WHO Diarrhoeal and Enteric Vaccines Advisory Committee

7-9 October 2008
Geneva
Executive Summary for SAGE members

SAGE last reviewed rotavirus vaccines in November 2005, when the safety and efficacy data from the multinational industry were presented. At this time SAGE made several recommendations for rotavirus vaccines, including (i) the need for efficacy trials in representative populations in Africa and Asia, (ii) the need to obtain data on the co-administration of rotavirus vaccines with EPI vaccines, especially OPV, and (iii) that a phased approach of rotavirus vaccine introduction would be appropriate in regions where the successful phase III trials were undertaken.

Much information has been generated in the intervening three years. The IVR Diarrhoea and Enteric Vaccines Advisory Committee (DEVAC) has continued to monitor and review the progress with rotavirus vaccine research, including the phase III efficacy trials with the GSK monovalent human rotavirus vaccine in Malawi and South Africa, and a phase II safety and immunogenicity study in HIV-infected infants. In addition, IVR hosted an international consultative meeting in November 2007 to consider the ongoing phase III clinical trials in 5 countries in Africa and in 2 countries in Asia, and to provide guidance for evaluating and extrapolating the phase III clinical trial data on rotavirus vaccines and to direct the future research agenda.

DEVAC was requested to examine the current data and situation with rotavirus vaccines, including the most recent data from the pharmaceutical industry for the two rotavirus vaccines, Rotarix™, (GSK Biologicals) and the pentavalent reassortant vaccine RotaTeq® (Merck and Co), to ratify the outcomes of the various WHO meetings and to provide guidance for the SAGE deliberations in November 2008.

After oral presentations by representatives from PATH, CDC, GSK and Merck and extensive discussion of the issues, DEVAC members endorsed the following points:

- In response to the WHO recommendation, clinical trials of rotavirus vaccines in representative developing country populations in Asia and Africa, including those with high infant mortality, poor sanitary conditions, and high maternal HIV prevalence, are completed or nearing completion.
- Rotavirus vaccines do not interfere with the immune response to OPV vaccines.
- While there is some effect of OPV vaccines on rotavirus vaccine-induced antibody levels, the clinical significance of this interaction is uncertain, and best determined through efficacy studies. In Latin America, efficacy estimates from trials with and without concomitant OPV administration are similar.
- Rotarix vaccine was well tolerated and immunogenic in HIV-infected infants, and showed no safety concerns with respect to the HIV status of the child.
- An interim analysis of the study of Rotarix vaccine in South Africa demonstrated an efficacy comparable to that reported in Latin American populations, (83% in South Africa vs 82-85% in Latin America). These results are very encouraging about the potential for rotavirus vaccines to reduce the significant morbidity due to rotavirus diarrhea in the world's poorest children.

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1 SAGE conclusions and recommendations. Weekly Epid Record 2006; 81: 8
• The cost of the vaccines will impact the uptake and sustainability of rotavirus vaccine programs in country. Coordinated efforts with GAVI, the manufacturers, and other international partners are needed to ensure the affordability of rotavirus vaccines for lower and lower middle income countries.
Rotavirus vaccines (Moderated by Kathy Neuzil, PATH)

1. Introduction: Current WHO Position (K. Neuzil)

The current WHO position on rotavirus vaccines was reviewed. In 2006, two new rotavirus vaccines were licensed by the multi-national pharmaceutical industry (Rotarix™, GSK Biologicals, Belgium and RotaTeq®, Merck & Co, USA) based on demonstrated efficacy and safety in large-scale clinical trials conducted in Latin America, Europe and the USA. As reflected in the WHO position paper, WHO strongly recommends the inclusion of rotavirus vaccination in the national immunization schedules in countries of the WHO American and European Regions. WHO has pre-qualified both vaccines for use in those same regions where the clinical trials have demonstrated safety and efficacy.

Recognizing that live oral vaccines have not always worked well in the developing world, WHO SAGE was not in a position to recommend global inclusion of rotavirus vaccines. WHO recommended that clinical efficacy studies with these vaccines were needed in Africa and in Asia, where infant mortality due to rotavirus is highest. WHO estimates that approximately 527,000 (475,000 - 580,000) infants and young children die each year due to rotavirus infection, and that 85% of these deaths occur in these two regions. SAGE further noted that additional efficacy studies do not need to be very extensive but should be representative of the respective regions.

