



Report of the Meeting

**Rotavirus Vaccines:
Evaluating Clinical Trial Data and Guiding Future Research**

Atlanta, November 2007

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List of Abbreviations

ACIP	Advisory Committee for Immunization Practices
AIIMS	All India Institute of Medical Sciences
CDC	Centres for Disease Prevention and Control
DALY	Disability adjusted life years
DCVRN	Developing Countries Vaccine Regulators Network
DTP1	<i>Diphtheria-Tetanus-pertussis</i> vaccines, first dose
DTP3	<i>Diphtheria-Tetanus-pertussis</i> vaccines, third dose
EMEA	European Medicines Evaluation Agency
EMRO	Eastern Mediterranean Regional Office
EPI	Expanded Programme for Immunization
FDA	Food and Drug Administration
GACVS	Global Advisory Committee for Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GDP	Gross domestic product
GMT	Geometric mean titre
HiB	<i>Haemophilus influenzae</i> type B vaccine
HIV	Human Immunodeficiency Virus
NIH	National Institutes of Health
NSP4	Non-structural protein 4 (of rotavirus)
OPV	Oral polio vaccine
OPV3	Oral polio vaccine, third dose
PAHO	Pan-American Health Organization
PATH	Programme for Appropriate Technology in Health
PMS	Post-marketing surveillance
RRV-TV	Rhesus reassortant rotavirus vaccine - tetravalent
SAGE	Strategic Advisory Group of Experts
TB	Tuberculosis
VAERS	Vaccine Adverse Events Reporting System
VLPs	Virus-like particles
VSD	Vaccine Safety Datalink
VP4	Viral protein 4 (of rotavirus)
VP6	Viral protein 6 (of rotavirus)
VP7	Viral protein 7 (of rotavirus)
WHO	World Health Organization

Background

Many recent advances in the field of rotavirus vaccines have occurred since November 2005, when the WHO's Strategic Advisory Group of Experts (SAGE) first reviewed the clinical trial data generated by the pharmaceutical industry on two live oral attenuated rotavirus vaccines, and produced a set of recommendations¹.

In January 2006, the large safety and efficacy studies of these two vaccines were published side by side in the *New England Journal of Medicine*, indicating a high safety profile with regard to intussusception, and good efficacy against severe rotavirus gastroenteritis in the populations evaluated in Latin America, US and Europe. The vaccines, Rotarix® (GSK Biologicals) and RotaTeq® (Merck & Co) were soon licensed in the country of manufacturer, by the EMEA and the FDA respectively, and are currently licensed in more than 100 countries globally. The vaccines are being introduced in high, middle, and low income countries within the same time frame.

In November 2006, the Global Alliance for Vaccines and Immunization (GAVI) Investment Case for rotavirus vaccines was approved, making it possible for international financing for rotavirus vaccines for GAVI-fund eligible countries.

One of the vaccines has been pre-qualified by WHO and the other is currently under review.

Finally, phase III clinical efficacy studies were initiated and are ongoing with both vaccine candidates in five countries in Africa and two in Asia, sponsored by the public health sector.

The WHO position on rotavirus vaccines was published in the *Weekly Epidemiological Record* August 10, 2007 and serves as a reference document for this meeting².

¹ *Conclusions and recommendations from SAGE. WER 2006; 81: 8*

² *Rotavirus Vaccines Position Paper. WER 2007; 82: 285-296*

Introduction

Dr Duncan Steele opened the meeting with welcome remarks to the participants and reviewed the objectives of the meeting, which included the following:

- Review the WHO position and the prequalification status of rotavirus vaccines
- Discuss the recommendations on rotavirus vaccines by WHO's Strategic Advisory Group of Experts (SAGE) and the Global Advisory Committee on Vaccine Safety (GACVS)
- Summarize the status of the Phase II/III rotavirus vaccine trials in developing countries
- Discuss scientific and technical challenges to rotavirus vaccine introduction in developing countries
- Outline potential solutions to facilitate introduction of rotavirus vaccines in developing countries

WHO strongly recommends the inclusion of rotavirus vaccination into the national immunization programmes of countries and regions where vaccine efficacy data suggest a significant public health impact, and where the appropriate infrastructure and financing mechanisms are available. However, until the full potential of the current rotavirus vaccines has been confirmed in all regions of the world, and in particular Africa and Asia, WHO is not prepared to recommend global inclusion of rotavirus vaccines.

