup> and Rotarix<sup>®</sup>, the maximum age for dose 1 differed by approximately 3 weeks (the RotaTeq<sup>®</sup> study used 6-12 weeks 0 days and the Rotarix<sup>®</sup> studies used 6-12 weeks 6 days or 6-14 weeks 6 days).
- Because the Rotarix<sup>®</sup> series has only 2 doses of vaccine whereas the RotaTeq<sup>®</sup> series has 3 doses, the maximum age for the last dose for the Rotarix<sup>®</sup> was younger than that for the RotaTeq<sup>®</sup> trial (the RotaTeq<sup>®</sup> study administered the final dose at  $\leq 32$  weeks 0 days and the Rotarix<sup>®</sup> study administered the final dose at  $\leq 24$  weeks 6 days).

### **Rotavirus vaccine program implementation**

- The experiences of Latin American countries in implementing rotavirus vaccination programs demonstrate the need for precise plans to ensure technical and programmatic feasibility and financial sustainability.
- Cold-chain storage capacity needs, transportation issues, and understanding the timing of vaccine distribution were reported to have been critically important in the introduction of rotavirus vaccine in Latin America.
- Administrative adaptations such as redesigning vaccination cards, modifying immunization information systems for coverage monitoring, staff training, and implementing monitoring systems for events supposedly attributable to vaccination or immunization were required in advance.

### **Integrating rotavirus vaccines with diarrheal control and other health interventions**

- Rotavirus vaccination programs should be coordinated with other interventions to prevent and treat childhood diarrheal diseases, including improvement of hygiene and sanitation, and use of oral rehydration therapy, zinc supplementation, and other effective treatments recommended by WHO.
- Clear communication strategies are needed to prevent misconceptions regarding the efficacy of rotavirus vaccines in preventing other diarrheal diseases among children.

### **Rotavirus disease surveillance and vaccine post-marketing surveillance**

- 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. However, absence of such surveillance should not be an obstacle to introducing rotavirus vaccine.
- As rotavirus vaccines are introduced into developing countries, postmarketing surveillance systems should be set up to monitor possible vaccine adverse effects, including intussusception.