Detailed Review Paper on Rotavirus Vaccines

To be presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, April 2009

Ad-hoc group of experts on rotavirus vaccines

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I. Rotavirus Epidemiology and Rationale for Vaccination

Key Points:

1. 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.

2. In developing countries, first rotavirus infections usually occur between 6-9 months of age, and 80% occur among infants <1 year old.

3. Developing countries often have year-round transmission, intense rotavirus exposure, and a diversity of circulating rotavirus strains.

4. 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.

5. Worldwide, around 40% of all pediatric hospitalizations for diarrhea are attributable to rotavirus infections.

6. 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.

7. Rotavirus vaccines are considered to be the optimal strategy to decrease the burden associated with severe and fatal rotavirus diarrhea.

1. Rotavirus disease burden

Rotavirus infects nearly every child by the age of 3-5 years. The median age of a primary rotavirus infection is younger in developing countries, ranging from 6 to 9 months (80% occur among infants <1 year old). Developing countries often exhibit one or more periods of more intense rotavirus circulation against a background of year-round rotavirus transmission and a great diversity of rotavirus strains. In contrast, the median age of primary infection is older in developed countries, ranging from 9 to 15 months (65% occur among infants <1 year old) caused by 4 to 5 common rotavirus strains. Despite nearly universal rotavirus infections early in life, these differences between developing and developed countries, as well as differences in health care access, childhood co-infections and co-morbidities, drive substantial differences in disease burden[1 2 3 4 5 6 7 8 9 10].

Table 1. Differences in the epidemiology of rotavirus in developing versus industrialized countries

Feature	Less-developed countries	Industrial countries
Seasonality	year-round *	winter
Case fatality	high	low
Age at infection:		
Median	6–9 months	9–15 months
By 1 year	80%	65%
Rotavirus strains	mixed	single
Serotypes	±more diverse	4 common types
Transmission (?)	multiple routes	single route
Inoculum (?)	larger	small

* note: may have periods of more intense rotavirus circulation

Courtesy of Bresee JS, Glass RI, Ivanoff B, Gentsch JR. Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. *Vaccine* 1999; 17:2207-22.

Every year, rotavirus gastroenteritis is estimated to cause approximately 527,000 (475,000-580,000) deaths globally among children <5 years old[11] [12]. Most of these deaths occur in developing countries and 90% of the rotavirus-associated fatalities occur in Africa and Asia alone[13]. 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[14]. Using standardized surveillance techniques[15] [16], the 2001-2008 report indicated a median rotavirus hospitalization detection rate of 34% in the Americas, 40% in both Europe and the Eastern Mediterranean, 41% in Africa, and 45% in South East Asia and the Western Pacific. These proportions are far greater than two previous estimates of rotavirus-attributable hospitalizations in international settings. A previous median rotavirus detection rate of 22% was reported in one review of studies that had been published during 1986-1999[12], and another review from 1990-2004 reported that a median of 29% of diarrheal hospitalizations were caused by rotavirus[17].

First rotavirus infections are most likely to result in moderate-severe cases of rotavirus gastroenteritis but subsequent infections are progressively milder. Velazquez et al.[18] found that the adjusted efficacy of a child's first natural rotavirus infection in protecting against subsequent natural rotavirus-associated diarrhea was 77%. This protection increased to 83% after two natural infections and to 92% after three natural infections. A study compared rotavirus-infected neonates with uninfected neonates who were followed for three years. A similar proportion of neonatally infected and uninfected infants had rotavirus infections during the follow-up period. Symptoms among those neonatally infected, however, were less frequent and less severe (P=0.003) leading to the conclusion that neonatal rotavirus infection protects against clinically severe disease during reinfection[19]. A similar finding was reported among a sample of Indian neonates infected nosocomially, most of whom had asymptomatic infections, resulting in a protective effect against rotavirus gastroenteritis lasting throughout the 2 year follow-up period, with protection concentrated in the first year of life[20].

Further background information on rotavirus virology, clinical epidemiology and disease burden is provided in *Appendix A*.

2. The Rationale for Vaccination as the Primary Preventive Measure

Control measures such as clean water initiatives and improvements to personal hygiene have led to dramatic declines in bacterial and parasitic gastroenteritis infections across the world, but rates of rotavirus infection and illness among children in industrialized and less-developed countries remain similar[21 22 23 24 25 26]. Hygienic measures are unlikely to lead to corresponding declines in rotavirus burden[13 27]. The ubiquity of the virus, its minute infectious dose, and its environmental stability greatly facilitate rotavirus transmission[28]. Despite the availability of oral rehydration solution, rotavirus continues to cause disease morbidity and mortality, even in areas having improved sanitation[29 30]. Since first infections have been shown to induce strong immunity against severe rotavirus re-infections[31], and since vaccination mimics such first infections without causing illness, vaccines have been identified as the optimal strategy to decrease the burden associated with severe and fatal rotavirus diarrhea. Clinical and population-based studies have demonstrated that the new rotavirus vaccines are safe and efficacious in preventing

severe rotavirus-associated diarrhea and mortality and reduce the impact upon public health resources.

II. Rotavirus Vaccine Efficacy and Safety in Pivotal Pre-Licensure Trials

Key Points:
1. Rotarix® is a live vaccine containing the attenuated monovalent G1, P[8] human rotavirus strain, and is 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.

2. RotaTeq® 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 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.

3. 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.

Brief Summary of Rotavirus Vaccines

1. Rotarix®

Rotarix® (produced by GlaxoSmithKline Biologicals, King of Prussia, Pennsylvania), is a live vaccine that contains the attenuated monovalent G1, P[8] human rotavirus strain. This vaccine is recommended by the manufacturer to be orally administered in 2 doses to infants at ages 2 and 4 months.

Rotarix ® efficacy has been evaluated in a large clinical trial of more than 63,000 infants from 11 Latin American countries and Finland, and was found to be safe and highly immunogenic. During the first year after vaccination, the efficacy of 2 doses of Rotarix ® against hospitalization due to severe rotavirus was 85% and 100% against more severe rotavirus gastroenteritis, as defined by the Vesikari 20-point scoring system[32]. After two-years of follow up the vaccine demonstrated 83.0% (95%CI=73.1, 89.7) efficacy in preventing rotavirus-related hospitalizations. Rotarix® was protective against hospitalizations due to all causes of gastroenteritis (VE=42.0% for the first year, 95%CI=27.2, 53.9). Rotarix® provided protection against a broad range of rotavirus serotypes during the study's 2-year period, including against the less common G9, P[8]

strain. However, compared with G1,P[8] (VE=82.1%, (64.6, 91.9) protection against the small number of observed G2,P[4] strains was somewhat lower (VE=38.6%, (<0, 84.2)[33].

In a randomized, double-blind, placebo-controlled study conducted in 6 European countries, Rotarix® was observed to be highly immunogenic[34]. Efficacy of Rotarix® against any grade of severity of rotavirus gastroenteritis through one rotavirus season was 87.1% (95% CI= 79.6, 92.1) and against severe rotavirus gastroenteritis, as defined by >=11 on the Vesikari scale, through one rotavirus season was 95.8% (95% CI: 89.6, 98.7). Rotarix® reduced hospitalizations for all cause gastroenteritis regardless of presumed etiology by 74.7% (95% CI= 45.5, 88.9). The efficacy of Rotarix® against severe rotavirus gastroenteritis through two rotavirus seasons was 90.4% (95% CI: 85.1, 94.1) and the efficacy of Rotarix® in reducing hospitalizations through two rotavirus seasons was 96.0% (95% CI= 83.8, 99.5). In contrast to the results of the trial in Latin America, good efficacy against G2,P4 serotypes (85.5%, 95% CI= 24.0, 98.5) in preventing severe rotavirus gastroenteritis was observed in the two-year combined follow-up results of Rotarix efficacy among children from 6 European countries[35].

An evaluation of the thermostability of Rotarix® in Thailand compared the immunogenicity of subjects receiving Rotarix® vaccine which had been stored for 7 days at 37 C versus those who received Rotarix vaccine held at 2-8 C. No difference in seroconversion rates was observed between the two groups (87.8% and 84.4% seroconverted, respectively)[36]. GSK has validated the Vaccine Vial Monitor (VVM) technology for this particular vaccine and has the capacity, upon request, to supply the vaccine with VVMs[37].

2. RotaTeq®

RotaTeq® is a pentavalent bovine–human, reassortant vaccine (produced by Merck and Company, Whitehouse Station, New Jersey). RotaTeq® contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains that express human rotavirus outer capsid proteins of five common circulating strains (G1, G2, G3, G4, and

P[8] (subgroup P1A). Three doses of this vaccine are administered orally to infants at ages 2, 4, and 6 months, concurrently with other vaccines given at this age.