The Global Advisory Committee on Vaccine Safety (GACVS) has reviewed safety data generated in the Phase III efficacy studies with Rotarix® (GSK Bio) and RotaTeq® (Merck) in several meetings. GACVS noted that these vaccines do not show an association with increased risk of intussusception within the confines of the clinical trials, and recommended that post-marketing surveillance is needed in countries wishing to introduce rotavirus vaccines. GACVS further noted that the evidence for a causal association between RotaTeq® and Kawasaki’s Disease was not strong and that there was no reason for concern.

a. WHO Meeting on Rotavirus Vaccines: Evaluating clinical Trial Data and Guiding Future Research, November 2007, Atlanta, GA

The WHO convened a meeting of global, regional, and country-level opinion leaders in Atlanta, GA in November 2007 in order to provide guidance for evaluating and extrapolating the clinical trial data on rotavirus vaccines and to direct the future research.

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2 WHO Rotavirus Vaccine Position Paper. Weekly Epid Record 2007; 82:
3 WHO mortality figures for rotavirus. www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/
4 GACVS recommendations. Weekly Epid Record 2006; 81: 16 and Weekly Epid Record 2008; 83: 43-44
agenda for rotavirus vaccines. The conclusions from this meeting were reviewed (meeting report attached)\(^5\).

Given the tremendous toll that rotavirus exerts in developing countries, the general consensus emerging from the meeting was that an absolute point estimate of efficacy below which vaccine is deemed to have “failed” is not appropriate. Vaccines with lesser efficacy in the developing world as compared to the industrialized would lead to substantial public health benefits.

As clinical trials will be conducted in selected sites, criteria for extrapolation of results to other countries or regions were discussed. Extrapolating these data to populations where rotavirus has not been evaluated would best be based on parameters that predict the immunologic and nutritional status and gut ecology of the infant and local environment. It was agreed that geographic location is likely not the best predictor of these parameters. Examples of criteria that could be used to extrapolate data from one country to another include the established WHO mortality strata, socio-economic factors, or epidemiological factors.

Many factors may contribute to reduced efficacy of live oral rotavirus vaccines in developing country populations, including differences in the epidemiology of rotavirus disease; competing infections with other enteric agents; maternal antibodies/antibodies in breastmilk; concomitant administration of OPV; or factors that impair the host immune response (e.g., malnutrition, interfering microbes, other infections such as HIV/malaria/TB). While these factors are unlikely to be pragmatically addressed for the programmatic use of rotavirus vaccines, understanding their impact may be important for evaluating how to enhance vaccine take in the event that efficacy is found to be lower than desirable in the ongoing trials. Not all of these data would be needed prior to a recommendation, and post-licensure effectiveness studies will be additional important sources of information on public health benefit.

2. Update on GSK Rotarix™ vaccine (N. Begg, GSK Biologicals)

\(a.\) OPV co-administration

In an immunogenicity trial in Bangladesh, the sero-conversion rate among subjects vaccinated with Rotarix™ at the same time as OPV was not statistically significant when compared to subjects in whom the vaccine was given separated by a two week interval. Immunogenicity studies in South Africa where Rotarix™ was co-administered with OPV indicated no interference of the sero-conversion rates or the GMC titres of the polio vaccine serotypes. A subsequent placebo controlled efficacy study in 6 Latin American countries, where OPV was given at the same visits at Rotarix™, demonstrated an efficacy of 82% against severe rotavirus gastroenteritis (RV GE) and 88% against RV GE requiring hospitalization. This is very similar to the observed efficacy (85% for severe RV GE) in the previous pivotal efficacy trial in the same population, where the vaccine

was not co-administered with OPV. It can therefore be concluded that there is no interference between OPV and Rotarix™.

b. **Data from Asia**

While GSK has not conducted a phase 3 efficacy study in a GAVI-eligible Asian country, the company did conduct an efficacy study in Hong Kong, Taiwan and Singapore. This study has been accepted by the WHO prequalification team as evidence to allow extension of prequalification of Rotarix™ to Asia. Efficacy in this study against severe RV GE was 100% for the first year of follow up, and 96% during the second year.