With regard to the immunization schedule for these vaccines, the WHO position paper emphasizes that vaccination should not be initiated for infants aged >12 weeks or in catch-up vaccination campaigns because of the potential higher risk of intussusception when the first dose is administered to infants aged >12 weeks. The vaccine course should be completed no later than 24 weeks of age (Rotarix®) or 32 weeks of age (RotaTeq®), depending on the vaccine, as per the manufacturers package insert for the vaccine.

Finally, WHO recommends that rotavirus vaccines should be introduced in association with careful post-marketing national surveillance. Well planned post-marketing surveillance should aim to evaluate any potential association with intussusception and to measure the health impact of the vaccine after introduction.

The work of three WHO committees or teams have direct bearing on the introduction of rotavirus vaccines, and are discussed below.

- 1) The 2005 SAGE recommendations on rotavirus vaccines are reflected in the WHO position paper which recommends the inclusion of rotavirus vaccines into the national immunization programmes of regions where vaccine efficacy data suggest a significant public health benefit. Lacking efficacy data of these vaccines in populations living in Africa and Asia, where conditions may negatively influence a live oral rotavirus vaccine, there was a recommendation to urgently generate data in these regions. The data are being generated in clinical trials co-ordinated by PATH and the pharmaceutical industry.

The SAGE recommendations have provided a framework for the interpretation and assessment of individual countries that would qualify for international financing for vaccine procurement and introduction.

- 2) The Global Advisory Committee for Vaccine Safety (GACVS) reviews the safety data generated with rotavirus vaccines on an ongoing basis. The initial assessment of the safety of current rotavirus vaccines in the large clinical trials was that the pre-licensing safety data for these vaccines was reassuring. However, GACVS has also recognized and emphasized the need for ongoing post-licensure safety monitoring for these vaccines. GACVS continues to monitor the situation with regular updates from the pharmaceutical industry and other interested partners such as the CDC, FDA and PAHO.
- 3) Finally, a broad overview of the WHO prequalification process was discussed. Currently, Rotarix® is pre-qualified for procurement by the GAVI, although the “indication for use does not yet extend to all regions of the world”. RotaTeq® has been submitted and is under review for WHO prequalification.

The current situation with vaccines being introduced into national immunization schedules in many countries, a positive GAVI-endorsement for the procurement of vaccine, increasing pressure for vaccine uptake by some groups and a limited recommendation for the use of the vaccines, has led to some confusion.

For instance, in the countries of the WHO Eastern Mediterranean Region, no countries are included in the vaccine trials nor in the stated recommendations. The countries in this region are unique in their geography, income, population and rotavirus epidemiology and disease burden. Some countries are situated in continental Asia and others in continental Africa. Data on rotavirus vaccine immunogenicity, efficacy and safety from these EMRO region countries are not available, nor planned at this time. Nevertheless, rotavirus vaccines are licensed in many of these countries and available in the private market of several. Certain GAVI-eligible countries in this region have expressed interest to introduce rotavirus vaccines and have applied for GAVI funding, yet it is unclear whether they will “qualify” for GAVI procurement, given the lack of regional efficacy data.

The situation for middle-income countries where rotavirus disease burden is high and mortality can vary substantially by country and even within country, is also vexing. Many of these middle-income countries have rotavirus vaccines available through the private market at a cost that is greater than vaccine cost in other high income countries. Some of these countries are still struggling to introduce HiB vaccines and no funding mechanism exists for nation-wide vaccine introduction, particularly for the poorest children, in these middle-income countries.