RotaTeq® efficacy has been evaluated in two phase III trials among healthy infants, including a large clinical trial of more than 70,000 infants enrolled primarily in the United States and Finland, and found to be highly immunogenic[38] [39] [40]. The efficacy of 3 doses of RotaTeq® against rotavirus gastroenteritis of any severity was 74% (95% confidence interval [CI] = 67%–79%) and against severe rotavirus gastroenteritis, as defined by >16 on the Clark scoring system, was 98% (CI = 90%–100%). The Clark 24-point scale has been shown to downgrade the severity of rotavirus gastroenteritis cases compared with the Vesikari 20-point scale[41]. The efficacy of RotaTeq against serotypes G1-G4, which were the predominantly strains circulating during the study, was 94.5 % (95%CI=91.2, 96.6) in preventing hospitalization/emergency department visits. Serotype-specific efficacy in preventing rotavirus gastroenteritis of any severity was statistically significant for both G1 serotypes (74.9%, 95%CI=67.3, 80.9) and G2 serotypes (63.4%, 95%CI=2.6, 88.2)[40]. Decreases in rotavirus hospitalizations and ED visits among fully vaccinated infants were consistent in Europe, the US, and Latin America, with reductions of 94.7% (95%CI=90.9, 96.9) in Europe, 94.9% (95% CI=84.0, 98.9) in the US, and 90.0% (95% CI=29.4, 99.8) in Latin America and the Caribbean[42].

With regards to thermostability, the package insert[43] for RotaTeq® specifies that the vaccine should be stored and transported under refrigeration at 2-8°C and is stable for up to 24 months within this temperature range. If RotaTeq® is inadvertently exposed or stored at temperatures above 2-8°C, potency is maintained for the maximum exposure times shown in the following table. If these times have elapsed or if RotaTeq® is exposed to temperatures above 30°C, the vaccine should be discarded. If RotaTeq® is inadvertently exposed to temperatures below 0°C, limited data suggest that the potency of the vaccine is maintained.

Table 2: RotaTeq® thermostability exposure thresholds

Maximum exposure temperature	Maximum exposure time
9-25°C	48 hours
OR	
26-30°C	12 hours

The U.N. prequalification statement for RotaTeq® remarks that no VVM technology has been validated for use with RotaTeq® as the currently available VVMs do not match the stability profile of the vaccine components. Merck and Company is working with WHO to identify and assess the feasibility of a suitable temperature monitoring device for RotaTeq®. It is therefore extremely important for the potency of this vaccine that the cold chain storage conditions are maintained from delivery to administration[37].

A comparison of the vaccine composition, titre, formulation, and other vaccine characteristics for Rotarix® and RotaTeq® is found in *Appendix B*.

The study characteristics and efficacy results of each vaccine from clinical trials are shown in *Appendix C*. Note that these clinical trials were conducted in different populations using different study designs, and different definitions of severe disease, and the relative predominance of circulating strains differs from trial to trial. Therefore, the results are not directly comparable.

The summary of vaccine effectiveness against specific rotavirus serotypes is presented for both vaccines in *Appendix D.*

III. Newly Available Data from Clinical Trials in Africa and Asia and Post-Introduction Vaccine Effectiveness Evaluations in the Americas

Key Points:

1. South Africa and Malawi clinical trials (Rotarix®)

a. In a large randomized, placebo-controlled 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® in preventing severe rotavirus gastroenteritis was 61% in combined study populations (77% in South Africa and 50% in Malawi).

b. Despite the lower vaccine efficacy in Malawi, the number of severe 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).

c. The public health impact of rotavirus vaccine introduction may be greater in Africa and Asia compared with other regions of the world due to higher background rates of rotavirus disease and the potential for higher numbers of prevented cases.

2. Hong Kong, Taiwan, and Singapore clinical trials (Rotarix®)

In clinical trials in several low or intermediate under-5 mortality rate Asian populations, Rotarix® was 96.1% effective in protecting against severe rotavirus gastroenteritis.

3. Nicaragua vaccine effectiveness case-control study (RotaTeq®)

In Nicaragua, an intermediate under-5 mortality rate South American country, RotaTeq® was 60% effective in preventing severe rotavirus gastroenteritis and was 78% effective against very severe rotavirus gastroenteritis in a post-licensure case-control study.

4. El Salvador vaccine effectiveness case-control study (Rotarix®)

Preliminary data from a post-licensure case-control vaccine effectiveness study in El Salvador, a low under-5 mortality country, will be presented.

5. United States post-licensure impact evaluation studies (RotaTeq®)

a. U.S. surveillance estimates 80-90% declines in severe rotavirus gastroenteritis cases and rotavirus positive laboratory tests during the 2008 post-licensure year compared with the pre-licensure period.

b. In a post-licensure, case-control study, RotaTeq® 3-dose vaccine effectiveness against rotavirus-related emergency department visits was 85-89% at a single, large U.S. medical center.

1. South Africa and Malawi clinical trials (Rotarix®)[44]

Recent results are available from a Phase III, double-blind, randomized, placebo-controlled trial evaluating the efficacy of rotavirus vaccines in two African countries. The primary endpoint of the study was to determine the efficacy of Rotarix® in preventing severe gastroenteritis (assessed by a Vesikari score $\geq$ 11) caused by circulating wild-type rotavirus strains from 2 weeks after the last dose until one year of age.

Further data are available to SAGE members in the Confidential Annex and will be presented at the April 2009 SAGE meeting.

2. Hong Kong, Taiwan and Singapore clinical trials (Rotarix®)

Preliminary placebo-controlled clinical trial results from three low-child under-5 mortality rate Asian populations (Hong Kong, Taiwan, Singapore) report that Rotarix® was highly effective (96.1%) in protecting against severe rotavirus gastroenteritis caused by G-1 and by circulating non-G-1 strains. No evidence was found of unexpected or severe adverse events attributable to this vaccine or its administration.

3. Nicaragua post-introduction vaccine effectiveness case-control study (RotaTeq®)

Nicaragua introduced RotaTeq® in its routine immunization program in October 2006. Vaccine effectiveness of three doses of RotaTeq® against severe rotavirus disease was assessed through a matched case-control study, using neighborhood and hospital controls[45]. Cases were children age-eligible to receive RotaTeq® who were treated for laboratory-confirmed rotavirus diarrhea at 4 hospitals in Nicaragua from June 2007 to June 2008. Among 285 cases, 93% were admitted, 88% required intravenous fluids, and 85% had G2P[4] strains. Using neighborhood and hospital controls combined, overall vaccine effectiveness of a complete 3-dose series of RotaTeq® against all cases was 46% (95% CI 18, 64), against severe cases was 60% (95% CI 34, 76), and against very severe cases was 78% (95% CI 40, 92). Three-dose vaccine effectiveness against severe cases in 8-

11 month-old children and ≥12-month-old children was 68% (95% CI 22, 87) and 35% (95% CI -41, 70), respectively, and against very severe cases was 63% (95% CI -80, 92) and 87% (95% CI 41, 97), respectively. Thus, the overall effectiveness of RotaTeq® in Nicaragua was lower than efficacy demonstrated in industrialized countries and appeared to decrease with increasing age. However, protection against very severe rotavirus diarrhea was greater and appeared to be well maintained through 18 months of life.

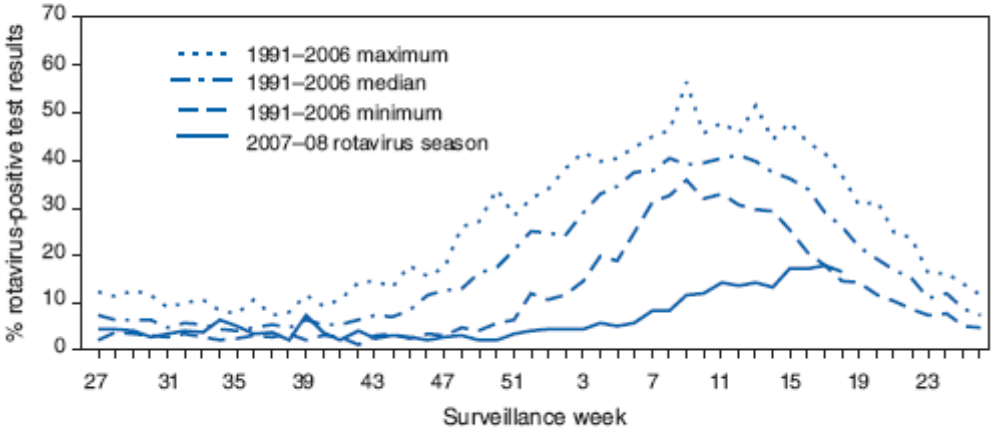
4. El Salvador post-introduction vaccine effectiveness case-control study (Rotarix®)

Preliminary data from a post-licensure case-control vaccine effectiveness study in El Salvador, a low under-5 mortality country, will be presented at the April 2009 SAGE meeting.