The company has also conducted an immunogenicity study in India. The sero-conversion rate was 58.3%; the results of this study led to subsequent licensure of Rotarix™ in India.

c. **Heat stability**

In a study conducted in Thailand, the immunogenicity of Rotarix™ was assessed in subjects vaccinated with lyophilized vaccine which had been reconstituted then stored at 37°C for 7 days, compared to subjects vaccinated with a vaccine stored at 2 – 8°C then reconstituted. There was no difference in the sero-conversion rate in subjects given the vaccine stored at 37°C (87.8%) compared to subjects given the vaccine stored at 2 – 8°C (84.4%).

d. **HIV positive subjects**

In a safety study in South Africa, HIV positive infants were vaccinated with either Rotarix™ or placebo (50 per group). There was no difference between the two groups in terms of solicited symptoms, CD4 count or HIV viral load. The shedding profile in the vaccine group was the same as for healthy infant recipients of Rotarix™. In the 8 episodes of RV GE that occurred during the study, none were due to vaccine virus. The sero-conversion rate (57%) was very similar to sero-conversion rates previously observed in healthy subjects in the same population in South Africa.

e. **Liquid formulation**

A liquid formulation of Rotarix™ was submitted for WHO pre-qualification in February 2008. The liquid presentation is a tube, with a volume per dose of 16.6 cc (in boxes of 50). This will be available from 2009.

3. **Update on Merck RotaTeq vaccine (M. Ciarlet, Merck Research)**

a. **OPV co-administration**

Because oral poliovirus vaccine (OPV) is widely used in developing countries and incorporation of a rotavirus vaccine into the EPI schedule is desirable, a study involving 735 healthy Latin American infants was conducted to assess safety and immunogenicity
of RotaTeq® when this was administered concomitantly with OPV. Infants were randomized to receive either RotaTeq® concomitantly administered with OPV or RotaTeq® 2 weeks prior to administration of OPV at approximately 2-, 4-, and 6-months of age for each group (there was no OPV birth dose). The time intervals between doses for the two treatment groups were selected based on the viral replication data for these two vaccines (RotaTeq® may replicate for up to 2 weeks; although it peaks at Day 4-6 post-vaccination typically after the first dose; whereas OPV may replicate for up to 6 weeks post-vaccination) and thus, the staggered group reflected a true non-concomitant schedule.

RotaTeq® and OPV administered concomitantly did not interfere with the sero-protection rates or immune response to poliovirus types 1, 2, or 3 when compared to non-concomitant use. Although concomitant administration of OPV was shown to slightly reduce the immune response to RotaTeq®, there is currently no evidence that protection against severe rotavirus gastroenteritis would be affected, as the sero-conversion rates were still high (>93%) and consistent with rates observed in previous studies demonstrating high (98-100%) vaccine efficacy against severe rotavirus gastroenteritis.

b. Study in HIV positive infants

HIV-infected infants are among the infants most vulnerable to the complications of rotavirus gastroenteritis. Initial assessments in the developed world suggest that RotaTeq® may be administered in these populations; further assessment may be warranted in a developing world setting. Given the prevalence of HIV in developing world populations, the safety and immunogenicity of RotaTeq® in infants born to HIV-positive mothers in the developing world will be evaluated in a clinical trial in collaboration with the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group. Enrollment is anticipated to start in several African countries early in the first half of 2009.

c. Early experience with RotaTeq® introduction

In 2005, SAGE recommended that early experience with rotavirus vaccines in the developing world be gained and shared with other countries and regions. An example of this is the implementation of RotaTeq® into the national immunization schedule in Nicaragua. In response to a large outbreak of rotavirus disease in Nicaragua, the government committed to introduce a rotavirus vaccine. Following their commitment, the Nicaraguan Ministry of Health partnered with Merck to demonstrate that the vaccine can be easily introduced and used in a GAVI-eligible country. The first dose of vaccine was administered on October 27, 2006, the first time in immunization history that a developing world country introduced a vaccine in the same calendar year as the vaccine was launched in the US public sector. One year later, coverage with 3 doses of RotaTeq® was approximately 75% nationally with over 300,000 doses administered. Rigorous post-vaccination safety surveillance with the support of the Pan American Health Organization, CDC and PATH has been conducted by the Ministry of Health; no safety concerns have been reported to date.
This demonstration project also offers the opportunity to conduct public health impact assessment activities. Both rotavirus disease surveillance and evaluation of vaccine effectiveness are ongoing. An active, hospital-based surveillance network to identify acute gastroenteritis cases among children less than 5 years of age has been established. A case-control study, using the cases identified in the active surveillance, is also planned to assess effectiveness of the vaccine in routine use in this developing country.