Strain diversity in this region is also variable and has led to regional concerns of vaccine efficacy and strain replacement. Given the natural molecular evolution of rotavirus strains, with the introduction of “new” rotavirus strains into the community prior to the introduction of rotavirus vaccines, as occurred with G9 strains in 1995 and G12 strains in 2002, caution should be exercised when talking about “strain replacement” in the post-rotavirus vaccine era. Nevertheless, the wide diversity of strains in developing countries may well affect their protective efficacy in infants and is of concern. Ongoing strain surveillance is recommended for this reason.

Using these examples, the potential for vaccine impact as well as the challenges of vaccine introduction that face the global community over the next 2-3 years was highlighted. The challenge for the meeting participants was to generate a scientific rationale and guidelines for evaluating the clinical trial data which will become available within the next year, and to direct the future research agenda for rotavirus vaccines.

Session 1: The Global Priority for Rotavirus Vaccine Development

Update on the introduction and safety of rotavirus vaccines (U Parashar, CDC)

Dr Umesh Parashar provided information on the current status of the introduction and safety of the rotavirus vaccines in the USA and Latin America. In February 2006, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of US infants with 3 doses of RotaTeq® at 2, 4 and 6 months of age. In Latin America, five countries (Brazil, Mexico, Panama, El Salvador, and Venezuela) have introduced RotaRix® in their routine EPI schedule. Nicaragua through a 3-year donation from the vaccine manufacturer (Merck & Co), has introduced RotaTeq® into their EPI schedule in October 2007.

The most accessible post-licensure vaccine coverage and safety monitoring data is available for the US, where the current post-licensure vaccine effectiveness evaluations are being conducted. In the US, no system for real-time monitoring of coverage exists. However, data from 6 sentinel registry sites that do have real-time regional coverage suggest that, at these sites, nearly half of all US infants may be fully vaccinated with 3 doses of RotaTeq® prior to the 2008 rotavirus season. With regard to age-adherence, 86% of the children in these registries received dose 1 between 6-12 weeks of age according to the ACIP recommendation. Similarly, in the Vaccine Safety Datalink (VSD), a cohort of US infants enrolled in managed care, 93% of the first doses were administered to infants 6-12 weeks of age.

The safety monitoring data from the US is also the most complete data available for the use of the vaccine, where available data do not indicate that RotaTeq® is associated with intussusception. In addition, the current safety monitoring data exclude an intussusception risk similar in magnitude to Rotashield®. Continued monitoring is ongoing to further assess the safety profile of the RotaTeq® vaccine in the US.

Approximately 9.1 million doses of RotaTeq® were distributed by the manufacturer as of the end of August, 2007. During the period February 1, 2006 to September 25, 2007, the passive reporting system VAERS (Vaccine Adverse Event Reporting System) received 160 intussusception reports following RotaTeq® administration in the US. A careful review of the data shows that within 1-7

days post-vaccination, 27 intussusception cases were reported compared with 50 expected background cases (RR=0.51; 95% CI=0.32-0.81); within 1-21 days, 38 cases were reported post-vaccination compared with the expected background of 151 cases (RR = 0.30; 95% CI = 0.20, 0.44). A limitation of this data is that the assumptions included 100% administration of the vaccine doses distributed and 100% reporting of cases to the VAERS, which are unlikely to be real. Nevertheless, there is no apparent signal of an association so far.

In VSD, 3 intussusception cases occurred within 30 days of 111,521 RotaTeq® vaccinations whereas 3.4 cases would be expected to occur by chance alone. The data after dose 1 only were also reviewed and indicated that the available data for dose 1 also did not identify a signal similar to Rotashield®. The slight increase in cases proximal to vaccination was noted, although this may be due to better reporting to VAERS if the intussusception occurred closer to the vaccination than later. ACIP has indicated that no adverse events signal has been detected, but that ongoing monitoring is crucial, particularly given that intussusception is a rare event and excluding smaller magnitude of risk will require additional data.