5. United States post-licensure impact evaluation studies

The United States introduced routine vaccination with rotavirus vaccine (RotaTeq®) in February 2006. Surveillance data in the US indicated a delayed and diminished rotavirus season from January through April 2008, a period of time approximately two years following US licensure and introduction of rotavirus vaccine[46]. By March, 2008, US immunization surveillance indicted that rotavirus vaccine coverage of 1 dose among US infants 3 months of age was approximately 56.0%, (range 12.4%-75.8%) with geographic variation. This US data indicated a median decline in rotavirus detection by 78.5% (range 70.9%-79.7%) from sentinel laboratories participating in the US National Respiratory and Enteric Virus Surveillance System compared with 15 years of previous data (Figure 1).

FIGURE 1. Percentage of rotavirus tests with positive results from participating laboratories, by week of year — National Respiratory and Enteric Virus Surveillance System, United States, 1991–2006 rotavirus seasons and 2007–08 rotavirus season*



* 2008 data current through week ending 3 May 2008. Data from July 2006–June 2007 were excluded from the (1991–2006) prevaccine baseline data because some persons tested likely received vaccine during that period.

Additionally, a population-based U.S. surveillance network, the New Vaccine Surveillance Network, detected an approximate 90% decline in severe rotavirus gastroenteritis visits to the hospital, ED, and outpatient providers during these months in 2008 compared with the previous two years. The onset and peak of the 2008 rotavirus season were delayed by several months resulting in a national truncation of the rotavirus season from 26 weeks in the pre-vaccine era to 14 weeks during the 2007-2008 season. Declines in rotavirus disease have not only been observed in children <2 years of age who are age eligible to have potentially received rotavirus vaccination, but also in older children 3-18 years of age. This finding raises the possibility that vaccination of a proportion of the population is resulting in indirect benefits to non-vaccinated persons in the community because of reduced rotavirus transmission (i.e., herd protection).

Post-licensure rotavirus vaccine effectiveness studies in the US during the winter/spring of 2007-2008 have been conducted and preliminary results are

available. In U.S. post-licensure surveillance, cases of rotavirus gastroenteritis requiring hospitalization or emergency department visits are considered severe, although clinical severity assessments are not typically performed. Vaccine effectiveness against rotavirus-related emergency department visits at a large medical center in Texas reported RotaTeq® 3-dose effectiveness to be 85% and 89% (using rotavirus negative subjects having acute gastroenteritis and acute respiratory illness {ARI} subjects as controls, respectively), 2-dose effectiveness to be 82% and 72%, and single-dose effectiveness to be 65%[47]. A population-based vaccine effectiveness study of RotaTeq® during the winters/springs of 2007 and 2008 at 3 medical centers in New York, Ohio and Tennessee preliminarily indicate 88% and 79% 3-dose effectiveness (using rotavirus negative controls having acute gastroenteritis and ARI controls, respectively), 72% and 78% 2-dose effectiveness, and single-dose effectiveness of 71% and 65%, against hospitalized or emergency department cases of rotavirus gastroenteritis[48].

A study of children in New York City (2008) similarly suggested that vaccination of a part of the population might offer indirect benefits to unvaccinated individuals by reducing transmission of rotavirus in the community and that significant reductions in rotavirus hospitalizations among unimmunized older age groups were due to possible indirect effects[49].

6. Status of other ongoing studies

As additional surveillance data and information on vaccine coverage are gathered, the impact of vaccination on rotavirus disease burden and the potential for herd immunity will be further assessed. A study on potential indirect benefits from Rotarix® vaccination in a developing country is currently underway in Bangladesh. A cluster-randomized effectiveness study evaluates the implementation of Rotarix® vaccination among children in two distinct Bangladeshi communities, one receiving the vaccination and one not receiving it. Comparisons of the rotavirus incidence in these communities will provide a better understanding of direct and potential indirect effects from rotavirus vaccines.

A Rotarix® immunogenicity, reactogenicity, and safety study was performed in India which demonstrated a seroconversion rate one month post-dose 2 of 58.3% (95% CI: 48.7, 67.4) compared with 6.3% (95% CI: 2.5, 12.5) in the placebo group. The reactogenicity and safety profile was similar for both groups[79].

RotaTeq® is being tested in A) a Phase III placebo-controlled study among Japanese infants (enrollment began August, 2008, recruiting), B) a safety, tolerability and immunogenicity study among Indian infants (enrollment began May, 2008, not recruiting), C) an efficacy, safety and immunogenicity study among infants from Mali, Ghana, Kenya, Bangladesh and Vietnam (enrollment began March 2007, follow-up planned through March 2009, results expected by 3rd quarter 2009 with possible presentation to SAGE in October 2009).

IV. Vaccine Safety, Co-Administration, and Special Populations

Key Points:
1. In December 2008, the Global Advisory Committee on Vaccine Safety (GACVS) reviewed additional new post-marketing safety data from the Rotarix® and RotaTeq® manufacturers, the Immunization Safety Office of the United States Centers for Disease Control and Prevention, 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® can be ruled out with confidence but the available postmarketing surveillance data are still too few to rule out, with confidence, a risk of substantially lower magnitude.

2. 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.

3. Rotarix® 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.

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

1. Vaccine Safety

Large pre-licensure clinical trials of both Rotarix® and RotaTeq® indicated that these rotavirus vaccines are safe and non-reactogenic and not putatively associated with severe vaccine adverse events, such as intussusception [32] [42] [50]. The results of these trials had been reassuring in providing information indicating that any risk of intussusception associated with either of the two new vaccines was lower than the level that had been associated with the (withdrawn) Rotashield® vaccine[51] and no higher than that of the background rate.

In December 2008 The Global Advisory Committee on Vaccine Safety (GACVS) reviewed safety data from clinical trials for Rotarix® and RotaTeq® and surveillance data from the manufacturer on RotaTeq® from several ongoing studies and concluded that

these data did not indicate an increased risk of intussusception following vaccination compared to background rates. The Committee reported that the ongoing vaccine safety studies were relatively small and the confidence intervals for the possible risk estimates were wide.

Post-licensure data from the US Centers for Disease Control and Prevention (CDC) were presented to the Advisory Committe on Immunization Practices (ACIP), based on the U.S. experience from approximately three years of RotaTeq® licensure in the US (> 14 million doses distributed). During this time, the CDC has been actively engaged in monitoring post-licensure data on vaccine adverse events. Data from the US Vaccine Safety Datalink was reported, including an analysis of 5 cases of intussusception (only 2 of which were validated after medical record review) among recipients of 205,000 doses of RotaTeq® which did not indicate an increased risk of intussusception and enabled a risk of the level of >1 intussusception case per 25,000 doses to be ruled out with reasonable confidence (a risk about 10-fold lower than that associated with Rotashield®)[52].

Rotarix® was introduced to the U.S. in 2008 and sample sizes studied for this vaccinated population remain small. However, data from the manufacturer presented to GAVCS in December 2008[53] indicated that approximately 32 million doses of Rotarix® have been distributed worldwide, predominantly to countries in Latin America, and rates of intussusception appear lower than background rates in crude analyses. Prospective studies of Rotarix® vaccine safety are ongoing in Mexico and Brazil, and the latter include HIV-infected and pre-term infants.

Data from Australia were presented to GAVCS at the December 2008 meeting which indicated limited clustering of intussusception among vaccinees <10 days post-vaccination (since Australia lets each state independently decide which vaccine to use, no differentiation of vaccination adverse events by RotaTeq® versus Rotarix® was indicated in this report). However, it was not clear whether the number of intussusception cases was above the background rate.

The GAVCS committee was encouraged by the description of the passive surveillance network (termed SANEVA) that is being developed in some Latin American countries, with facilitation by PAHO. By the time of this meeting, no clear signals of vaccine related adverse effects were apparent but further strengthening of the surveillance network is ongoing. These studies are also accumulating data regarding the background natural frequency of intussusception among infants[50].

In summary, the GAVCS committee was reassured that a risk of intussusception of the order of that which had been associated with the Rotashield® vaccine could be ruled out with confidence, but the available post-marketing surveillance data were still too few to rule out, with confidence, a risk of substantially lower magnitude[50].