The main objectives of the hospital-based surveillance study are: (i) Three-year active hospital-based surveillance study to coincide with partnership program (Merck – Ministry of Health, Jan 2007 to Dec 2009); (ii) Estimate the proportion of acute gastroenteritis (AGE) cases attributable to rotavirus in hospital and urgent care facilities in children < 5 years of age by serotype and severity; and (iii) Identify rotavirus positive AGE cases eligible for vaccine effectiveness analyses. Conversely, the objective of the case-control study is to estimate the vaccine effectiveness of RotaTeq® in a routine vaccination program.

Preliminary data were presented for the surveillance study, in which 2,046 subjects were enrolled as of April 2008. Rotavirus was associated with a substantial proportion of pediatric urgent medical visits or hospitalizations for AGE in February to March 2007 (the rotavirus season in Nicaragua). Of the 2,046 subjects, 1,977 subjects (96.6%) contributed stool samples, and rotavirus laboratory data were available for 498 samples, as determined by enzyme-linked immunoassay (ELISA). In addition RT-PCR data to determine the genotypes of the rotavirus-positive samples was available for 91 rotavirus-positive samples. Among rotavirus positive samples tested (n=91), rotavirus genotypes G2 and G4 represented the majority of the rotavirus cases, while the genotype G1 was not detected. The surveillance data reported were for a period prior to any expected impact of the vaccination program for RotaTeq® in Nicaragua. The ongoing rotavirus surveillance system is currently being utilized as a platform for the case-control study of rotavirus vaccine effectiveness, using rotavirus-positive cases and matched controls from the hospital and community settings. Controls are being recruited since February 2008 and the targeted completion of the surveillance and effectiveness study is to coincide with end of Merck – Ministry of Health partnership.

4. Closed Session (no industry representatives) – Moderated by K. Neuzil

a. Update on Clinical Trials in Developing Countries in Africa and Asia

The Rotavirus Vaccine Programme (RVP), a collaborative initiative between PATH, WHO and the US CDC, has been working with both pharmaceutical rotavirus vaccine manufacturers to design and conduct trials in representative populations in developing countries in Africa and Asia in response to the WHO recommendation. A placebo-controlled efficacy study of the monovalent human rotavirus vaccine (Rotarix™) has completed enrollment in Malawi and South Africa. An effectiveness study of Rotarix™ started in September 2008 in Bangladesh. For the pentavalent bovine-human rotavirus reassortant vaccine (RotaTeq®), two multi-centre, placebo-controlled efficacy trials are on-going. Participating sites are located in Ghana, Kenya and Mali for the African study
and in Bangladesh and Viet Nam for the Asian study. Enrollment is complete, and results are expected in third quarter 2009.

In response to recommendations by the WHO, the studies are designed to examine issues specific to infants in developing countries and include questions related to the number of doses and co-administration with OPV and other EPI vaccinations. Clinical outcomes to be investigated include the protection against severe rotavirus diarrhoea, serotype-specific protection, where possible, any-cause severe gastroenteritis, and hospitalization and/or supervised rehydration therapy.

b. **Phase III Randomized, Controlled Trial of Rotarix™ in South Africa & Malawi**

Infants in this study were randomized to receive either three doses of Rotarix™ together with routine EPI immunizations (given concomitantly with DTP1, DTP2 and DTP3); one dose of placebo and two doses of Rotarix™ (Rotarix™ given concomitantly with the administration of DTP2 and DTP3); or three doses of placebo. For the primary analysis, infants receiving either two or three doses of Rotarix™ will be pooled for comparison to those receiving only placebo. The primary endpoint of the study is to determine if Rotarix™ is efficacious in preventing severe gastroenteritis (Vesikari score ≥ 11) caused by circulating wild-type rotavirus strains from 2 weeks after the last dose to approximately 12 months of age. A series of secondary endpoints are specified, including the efficacy of Rotarix™ in preventing gastroenteritis of any severity caused by wild-type rotavirus; the efficacy of two doses of Rotarix™ versus placebo; the efficacy of three doses of Rotarix™ versus placebo; strain-specific efficacy; efficacy against severe gastroenteritis of any cause; efficacy into the second year of life; as well as the safety and immunogenicity of Rotarix™.