The various surveillance systems and analyses noted here apply different methodological approaches to assessing any potential vaccination risk with the intussusception outcome. Nonetheless, any potential valid relationship between vaccine and intussusception should be observed within a short period of time following the vaccination date, as was observed in the association between the withdrawn Rotashield® vaccine and risk of intussusception, and the studies mentioned here apply this concept of temporal distance in their methodologies[51].

CDC also monitors the safety of rotavirus vaccines for other adverse events including hematochezia, Kawasaki syndrome, seizures, meningitis and encephalitis, myocarditis and gram-negative sepsis in the US. No associations between RotaTeq® and these conditions have yet been detected[52 54].

2. Co-administration with Other Vaccines, Particularly OPV

In various settings described below, co-administration of live, oral rotavirus vaccines with OPV and other routine childhood vaccinations has been shown to not interfere with the immunogenicity or safety of these vaccines. In pre-licensure studies for both Rotarix® and RotaTeq®, concomitant vaccination with other childhood vaccines was addressed and no interference was observed[38 55]. The

immune response to any of the 3 polio antigens has not been impaired by simultaneous administration of OPV 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[43]. Successful co-administration of these vaccines would facilitate the integration of rotavirus vaccination into the WHO Expanded Programme on Immunization (EPI). Furthermore, such concomitant vaccination strategy is likely to be advantageous in boosting rotavirus vaccination compliance and coverage[56].

Ciarlet et al. studied the immunogenicity and safety of RotaTeq® vaccine co-administration with OPV in an open-label, multicenter study. In this sample of Latin American infants, RotaTeq® did not interfere with immune responses to OPV. Co-administration of RotaTeq® with OPV resulted in a 46% lower serum antirotavirus IgA geometric mean titer after 3 doses compared with infants receiving a staggered regimen (i.e. rotavirus given two weeks apart from OPV), but seroresponse rates remained high (anti-rotavirus IgA was elicited in 93% of infants concomitantly receiving both vaccines). Comparable safety profiles were observed for infants receiving both vaccines concomitantly versus the staggered regimen[57].

Steele et al. conducted a double-blind, placebo-controlled phase III trial of concomitant Rotarix® and OPV administration among South African infants. Using two vaccination schedules (at 6-10 weeks and 10-14 weeks), co-administration with OPV did not decrease the sero-protection rates against poliovirus serotypes 1, 2, and 3, as measured by the sero-conversion or GMCs of polio serotype specific antibody responses. Anti-rotavirus IgA antibody sero-conversion rates were higher for those infants receiving the 10-14 week regimen compared with the 6-10 weeks, (55-61% versus 36-43%, respectively). Rotarix® was safely and effectively co-administered with routine EPI immunizations including OPV[58].

In a study of Bangladeshi infants, Rotarix® administered concomitantly with OPV was also shown to be safe and immunogenic. One month after the vaccination series, Zaman et al. observed that the seroconversion rates for rotavirus IgA antibodies were not significantly different among infants receiving simultaneously co-administered vaccines (56.5%, 95% CI=44.0, 68.4) and those receiving the vaccines 15 days apart (66.7%, 95% CI=54.0, 77.8) but for both vaccine groups the rates were significantly greater compared with the placebo group (18.6%, 95% CI=10.3, 29.7), $P<0.001$). Rotavirus seroconversion rates were comparable to those observed among South African, Latin American, and Indian infants. The authors conclude that any potential interference of OPV upon Rotarix® would be highest when administered with the first OPV dose, when replication of OPV would be expected to be greatest[56].

3. HIV-infected populations

WHO requested that rotavirus vaccination in HIV-positive children be studied[11]. Previously, Pavia et al. had reported that diarrhea among young Zairean children who were HIV-infected was more severe than among uninfected children, although this relationship was not specific to rotavirus infections[59]. Cunliffe et al. studied the effect of HIV infection on rotavirus outcomes among children in Malawi and found no significant differences in rotavirus disease severity between HIV-infected and non-infected children, although fewer rotavirus illnesses were observed among HIV-infected children. Rotavirus shedding was more common among HIV-infected children (21%) than non-infected children (4%) during follow-up (P=0.05) but this shedding was not associated with diarrhea[60].

In a South African study of HIV-positive children receiving co-administered routine childhood vaccines with Rotarix®, the rotavirus vaccine was well tolerated and immunogenic[61]. Data were comparable with the safety and immunogenicity results (anti-RV IgA seroconversion rate: 36%–61%) from a previous study conducted on healthy South African infants[58]. Compared with those receiving placebo, the South African HIV-positive Rotarix® recipients were not observed to exhibit significant differences in study

symptoms, CD4 counts, or HIV viral load, indicating that their immune deficiency condition was not aggravated.

In the Malawi and South Africa Phase III, double-blind, randomized, placebo-controlled trial evaluating the efficacy of rotavirus vaccines, children born to mothers with HIV infections were not restricted from participation.

4. Breast-feeding and Pre-term Infants

Breast-feeding was permitted in clinical studies of Rotarix® with no restrictions on when the infant was breastfed in relation to vaccination. There was no evidence suggesting that breast-feeding reduced the protection against rotavirus gastroenteritis afforded by Rotarix®[34].

Breastfeeding did not reduce the efficacy of RotaTeq® in post-hoc analyses of the clinical efficacy study[62]. Efficacy of RotaTeq® against G1–G4 rotavirus gastroenteritis of any severity through the first rotavirus season was similar for the infants who were never breastfed (68.3%, 95% CI= 46.1, 82.1) and the infants who were exclusively breastfed (68.0%, 95% CI=53.8, 78.3) in this study. Efficacy against severe G1–G4 rotavirus gastroenteritis was also similar for never breastfed (100%; 95% CI=48.2, 100) and exclusively breastfed infants (100%, 95% CI=79.3, 100).

Although small numbers of preterm infants have been studied in clinical trials of both vaccines the safety and efficacy of vaccines has been similar in these infants to that in full term infants.

V. Vaccine schedules and age restrictions

Key Points:

1. Use of a 3-dose Rotarix® 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 only 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.

2. 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.

3. 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 immunogenic advantages a 3-dose Rotarix®schedule is practical from a programmatic perspective as it matches the dosing of other EPI vaccines, so staff training is straightforward.

4. A 3-dose rotavirus vaccine schedule is essential in any setting where RotaTeq® and Rotarix® may be interchanged.

5. The full potential of rotavirus vaccines can not be realized without expanding the maximum age of first and last vaccine dose administration.

Scheduling considerations, including the studied ages for vaccine doses, are not directly comparable between Rotarix® and RotaTeq® due to differences in the design of each vaccine's clinical trials and the fact that a head-to-head comparison between the two vaccines has not been conducted. The Rotarix® manufacturer (GSK Biologicals) currently recommends 2 doses of vaccine, whereas the RotaTeq® manufacturer (Merck and Company) recommends 3 doses.

In clinical trials, Rotarix® vaccine was evaluated in a variety of schedule options including: 6 and 10 weeks; 10 and 14 weeks; 2 and 3 months; and 2 and 4 months. Each of these schedules, except for 10 and 14 weeks, correspond to the timing of giving the first and second doses of OPV and diphtheria-tetanus-pertussis (DTP)-containing vaccines[32]. RotaTeq® vaccine was evaluated during clinical trials using 6, 10 and 14 weeks; 2, 3 and 4 months; and 2, 4 and 6 month schedules, which correspond to the

timing of the first, second and third doses of OPV and DTP vaccines[40].

Data are not available showing the superiority of the 3-dose Rotarix® schedule versus a 2-dose schedule. In the recent clinical trial of Rotarix® in African countries, no significant difference in vaccine efficacy was observed in Malawi between 2 and 3 doses of this vaccine. The performance of 3 Rotarix® doses appeared more efficacious in the South Africa arm of this clinical trial, however this finding was not statistically significant[63].

In the absence of conclusive scientific data indicating that 2 versus 3 doses of Rotarix® is superior, any international recommendation for rotavirus vaccines must consider programmatic factors, such as how the schedule corresponds with Expanded Program on Immunization (EPI) vaccine schedules currently used by developing countries, and account for the likelihood of children receiving a protective full course of rotavirus vaccination.

As previously noted, the co-administration of live, oral rotavirus vaccines with OPV and other routine childhood vaccinations has been shown to not interfere with the immunogenicity or safety of these vaccines. However, co-administration with OPV does appear to reduce the rotavirus vaccine immune response at the first dose. Importantly, immune responses to subsequent rotavirus vaccine doses are not affected by OPV administration. The lower immune response when the first dose of rotavirus vaccine 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.

If rotavirus vaccines are to be co-administered with OPV in a setting with an EPI vaccination schedule beginning at 6 weeks of age, the second dose of Rotarix® may not be immunologically sufficient to provide adequate immunity against severe rotavirus

disease. Therefore, the Ad-hoc Group of Experts recommends that all countries with a 6, 10, and 14 week EPI schedule use a 3-dose rotavirus vaccine schedule, for both Rotarix® and RotaTeq®. A 2-dose schedule at 10, 14 weeks is also assumed to be programmatically deficient since this would likely result in a failure for children in developing countries to be administered the full course of vaccines due to the restrictive upper age limit for rotavirus vaccine administration resulting from an apprehension to administer rotavirus vaccines during the ages of heightened intussusception risk. Immunization programs also do not have the flexibility of administering "catch-up" rotavirus vaccinations due to this upper age limit. Therefore, children who miss a dose at 10-weeks of age and receive a first dose at 14 weeks may not subsequently receive a second dose due to the upper age limit and would remain immunologically susceptible to rotavirus infections under a 10, 14 week schedule option. For countries starting vaccinations at or after 2 months of age, the choice would continue to exist for administering either 3-doses of either vaccine (in high under-5 mortality rate countries), or 2-doses of Rotarix® / 3 doses of RotaTeq® in low and intermediate under-5 mortality rate countries at 2, 4, and 6 months of age.

No studies address the interchangeability of the two rotavirus vaccines. The U.S. Advisory Committee on Immunization Practices (ACIP) recommends that the rotavirus vaccine series be completed with the same product whenever possible. However, vaccination should not be deferred because the product used for a previous dose(s) is not available or is unknown. Instead, the series should be completed with a total of 3 rotavirus vaccine doses administered, even if the vaccine type is interchanged, with a minimum dose interval of 4 weeks. Thus, for simplicity in practical usage of these vaccines in areas having variable vaccine availability and/or inadequate personal vaccination record-keeping, the Ad-hoc Group of Experts recommends a 3-dose rotavirus vaccine schedule in any setting where Rotarix® and RotaTeq® may be potentially interchanged.

Based on data from the major clinical efficacy studies and from reassuring post-licensure monitoring data[51], the U.S. ACIP loosened rotavirus vaccination age restrictions to allow

the first dose to be administered before 14 weeks, 6 days of age, and the last dose before 32 weeks of age[64]. (Table) The U.S. ACIP harmonized these age recommendations for both licensed vaccines. In addition to not posing vaccine safety concerns, these adjusted age recommendations were predicted to increase the proportion of US children who would receive a first dose of vaccine by 7%, and an additional 8% would receive all 3 doses[65]. For an international recommendation which would cover countries where missed doses are an even greater concern than in the U.S., this loosening of the age recommendations was also considered favorable by this Ad-hoc Group of Experts.

Table 3. Current U.S. recommended schedule for administration of rotavirus vaccine

	RotaTeq®	Rotarix®
Number of doses in series	3	2
Recommended ages for doses	2, 4, and 6 months	2 and 4 months
Minimum age for first dose	6 weeks	
Maximum age for first dose	14 weeks 6 days	
Minimum interval between doses	4 weeks	
Maximum age for last dose	8 months 0 days	

Larger decisions regarding the scheduling and age-recommendations for rotavirus vaccines should incorporate any potential added risk of adverse events (e.g., intussception) with the potential benefits in rotavirus mortality reductions. Patel, et al. conducted a scenario analysis comparing when the first vaccine dose is strictly administered before 12 weeks of age compared with a free strategy of vaccine administered before 1 year of age using data on rotavirus disease, vaccine safety and efficacy, and current diphtheria-tetanus-pertussis vaccination rates, and by incorporating hypothetical risks of intussusception[66]. Assuming vaccine efficacy of 50% and 75% for dose 1 and 2 respectively and a hypothetical 6-fold and 3-fold increased relative risk of intussusception within 7 days of dose 1 and dose 2, respectively, initiating rotavirus immunization before 12 weeks of age would prevent 194,564 of the 517,959 annual rotavirus-associated deaths among children < 5 years, while potentially resulting in 1,106 fatal intussusception events. Administration of the first dose to infants up to 1 year of

age would prevent an additional 54,087 rotavirus-associated deaths (total = 248,651) while potentially resulting in an additional 1,226 intussusception deaths (total =2,332). Thus, in developing countries, the additional lives saved by broadening the age restrictions for initiation of rotavirus vaccination would far outnumber the hypothetical excess intussusception deaths that might accompany such an approach.

VII. Vaccine Cost-Effectiveness and Decision-Making Regarding Program Implementation

Key Points:
1. Several recent cost-benefit models identify use of rotavirus vaccines to be a cost-effective intervention.

2. Health benefits would be greatest in Africa (180 DALYs averted per 1,000 vaccinated) and Southeast Asia (102 DALYs averted per 1,000 vaccinated).

3. From 2007-2025, rotavirus vaccine would prevent 2.4 million child deaths in low-income countries, primarily in Southeast Asian and African countries. 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.

4. Decisions regarding the introduction of rotavirus vaccination programs are multi-faceted and should consider disease burden, vaccine effectiveness, and cost-effectiveness.

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

1. Cost-effectiveness and affordability

Atherly et al. used a demand forecast model to predict adoption of rotavirus vaccine in the poorest countries in the world, then modeled health outcomes and direct costs of a hypothetical birth cohort in the target population for scenarios with and without rotavirus vaccine[67]. The analysis found that vaccination would prevent 2.4 million rotavirus deaths and avert over 82 million disability adjusted life years (DALYs) in 64 of the 72 GAVI-eligible countries introducing vaccine from 2007-2025. Under the baseline scenario with an initial vaccine price of $7/per dose for a 2-dose course with a gradual decrease beginning in 2012 and stabilizing at $1.25/dose by 2017, vaccination was very cost-effective in all GAVI-eligible countries using each country's gross domestic product (GDP) per DALY averted as a threshold.

Rheingans et al. developed a cost-effectiveness model which assumed current vaccination coverage and timing and which found that rotavirus vaccination would annually prevent 228,000 deaths, 13.7 million hospital visits, and 8.7

million DALYS in developing countries[68]. Using the assumption of $5 per vaccine dose and a 2-dose vaccine course, the model found vaccination to be a very cost-effective strategy with cost-effectiveness depending most on vaccine price and on reaching children at highest risk of mortality.

A 2006 analysis of children in a single U.S. birth cohort followed to age 5 years estimated that the U.S. rotavirus vaccination program administering RotaTeq® would result in 255,000 fewer physician visits, 137,000 fewer ED visits, 44,000 fewer hospitalizations and 13 fewer deaths. From the U.S. societal perspective (medical and non-medical costs), at the price of $62.50 per dose, vaccination would cost $138 per case averted, $3024 per serious case averted, and $197 190 per life-year saved, at a total cost of $515 million to the U.S. health care system and $216 million to U.S. society[69]. This analysis was repeated in 2008 for Rotarix® and found estimates of cost-effectiveness similar to those of RotaTeq®[70]. No known published study includes the potential impact of rotavirus vaccination indirect effects upon the cost-effectiveness estimates of rotavirus vaccines. However, these would be expected to have additional favorable impact upon such estimates.

2. Decision-making regarding vaccine introduction

Countries where deaths among children due to diarrhoeal diseases account for ≥10% of under-5 mortality rate should prioritize the introduction of rotavirus vaccine into their routine immunization programmes. Countries where deaths among children due to diarrhoeal diseases account for <10% of under-5 mortality rate should also consider the introduction of rotavirus vaccines based on anticipated reduction in mortality and morbidity from diarrhoea, savings in health care costs, and the cost-effectiveness of vaccination.

Decisions regarding the introduction of rotavirus vaccination programs are multi-faceted and consider disease burden, vaccine effectiveness, and cost-effectiveness. Historically, decisions whether or not to implement childhood

vaccination programs in developing countries have been driven by considerations of disease burden[71].

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.

VII. Vaccine Program Implementation and Vaccine Delivery Logistics

Key Points:
1. 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.

2. 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 the Latin Americas.

3. Administrative adaptations, such as redesigning vaccination cards and 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.

Eight countries in Latin America (Brazil, Ecuador, El Salvador, Panama, Mexico, Nicaragua, Venezuela, and Bolivia) have introduced rotavirus vaccine. The summary experiences across seven of these countries (all of the above except Bolivia, which introduced rotavirus vaccination in 2008) indicate that other countries considering the introduction of rotavirus vaccination programs must have precise plans to ensure technical, programmatic and financial sustainability of the progam[72].