For both South Africa and Malawi, all infants enrolled in this study will be followed to 12 months of age for the primary analysis. Because rotavirus has a strong seasonality in South Africa, enrollment of infants in South Africa was limited to the periods prior to known transmission. Over the course of two years, two separate annual cohorts were enrolled in South Africa for follow-up during the 2006 and 2007 rotavirus seasons. In Malawi, where transmission of rotavirus occurs year-round, enrollment occurred uninterrupted until full enrollment was reached. Follow-up to 12 months of age was completed in Malawi in July 2008.

c. **Interim Analysis in South Africa**

An interim analysis of the data was conducted in first quarter 2008. The interim analysis was conducted only among infants in the cohorts from South Africa who have experienced a full rotavirus season (cut-off date of August 31, 2007) during their first year of life. The analysis was conducted by an independent biostatistician, who is both external to and independent from GSK and PATH. For the interim analysis, only the primary study endpoint of severe gastroenteritis caused by wild-type rotavirus and the secondary endpoint of rotavirus gastroenteritis of any severity were analyzed. In addition,

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6 Madhi S et al. 9th International Rotavirus Symposium. Istanbul, Turkey, June 2008
the strains of rotavirus associated with each event of severe gastroenteritis were identified and tabulated.

A total of 2928 infants were included in the interim analysis. Of these, 1952 infants received either two or three doses of Rotarix™ and 976 subjects received placebo. Baseline variables were similar in the groups receiving Rotarix™ and placebo, including age at dosing, gender, race, height, and weight.

The percentages of subjects receiving Rotarix™ and placebo with severe rotavirus gastroenteritis were 0.5% and 2.7%, respectively, corresponding to an efficacy of Rotarix™ in preventing severe rotavirus gastroenteritis of 82.7% (95% confidence interval: 61.9% to 92.9%) (see table). The percentages of subjects receiving Rotarix™ and placebo with rotavirus gastroenteritis of any severity were 2.9% and 8.7%, respectively, corresponding to an efficacy of Rotarix™ in preventing rotavirus gastroenteritis of any severity of 66.5% (95% confidence interval: 52.6% to 76.5%).

<table>
<thead>
<tr>
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<th>Rotarix™ (N—1952)</th>
<th>Placebo (N—976)</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe RV gastroenteritis</td>
<td>9 (0.5)</td>
<td>26 (2.7)</td>
<td>82.7 (61.9 to 92.9)</td>
</tr>
<tr>
<td>RV gastroenteritis of any severity</td>
<td>57 (2.9)</td>
<td>85 (8.7)</td>
<td>66.5 (52.6 to 76.5)</td>
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The interim results demonstrate Rotarix™ is protective in a setting where multiple serotypes circulate (G1 and non-G1). Rotavirus serotypes G1, G2, G3, G8, G9, G12 were detected. Among cases included in the interim analysis, the most common serotype identified in the study was G1P[8] (56%), followed by G2P[4] (11.2%), G3P[8] (9.1%), G12P[6] (8.4%), G8P[4] (4.2%) and G9P[6] (1.4%), thus almost 35% of strains had neither neutralizing antigen found in the vaccine (i.e. G1 or P[8]).

The infants from South Africa included in the interim analysis come from impoverished townships and communities in and around Johannesburg and Pretoria, communities with high prevalence of HIV infection among adults. In addition, the vaccine was co-administered with OPV and breastfeeding practices were not interrupted at the time of immunization. These interim results are very encouraging about the potential for Rotarix™ to reduce the significant morbidity due to rotavirus diarrhea in the world’s poorest countries.