Foremost among the "lessons learned" in these Latin American countries is the realization that policy development is facilitated by the coordination between political and technical decisions. 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 the Latin Americas. Additionally, administrative adaptations, such as redesigning personal vaccination cards and database modifications, were required in advance of vaccination introduction. And, efforts must be made to ensure the appropriate training of vaccination program staff persons, particularly on the approved preparation of the vaccine, the recommended age ranges for vaccination and intervals between vaccine doses, outreach strategies, and the understanding and communication of potential vaccine adverse events. In the future, new

vaccine presentations (liquid form) will require significantly less cold chain volume.

VIII. Integration with Diarrheal Control and Other Health Interventions and Communication

Key Points:
1. 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.

2. Clear communication strategies are needed to prevent misconceptions regarding the efficacy of rotavirus vaccines in preventing other diarrheal diseases among children.

1. Integration with Diarrheal Control and Other Health Interventions

Rotavirus vaccination programs should be coordinated with other interventions to prevent and treat childhood diarrheal diseases, including hygienic and sanitary improvements, awareness of and use of oral rehydration therapy, zinc supplementation and other effective treatments recommended by WHO[11]. Rotavirus vaccination introduction should not compete against, or try to replace, these effective public health interventions[73].

2. Communication

WHO recommends that clear communication strategies be implemented to ensure that key messages to health-care workers and the general public are accurate and complete in order to prevent misconceptions. For example, parents and health care providers should be educated that rotavirus is the cause of some but not all diarrhea and that rotavirus vaccination will not prevent all causes of diarrhea[11].

The WHO Department of Vaccines and Biologicals, "Introduction of Rotavirus Vaccines into National Immunization Programs: Management manual including operational information for health workers" can be used as a guide for communication messages targeted to health-care workers[74] (excerpted messages may be found in *Appendix E*).

IX. Surveillance of Rotavirus Disease and Postmarketing Surveillance to Monitor Vaccine Safety

Key Points:
1. 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 the 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.

2. As rotavirus vaccines are introduced into developing countries, postmarketing surveillance systems should be set up to monitor possible vaccine adverse effects, including intussusception.

Rotavirus disease surveillance is important to assess the incidence of severe rotavirus disease over time, to measure the effectiveness and impact of vaccination in reducing the rotavirus morbidity and mortality, to assess potential changes in rotavirus epidemiology and serotype distribution[11]. Surveillance data are critical for clarifying the burden of disease and understanding the diversity of strains in order to guide decision-making on vaccine introduction. After implementation of vaccination, these data are needed for evaluating the impact of immunization programmes. As rotavirus vaccines are introduced into developing countries, postmarketing surveillance systems should be set up to monitor possible vaccine adverse effects, including intussusception.

However important these activities are, the introduction of such surveillance programs should not constitute an obstacle to the implementation of any country's rotavirus vaccination program.

Since 2001, regional networks of sentinel hospital-based sites have been established in 35 countries located in each of the six WHO regions worldwide[14]. Standard guidelines for the collection and dissemination of new rotavirus vaccine surveillance data have been described and formal data standards have been provided to WHO Regional Offices by the end of 2008[15] [16]. As described in the 2008 WHO "*Summary report on meeting to standardize new vaccines surveillance data to be collected, shared and reported"*,

> "A 'layered approach' to the surveillance network structure has been proposed by WHO for sentinel-based surveillance for rotavirus. In the first layer, "core"

> sentinel sites collect data on under-5 children hospitalized for acute diarrhoea, and provide stool specimens for laboratory analyses. This requires technical expertise to identify suspect cases, and laboratory capacity to conduct rotavirus diagnostic tests and genotyping. In another layer, at least one site per region or sub-region also performs 'enhanced' surveillance for rotavirus. This includes the collection of population-based surveillance data. Although hospital-based disease rates and case-fatality ratios can be applied to national data to generate national disease-burden estimates, high quality incidence rates derived from population-based denominators can provide additional and useful information, especially for evaluating vaccine impact and safety."

Due to inconsistencies in rotavirus laboratory testing and reporting in routine clinical practice, it is important to consider the establishment and continuation of active rotavirus surveillance programs where feasible. These active surveillance programs are useful in monitoring the impact of the vaccination program and any changes in rotavirus epidemiology. Fecal specimens collected by such surveillance programs should be tested for rotavirus positivity and, where practical, assessments of rotavirus serotype should be included. Despite secular geo-temporal variability in rotavirus serotype distributions, serotype trends over time and location should be assessed to identify any emergence of novel rotavirus serotypes or long-term changes to the predominant circulating strains. However, since serotype distribution varies naturally over time and location, changes in serotypes in the period following vaccine introduction should not necessarily be interpreted as being a result of vaccine introduction.

Post-marketing surveillance for rotavirus vaccine safety has been implemented in several countries that introduced the vaccine early. As an example, a network has been developed in Latin American countries, termed "SANEVA", with facilitation by PAHO. No clear signals of vaccine-related adverse effects are yet apparent from this network, but further strengthening of the surveillance activities is a priority. The Global Advisory Committee on Vaccine Safety (GACVS) reviewed the latest data from the Americas and Australia at its December meeting. Although the risk of intussusception and other severe

adverse events appears very low, GACVS emphasized the importance of continuing to accumulate post marketing surveillance data and stressed particularly the importance of setting up surveillance systems for such effects as the vaccines were introduced into increasing numbers of developing countries.

X. Extrapolating vaccine efficacy data

Underlying concepts:
1. Vaccine efficacy is substantial but lower in developing countries than in earlier trials in Europe and in North and South America. Vaccine safety continues to be acceptable in all settings studied.

2. In developing countries with high rotavirus disease incidence, even moderate to low vaccine efficacy translates into significant numbers of severe rotavirus gastroenteritis cases prevented and into significant public health impact. More rotavirus disease burden may be prevented in developing countries despite lower vaccine efficacy than in countries with low rotavirus disease burden and higher vaccine efficacy.

3. 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 may be extrapolated for use in populations in the same under-5 mortality rate category.

Experience with previous live oral rotavirus vaccines and with other oral vaccines (e.g., OPV, typhoid, cholera) has raised potential concerns about diminished performance of rotavirus vaccines in low income, developing country settings where many factors (e.g., concurrent enteric infections, malnutrition, co-morbidities, other oral vaccines) may interfere with vaccine performance. Thus, in its 2007 position paper[11], which was based on the 2005 SAGE recommendations, WHO limited the indication for use of rotavirus to countries in the Americas and Europe where the safety and efficacy of the vaccine had been established. Additional data from low income populations, particularly from Africa and Asia, were requested to extend the indication for use globally in the WHO position paper. The recently available results from clinical trial studies in Africa and Asia and vaccine effectiveness data from Latin America provide evidence to inform a global recommendation for vaccine use.

Recognizing that conducting clinical trials in every region or population is neither necessary nor practical, a need exists for extrapolating the results of rigorously conducted clinical trials and supporting studies to other populations. These extrapolations should capture a variety of factors, potentially including background rates of severe rotavirus

gastroenteritis among the unvaccinated population, the prevalence of other health conditions, differences in viral transmission, maternal practices and protective antibodies, and other population characteristics[75] [76] [77]. These factors are not necessarily consistent across a geographical region (e.g., the large variation in Asia between high income countries like Korea and Japan and low income countries in the Indian subcontinent). A meeting of experts convened by WHO in 2007 to discuss this issue found consensus that the breadth of these factors relative to the performance of live oral vaccines may be better captured by an existing tool for evaluating multi-factorial health comparisons of populations, such as under-5 year old mortality rate categories which provide a more homogenous grouping of countries across these parameters. For the purposes of the WHO SAGE, the performance of rotavirus vaccines in populations falling under similar under-5 mortality rate categories allows acceptable comparisons of vaccine performance in terms of population and socioeconomic parameters and is potentially more predictive of how oral vaccines might perform in a country than the country's geographical location[78].

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Appendix A. Summary of rotavirus virology, clinical presentation, and epidemiology

Rotaviruses belong to the *Reoviridae* family, genus *Rotavirus*. The viruses possess a segmented, double-stranded RNA genome with each segment coding for a structural or nonstructural protein. Structural proteins that comprise the outer viral capsid are used to define serotype nomenclature. The proteins VP4 and VP7 induce type-specific neutralizing antibodies and are involved in protective immunity. To date, rotavirus serotypes consist of 19 G-types and 28 [P]-types with extensive potential for gene reassortment. Of the possible rotavirus type combinations, fewer than twenty serotypes are most commonly found in humans and their relative prevalence and distribution changes over time.

The clinical spectrum of rotavirus illness ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death. Following an incubation period of 1–3 days, the illness often begins abruptly, and vomiting often precedes the onset of diarrhea. Gastrointestinal symptoms generally resolve in 3–7 days. Up to one–third of patients have a temperature of >39°C. Several recently published studies indicate that rotavirus infections are more severe than disease caused by other gastrointestinal pathogens. Antigenemia was detected in the serum of >90% of rotavirus positive children until approximately 5 days following symptom onset, indicating that natural rotavirus infections may commonly spread beyond the intestines into the blood stream, causing systemic viremia. No specific antiviral therapy is available.

Rotavirus is highly communicable, with a small infectious dose of < 100 virus particles[78] and is shed in high concentrations in the stools of infected children. The virus is transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites. Rotaviruses also are likely transmitted by other modes, such as fecally contaminated food and water and possibly via respiratory droplets. Repeated

infections occur from birth to old age, but natural immunity renders the majority of infections asymptomatic after the first years of life.

Appendix B. Characteristics of live, attenuated oral rotavirus vaccines, RotaTeq® and Rotarix®

	RotaTeq®, Merck	Rotarix®, GSK
Parent rotavirus strain	Bovine strain WC3 (type G6P7[5])	Human strain 89-12 (type G1P1A[8])
Vaccine composition	Reassortant strains G1 x WC3 G2 x WC3 G3 x WC3 G4 x WC3 P1A[8] x WC3	Human strain 89-12 (type G1P1A[8])
Vaccine titer	≥2.0–2.8 x 10^6 infectious units (IU) per dose, depending on serotype	≥$10^{6.0}$ median cell culture infective dose (CCID50) after reconstitution, per dose
Cell culture substrate	Vero cells	Vero cells
Formulation	Liquid requiring no reconstitution	Vial of lyophilized vaccine with a prefilled oral applicator of liquid diluent (1 ml)
Applicator	Latex-free dosing tube	Tip cap and rubber plunger of the oral applicator contain dry natural latex rubber. The vial stopper and transfer adapter are latex-free.
Other content	Sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture median, and trace amounts of fetal bovine serum.	Lyophilized vaccine: amino acids, dextran, Dulbecco's modified Eagle Medium sorbitol, and sucrose. DMEM contains: Liquid diluent contains calcium carbonate, sterile water, and xanthan
Preservatives	None	None
Shelf life	24 months	24 months
Storage	Store refrigerated at 2ºC to 8º C (36ºF to 46ºF). Administer as soon as possible after being removed from refrigeration. Protect from light.	Storage before reconstitution: Vials of lyophilized vaccine-refrigerate at 2ºC to 8º C (36ºF to 46ºF); Diluent may be stored at a controlled room temperature of 20ºC to 25ºC (68ºF to 77ºF). Protect vials from light Storage after reconstitution: Administer within 24 hours of reconstitution. May be stored refrigerated at 2ºC to 8ºC (36ºF to 46ºF) or at room temperature up to 25ºC (77ºF), after reconstitution.
Volume per dose	2 ml	1 ml

Appendix C. Study characteristics and summary of efficacy results of Rotarix® and RotaTeq® pivotal efficacy trials

	RV1 Study 023	RV1 Study 036		RV5 REST Study	
Study locations	Latin America	Europe		Clinical efficacy: Finland and U.S. Healthcare utilization cohort: 11 countries (80% of infants from Finland and US)	
Randomization vaccine: placebo	1:1	2:1		1:1	
Number infants in analysis					
Year 1 ATP	17,867	3,874		4,512	
Year 2 ATP	14,237	3,848		1,569	
				Healthcare utilization cohort: 57,134	
Age at doses, per protocol	Dose 1: 6–12 wks (12 weeks 6 days) 1 country: 6–13 wks (13 weeks 6 days) Dose 2: 1–2 mn later, at age ≤24 wks (24 weeks 6 days)	Dose 1: 6–14 wks (14 weeks 6 days) Dose 2: 1–2 mn later, at age ≤24 wks (24 weeks 6 days)		Dose 1: 6–12 wks (12 wks 0 days) Subsequent doses: 4–10 wks apart Dose 3: age ≤32 wks (32 wks 0 days)	
Primary efficacy endpoint	Prevention of severe rotavirus GE caused by circulating wild-type strains from 2 weeks after dose 2 until age one year	Prevention of rotavirus GE of any severity caused by circulating wild-type strains from 2 weeks after dose 2 until end of 1st rotavirus season		Prevention of wild-type G1–G4 rotavirus GE 14 or more days after dose 3 through 1st full rotavirus season after vaccination	
Any rotavirus GE		Thru 1st season		Thru 1st full season (G1–G4)	
		24/2,572 V	94/1,302 P	82/2,207 V	315/2,305 P
		87 (80, 92)		**74 (67, 80)**	
		2nd season		2nd full season (G1–G4)	
		61/2,554 V	110/1,294	36/813 V	88/756 P
		72 (61, 80)		**63 (44, 75)**	
		Thru 2nd season[a]			
		85/2,572 V	204/1,302 P		
		79 (73, 84)			

Severe rotavirus GE	To age 1 year: clinical [b]					
	12/9,009 V	77/8,858 P				
	85 (72, 92)					
	To age 1 year: Vesikari ≥11[c]		Thru 1st season: Vesikari ≥11		Thru 1st full season: Clark>16 (G1–G4) [d]	
	11/9,009 V	71/8,858 P	5/2,572 V	60/1,302 P	1/2,207 V	51/2,305 P
	85 (71, 93)		**96 (90, 99)**		**98 (88, 100)**	
	2nd year[a]: Vesikari ≥11		2nd season[c] :Vesikari ≥11		2nd full season: Clark >16 (G1–G4)	
	19/7,175 V	101/7,062 V	19/2,554 V	67/1,294 P	2/813	17/756
	81 (70, 89)		**86 (76, 92)**		**88 (49, 99)**	
	To age 2 years[e]: Vesikari ≥11		Thru 2nd season[a]*:* Vesikari ≥11			
	28/7,205	154/7,081	24/2,572 V	127/1,302 P		
	82 (73, 89)		**90 (85, 94)**			
Hospitalization for rotavirus GE	To age 1 year:		Thru 1st season:			
	9/9,009 V	59/8,858 P	0/2,572 V	12/1,302 P		
	85 (70, 93)		**100 (82, 100)**		Healthcare utilization cohort: (G1–G4) [f]	
	2nd year[a]		2nd season[c]		6/28,646 V	144/28,488 P
	15/7,175 V	80/7,062 P	2/2,554 V	13/1,294 P	**96 (91, 98)**	
	82 (68, 90)		**92 (66, 99)**			
	To age 2 years[e]:		Thru 2nd season[a]			
	22/7,205 V	127/7,081 P	2/2,572 V	25/1,302 P		
	83 (73, 90)		**96 (84, 100)**			

GE, gastroenteritis V, vaccine group P, placebo group ATP, according-to-protocol
Trials were conducted in different countries and have other differences, including different case definitions and durations of follow-up, so direct comparisons of efficacy results between the trials can not be made.
Efficacy assessment periods began two weeks after last dose of series in the per-protocol analyses
[a]"Thru 2nd season" results are the efficacy results from the combined efficacy period, based on 2572 RV1 recipients and 1302 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to the end of the first rotavirus season) and 2554 RV1 recipients and 1294 placebo who entered the second efficacy period (from the visit at the end of the first rotavirus season up to the visit at the end of the second rotavirus season).
[b]Clinical definition: severe GE defined as diarrhea (3 or more loose or watery stools within 24 hours), with or without vomiting, that required overnight hospitalization or rehydration therapy equivalent to WHO plan B (oral rehydration) or plan C (intravenous rehydration) in a medical facility.
[c]Vesikari score: severe GE defined as ≥11 on this 20-point clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed.
[d]Clark score: severe GE defined as >16 on this 24-point clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes

[e] "To age 2 years" results are the efficacy results from the combined efficacy period, based on 7205 RV1 and 7081 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to age 1 year) and 7175 RV1 and 7062 placebo recipients who entered the second efficacy period (from age 1 year up to age 2 years)

[f] Efficacy results based on G1-G4 rotavirus-related hospitalizations among 28,646 RV5 recipients and 28,488 placebo recipients in the healthcare utilization cohort analysis contributing ~35,000 person-years of total follow-up during the first year, and a subset of the cohort (2,502 infants total) contributing ~1,000 person-years of follow-up during the second year.