Efficacy against severe rotavirus gastroenteritis is only one of several important outcomes under investigation in this. The analysis of both the primary outcome for the Malawi and South Africa cohorts should be available in late October, in time for presentation to SAGE. The full analysis of this study, expected in late 2008, will address the full range of trial endpoints at both sites, including the efficacy of the different dose schedules, efficacy against all-cause severe gastroenteritis, and immunogenicity.
5. **Post-Licensure Monitoring of the Uptake, Safety, and Effectiveness of Rotavirus Vaccination in the United States (U Parashar, CDC, Atlanta GA)**

   **a. Rotavirus Vaccine Uptake and Adherence to Age Recommendations**

To assess rotavirus vaccination coverage and adherence to the vaccination schedule, CDC examined data from immunization information systems (IIS) sentinel sites. IIS data are derived from confidential, computerized records of vaccine administration collected from multiple health-care providers within a defined geographic area (e.g., a state or city). The analyses focused on population-based IISs of Arizona, the District of Columbia, Michigan, Minnesota, Montana, and Oregon, which were participants in CDC's IIS sentinel site project during 2004--2007. Sentinel sites are a subset of the state IIS coverage area and represent ≥10,000 children aged <6 years in contiguous geographic counties, postal code areas, or U.S. Census tracts. These surveillance areas have high health-care provider participation and child enrollment (>90%) in the IIS. Procedures are in place in these sites to increase completeness and accuracy of the data (e.g., routine comparisons of IIS records with health-care provider data).

At the six IIS sentinel sites, vaccination coverage increased from the third quarter of 2006 to the second quarter of 2007. As of May 15, 2007, 1-dose rotavirus vaccination coverage among infants aged 3 months at IIS sentinel sites ranged from 40.1% to 65.4% (mean: 49.1%). Rotavirus vaccination coverage estimates were compared with coverage estimates of other infant vaccines. At IIS sentinel sites, 1-dose coverage at age 3 months ranged from 69.3% to 90.4% (mean: 84.1%) for pneumococcal conjugate vaccine (PCV7) and from 69.5% to 92.3% (mean: 85.7%) for diphtheria, tetanus, and acellular pertussis (DTaP) vaccine. At IIS sentinel sites, 45,659 (85.9%) of 53,143 first doses were administered within the recommended age range of 6--12 weeks. When analysis of data was restricted to infants who received ≥3 doses, 21,395 (95.0%) of 22,526 first doses were administered within the recommended age range. Of all doses, 0.2% were administered at age <6 weeks and 1.6% at age >32 weeks.

   **b. Post-Licensure Safety Monitoring, Especially for Intussusception**

In the United States, the post marketing safety of RotaTeq® is being monitored jointly by CDC and the Food and Drug Administration (FDA) through both evaluation of reports to VAERS and active surveillance using data from the Vaccine Safety Datalink (VSD). VAERS is a passive national surveillance system that receives reports of adverse events after vaccination from various sources, including vaccine manufacturers, health-care providers, immunization programs, and vaccine recipients. VAERS reports of serious adverse events after RotaTeq® vaccination are reviewed daily by staff physicians and epidemiologists at CDC and FDA. Health-care providers are contacted to verify diagnoses and obtain additional clinical information and vaccination history. VSD is a collaborative project between CDC and several large U.S. health maintenance organizations (HMOs) in which computerized vaccination data can be linked to medical outcomes.
To assess a potential association between intussusception and RotaTeq® vaccination, the number of intussusception reports to VAERS after RotaTeq® vaccination was compared with the number of intussusception cases expected to occur by chance alone (i.e., the background cases of intussusception). Because the background rates of natural intussusception and number of vaccine doses administered vary substantially by age, the analysis was stratified into three age groups (6--14 weeks, 15--23 weeks, and 24--35 weeks). The observed reports of intussusception were compared with the expected number of cases of intussusception for the three age groups within 1--21 days and 1--7 days after RotaTeq® vaccination. The background rates of intussusception for the three age groups were determined from hospital discharges coded with the International Classification of Diseases, Ninth Revision code for intussusception (560.0) at the VSD study sites for 2000--2004, when no rotavirus vaccine was in use. The expected number of background cases for risk periods of 1--21 days and 1--7 days were calculated by multiplying the VSD background rates of intussusception for each age group by the estimated number of vaccine doses administered to that age group. For these calculations, the following was assumed: 1) administered doses of vaccine approximated the total number of doses of RotaTeq® distributed by the manufacturer and 2) the national distribution of vaccine doses to infants in these three age groups approximated the distribution of vaccine doses administered in each of the three age groups in VSD.

Observed versus expected reporting rate ratios (RRs) with 95% confidence intervals (CIs) were calculated using the exact age-stratified Poisson test.