Appendix D. Summary of efficacy against type-specific rotavirus gastroenteritis in Rotarix® and RotaTeq® trials

Study	Rotarix® Study 023		Rotarix® Study 036		RotaTeq® REST Study*	
Locations, randomization	Latin America; 1:1		Europe; 2:1		Clinical efficacy: Finland and U.S. Healthcare utilization cohort: 11 countries (80% of infants from Finland and US); 1:1	
Type						
G1P8					Thru 1st full season: any severity	
					72V	286P
					75 (67, 81)	
	To age 1 year: severe (clinical)[a]					
	3V	36P				
	92 (74, 98)					
	To age 1 year: Vesikari ≥11[b]		Thru 1st season: Vesikari ≥11			
	3V	32P	2V	28P	Hospitalization/ED visits	
	91 (71, 98)		**96 (85, 100)**		16V	328P
	To age 2 years: severe (clinical)		Thru 2nd season: Vesikari ≥11		**95 (92, 97)**	
	10V	55P	4V	57P		
	82 (65, 92)		**96 (90, 99)**			
G2P4					Thru 1st full season: any severity	
					6V	17P
					63 (3, 88)	
	To age 1 year: Vesikari ≥11		Thru 1st season: Vesikari ≥11			
	5V	9P	1V	2P	Hospitalization/ED visits	
	45 (-81, 86)		**75 (-386, 100)**		1V	8P
	To age 2 years: severe (clinical)		Thru 2nd season: Vesikari ≥11		**88 (<0, 99)**	
	5V	8P	2V	7P		
	39 (-113, 84)		**86 (24, 99)**			
G3P8					Thru 1st full season: any severity	
					1V	6P
					83 (<0, 100)	
	To age 1 year: severe (clinical)		Thru 1st season: Vesikari ≥11			
	1V	8P	0V	5P	Hospitalization/ED visits[b]	
	88 (8, 100)		**100 (45, 100)**		1V	15P
	To age 2 years: severe (clinical)		Thru 2nd season: Vesikari ≥11		**93 (49, 99)**	
	3V	14P	1V	8P		
	79 (25, 96)		**94 (53, 100)**			

G4P8					Thru 1st full season: any severity	
					3V	6P
					48 (<0, 92)	
	To age 1 year: severe (clinical)		Thru 1st season: Vesikari ≥11			
	1V	2P	0V	7P	Hospitalization/ED visits[b]	
	NA		**100 (65, 100)**		2V	18P
	To age 2 years: severe (clinical)		Thru 2nd season: Vesikari ≥11		**89 (52, 98)**	
	7V	14P	1V	11P		
	62 (4, 87)		**95 (68, 100)**			
G9P8					Thru 1st full season: any severity	
					1V	3P
					65 (<0, 99)	
	To age 1 year: severe (clinical)		Thru 1st season: Vesikari ≥11			
	2V	21P	2V	19P	Hospitalization/ED visits	
	91 (62, 99)		**95 (78, 99)**		0V	14P
	To age 2 years: severe (clinical)		Thru 2nd season: Vesikari ≥11		**100 (70, 100)**	
	9V	66P	13V	44P		
	87 (73, 94)		**85 (72, 93)**			

Appendix E. Excerpt from The WHO Department of Vaccines and Biologicals, "Introduction of Rotavirus Vaccines into National Immunization Programs: Management manual including operational information for health workers"[78]

Who can get rotavirus? Nearly all children in the world, regardless of where they live, will suffer at least one rotavirus infection in the first three to five years of life. However, more than 80% of rotavirus deaths occur in developing countries, where prompt medical care may be out of reach.

How is rotavirus spread?

Rotavirus is highly contagious. Rotaviruses are spread primarily by the faecal-oral route, directly from person-to-person, or indirectly via contaminated fomites.

What are the symptoms of rotaviruses?

Clinical illness from rotavirus infection ranges from mild watery diarrhoea of limited duration, to severe diarrhoea with vomiting that may result in dehydration and death if appropriate treatment is not available. Following an incubation period of 1–2 days, the illness can begin abruptly, and vomiting often precedes the onset of diarrhoea. Up to one-third of patients may have a temperature greater than 39° C. Gastrointestinal symptoms generally resolve within 3–7 days. Children with rotaviruses often suffer frequent vomiting that make it difficult to administer oral rehydration solution (ORS) at home, and medical care is required. It is not possible to distinguish rotavirus from other causes of gastroenteritis on clinical grounds alone, and a laboratory test is required to confirm the diagnosis. The first infection is usually the most severe; later infections may be milder or asymptomatic due to previous acquired cross-immunity.

How can rotavirus infection be prevented?

Improvements in sanitation, safe water supply, increasing use of oral rehydration solution (ORS), promotion of breastfeeding and improvement in children's nutrition are important to prevent and manage diarrhoeal disease. However, such interventions have limited benefits in preventing rotavirus infection. Childhood rotavirus vaccination is the best method to prevent severe disease and deaths.

Is there a vaccine against rotavirus?

Two orally-administered, live, attenuated vaccines against rotavirus infection have been demonstrated to be safe and highly efficacious in large-scale clinical trials; Rotarix™, manufactured by GlaxoSmithKline Biologicals, and RotaTeq™, manufactured by Merck and Co. They provide good protection against severe rotavirus-related diarrhoea in young children, but they do not provide 100% protection against the infection. Both vaccines are prequalified by WHO, and have already been introduced into the routine childhood immunization in many countries. The current rotavirus vaccines differ in antigen composition and immunization schedule, but they are considered equally safe and efficacious by WHO.

Who should get the rotavirus vaccine?

Generally, all children should receive rotavirus vaccine in infancy.

Rotavirus vaccines must never be injected.

Can the rotavirus vaccines be co-administered with other vaccines?

Rotavirus vaccines may be given at the same time as other childhood vaccines, such as oral polio (OPV), inactivated polio (IPV), diphtheria-tetanus-acellular pertussis (DTaP),

diphtheria-tetanus- whole cell pertussis (DTwP), Hepatitis B (HepB) vaccine, *Haemophilus influenzae* type b (Hib) vaccine, or pneumococcal conjugate vaccine (PCV).

Is there any reason why a child should not be given rotavirus vaccine?

A child who had a serious allergic reaction after a previous dose of rotavirus vaccine, or to a vaccine component, should not be vaccinated.

What are the precautions to rotavirus vaccine administration?

Until more information is available on the safety and efficacy of administering these vaccines to infants with pre-existing chronic gastrointestinal conditions, to infants who are potentially immunocompromised, and those who are HIV-exposed or infected, physicians should assess the potential risks and benefits of rotavirus vaccination on an individual basis. In infants with ongoing moderate to severe gastroenteritis or serious febrile illness, vaccination may be postponed until the child completely recovers. The presence of minor infections, however, is not a contraindication for vaccination.

What are the possible adverse events following rotavirus vaccine?

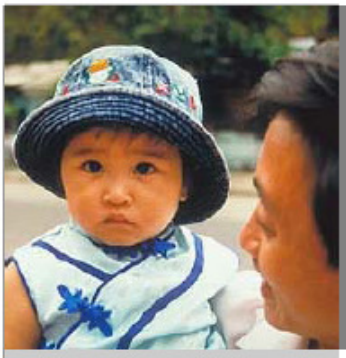
Current rotavirus vaccines are generally well tolerated. They do not appear to cause any serious adverse events. A small proportion of infants receiving the vaccine may suffer short episodes of mild diarrhoea, vomiting or fever in the week following vaccination. Any adverse events and other problems related to the vaccines should be reported through the existing AEFI Reporting System established by the National Immunization Programme.

In the 1990s, a different type of rotavirus vaccine was withdrawn after reports of intussusception — an acute bowel obstruction in which one segment of bowel becomes infolded within another segment — following vaccination. Most cases of intussusception occurred in infants aged ≥90 days at the time of the first dose. The current rotavirus vaccines have been tested in large clinical trials involving more than 70 000 children, and have not been associated with intussusception. Data from countries where the new rotavirus vaccines have already been introduced in routine infant immunization have not shown association of the vaccines with any serious adverse events. However, data currently available are still too few to rule out, with confidence, a risk of small magnitude.

How should the rotavirus vaccines be stored?

Rotavirus vaccines should be stored between 2°C and 8°C**.**

Appendix F. Executive Summary from the Investment Case for GAVI Secretariat, "Accelerating the introduction of rotavirus vaccines into GAVI-Eligible Countries" October 2006, PATH Rotavirus Vaccine Program.
THE FULL APPENDIX F IS POSTED ON THE SAGE MEETING SHAREPOINT



Accelerating the Introduction of Rotavirus Vaccines into GAVI-Eligible Countries

Investment Case for
GAVI Secretariat

Submitted by
PATH's Rotavirus Vaccine Program
in collaboration with
WHO and the US CDC

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