During February 1, 2006—August 30, 2008, VAERS received 683 reports of serious adverse events after RotaTeq® vaccination, including 328 reports of intussusception that were confirmed using the Brighton Collaboration case definition. Of these 328 reports, 115 occurred in infants within 1--21 days of vaccination, including 62 that occurred within 1--7 days of vaccination. As of August 30, 2008, the manufacturer had distributed 21 million doses of RotaTeq® (Merck, unpublished data). By applying background intussusception rates to the estimated distributed doses per age group, an expected number of 360 intussusception cases was calculated for the period 1--21 days after vaccination; 115 of these cases would be expected to occur at 1--7 days after vaccination. Thus, the number of cases of intussusception reported through VAERS was not elevated above the age-adjusted background rates of intussusception for either 1--21 days (RR = 0.31; CI = 0.23--0.41) or 1--7 days (RR = 0.48; CI = 0.34--0.69) after RotaTeq® vaccination. Sensitivity analysis using assumptions ranging from 50%-100% in reporting completeness and 50%-100% of doses distributed being administered were presented. A scenario of 50% reporting and 50% doses distributed being administered yielded a significantly elevated relative risks of 1.89 (1.41--2.54) and 3.93 (2.36--6.56) within 1-7 days of any dose and 1-7 days of dose 1, respectively.

During February 1, 2006--February 15, 2008, a total of approximately 165,000 doses of RotaTeq® were administered to infants in VSD-monitored HMOs. Five cases of intussusception within 30 days of vaccination were reported among these recipients, compared with 5.4 expected cases. No cases of intussusception were reported within 1 week of vaccination.
Thus, after 2 years of monitoring, VAERS did not identify an increased risk of intussusception within 21 days after RotaTeq® for any dose. VAERS identified an apparent clustering of intussusception cases during the first 7 days after the first dose of RotaTeq®, but firm conclusions cannot be derived because of many limitations of VAERS. VSD active surveillance project has not identified events in days 1-7 following any dose.

c. Impact of Rotavirus Vaccination on Disease Trends

In the continental United States, rotavirus activity follows a distinct winter-spring seasonal pattern. In winter months, approximately 50% of hospitalizations and ED visits and 30% of outpatient visits for acute gastroenteritis among U.S. children are caused by rotavirus. To summarize rotavirus activity through May 3, during the current 2007--08 season, CDC analyzed data from the National Respiratory and Enteric Virus Surveillance System (NREVSS) and the New Vaccine Surveillance Network (NVSN).

NREVSS is a voluntary network of U.S. laboratories that provides CDC with weekly reports of the number of tests performed and positive results obtained for a variety of pathogens. For rotavirus, results of antigen testing using commercially available enzyme immunoassays (EIAs) are reported. Clinical and epidemiologic data are not obtained. During July 1991--June 2007, for each season, a median of 66 laboratories (range: 58--77) contributed rotavirus testing data to NREVSS. To approximate the median from previous seasons, 70 laboratories reporting directly to CDC were included in the 2007--08 analyses. To compare detection rates of rotavirus during the 2007--08 season with pre-vaccine seasons, NREVSS data were aggregated by surveillance week for the period July 1991--June 2006 (i.e., maximum, median, and minimum) and compared with results for July 2007--May 3, 2008. Data from July 2006--June 2007 were excluded from the pre-vaccine (1991--2006) baseline data because some persons tested likely received vaccine during that period. To explore trends in rotavirus testing practices and results, additional comparisons were performed using only data from 32 laboratories that consistently reported >30 weeks of data per year during July 2000--June 2007 and reported >2 months during July 2007--May 2008.

Since 2006, NVSN has consistently conducted prospective, population-based surveillance during January--May for rotavirus gastroenteritis among children aged <3 years residing in three U.S. counties (Monroe County, New York; Hamilton County, Ohio; and Davidson County, Tennessee). NVSN collects epidemiologic and clinical information on children with symptoms of acute gastroenteritis (i.e., diarrhea or vomiting) in inpatient, ED, and sentinel outpatient clinic settings. Fecal specimens are obtained and tested for rotavirus by commercial EIA tests (Premier Rotaclone, Meridian Biosciences, Cincinnati, Ohio). For this analysis, the number and proportion of acute gastroenteritis patients aged <3 years whose fecal specimens tested positive for rotavirus at NVSN sites during January--April in the years 2006, 2007, and 2008 were examined.

Based on NREVSS data, the onset of national rotavirus activity during the 2007--08 season appeared delayed by approximately 2--4 months compared with the 15 pre-vaccine rotavirus seasons (July 1991--June 2006). During 1991--2006, median onset
occurred in mid-November (week 46; range: week 41 to 52). In 2008, onset of rotavirus activity occurred in late February (week 9). The proportion of all rotavirus tests that were positive from mid-November 2007 to mid-April 2008 (week 46 in 2007 to week 16 in 2008) was below the minimum level reported during 1991--2006. Whereas in all previous seasons the proportion of tests that were positive peaked by March (week 12) to a median of 41.0% (range: 30.6%--45.5%), in 2008 only 13.5% of tests were positive in week 12, and only 17.8% were positive at the season peak at the end of April (week 17). Since reaching that peak, the percentage of rotavirus positive tests has continued to decline. For the week ending May 31, 2008 (week 22), the proportion of tests positive for rotavirus was 11.1%. The delayed season and atypically low percentage of rotavirus-positive tests has been observed in all four U.S. census regions.

Data from the 32 NREVSS laboratories that reported >30 weeks of data per year during July 2000--June 2007 and reported >2 months during July 2007--May 2008 were analyzed. During July 2, 2000--May 3, 2008, the 32 laboratories reported a total of 121,100 rotavirus antigen detection tests with 26,478 positive results (21.9%). Although some year-to-year variation occurred during this period in the total number of tests and the number that tested positive for rotavirus antigen, both numbers were substantially lower during the 2007--08 rotavirus season than during any of the pre-vaccine seasons. When the total number of rotavirus tests performed during January 1, 2008--May 3, 2008 (weeks 1--18) was compared with the total number performed during these same weeks in each of the seven preceding rotavirus seasons, the number of 2008 tests was lower by a median of 37.0% (season range: 27.0%--45.9%). The number of tests that were positive for rotavirus was lower by a median of 78.5% (season range: 70.9%--79.7%). Similar declines were observed in all regions.

In NVSN, 405, 481, and 283 children aged <3 years were enrolled during January 1--April 30 in 2006, 2007, and 2008, respectively. Among enrolled children, the overall percentage of fecal specimens testing positive for rotavirus was 51% in 2006, 54% in 2007, and 6% in 2008. Smaller percentages of positive results were observed at all inpatient, ED, and outpatient clinic sites in 2008 compared with 2006 and 2007.

These findings indicate that, when compared with the 15 previous seasons spanning 1991--2006, rotavirus activity during the current season appeared delayed in onset by 2--4 months and diminished in magnitude by >50%. Additional surveillance and epidemiologic studies are needed to confirm the impact of rotavirus vaccination on the 2007--08 season and to monitor the impact of the vaccine on the incidence and epidemiology of rotavirus during future seasons.
6. Summary of Discussion

After discussion, DEVAC members endorsed the following points:

- In response to the WHO recommendation, clinical trials of rotavirus vaccines in representative developing country populations in Asia and Africa, including those with high infant mortality, poor sanitary conditions, and high maternal HIV prevalence, are completed or nearing completion.

- Rotavirus vaccines do not interfere with the immune response to OPV vaccines.

- While there is some effect of OPV vaccines on rotavirus vaccine-induced antibody levels, the clinical significance of this interaction is uncertain, and best determined through efficacy studies. In Latin America, efficacy estimates from trials with and without concomitant OPV administration are similar.

- An interim analysis of the study of Rotarix vaccine in South Africa demonstrated an efficacy comparable to that reported in Latin American populations, (83% in South Africa versus 82-85% in Latin America). These results are very encouraging about the potential for rotavirus vaccines to reduce the significant morbidity due to rotavirus diarrhea in the world's poorest children.

- The cost of the vaccines will impact the uptake and sustainability of rotavirus vaccine programs in country. Coordinated efforts with GAVI, the manufacturers, and other international partners are needed to ensure the affordability of rotavirus vaccines for lower and lower middle income countries.
List of Participants:

**DEVAC members**
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Prof John Clemens, International Vaccine Institute, Seoul, Republic of Korea
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**Observers/invited presenters**
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