In addition, ongoing collaborations between PAHO, CDC, PATH and ministries of health to assess post-licensure vaccine impact and safety in the Latin Americas are underway. Two case-control vaccine effectiveness studies are ongoing in Nicaragua and El Salvador. Plans are also in place to assess risk of intussusception after rotavirus vaccination through a case-series and case-control method in Brazil and Mexico. Finally, the vaccine manufacturers also have several ongoing post-licensure safety and effectiveness studies in Europe and in Latin America and data from these studies will likely become available in the next 1-2 years.

Challenges to rotavirus vaccine introduction in developing countries (D Steele, WHO)

Dr Duncan Steele briefly reviewed the progress and challenges in the development of rotavirus vaccines over the previous 20-30 years and highlighted the international prioritization for these vaccines. The potential impact on reducing childhood deaths through vaccination, particularly in Asia and Africa where rotavirus vaccines have the greatest need is impressive and would contribute

to the Millennium Development Goals. Despite this and the recent successes recorded for rotavirus vaccines, significant barriers continue to exist for live oral rotavirus vaccines and include:

- vaccine efficacy in high-mortality regions;
- safety of rotavirus vaccines in low-income versus middle and high income countries;
- safety and efficacy in vulnerable sub-populations (e.g., HIV-positive, malnourished infants);
- programmatic barriers in countries for their introduction;
- financial barriers including absolute cost of vaccine; and
- vaccine supply issues

Experience with other live oral vaccines have shown limited immunogenicity or reduced efficacy in populations living in regions with low socio-economic conditions, poor water and sanitation, or high endemicity of the disease, or where enteric infections are common with high morbidity. Many factors may play a role in the diminished efficacy of live, oral vaccines seen in developing countries, including circulating maternal antibodies, malnutrition, low birth-weight, immunodeficiency, co-infections with other enteric agents, and other disease co-morbidities. For these and other reasons, live, oral rotavirus vaccines previously have not performed well in developing countries and the potential impact on new rotavirus vaccines should be considered.

There is also the potential for interaction or interference with OPV, which is still widely used in developing countries. Immunogenicity data from several studies indicates that the current rotavirus vaccines do not affect the sero-conversion to any of the three poliovaccine serotypes, or the geometric mean titres (GMT) of the OPV response after the full course of doses. Rotavirus antibody titres were lower after the first dose of rotavirus vaccine when given concomitantly with OPV, but were similar after the second or third dose.

Programmatic issues for attaining high vaccine coverage in developing countries in the infants at risk, within the WHO recommended age brackets and in hard-to-reach areas, will remain a real challenge to rotavirus vaccine introduction. Vaccine coverage of routine EPI vaccines is less than ideal in regions with the greatest need for rotavirus vaccines. Cold-chain capacity and the immunization delivery capacity will need particular attention in resource poor settings, where the immunization systems are already over-burdened.

Vaccine financing is improving but substantial work still remains to be done. For example, even with co-financing from donors, low income countries may not be able to afford vaccine in the short or long-term.

Status of the studies of the licensed vaccines (P Dennehy)

Dr Penny Dennehy summarized the latest RotaTeq® and Rotarix® clinical trials data and focused the discussion on topics of heterotypic protection, partial-dose vaccine efficacy, vaccine virus shedding, and safety and efficacy in vulnerable groups, such as malnourished and HIV positive infants.

Strain-specific protection: With the exception of protective efficacy against P[4]G2 strains, both vaccines demonstrated excellent vaccine efficacy (>85%) against severe rotavirus disease from all circulating strains during the trials in Europe, Latin America, and US sites. Lower efficacy (~40%) of Rotarix® against P[4]G2 strains was noted in the Latin America cohort, although this was 86% in the European cohort. RotaTeq® also demonstrated good protection against severe diarrhoea with P[4]G2 strains (88%). However, limited sample size with wide confidence limits preclude firm conclusions of efficacy against the P[4]G2 strain at this time.

Partial dose protection: The vaccine trials were not designed to assess protection from less than full dose-series and data were limited as few children with partial dose-series exist in the trials. However, post-hoc analysis for RotaTeq® demonstrated a rate reduction in rotavirus gastroenteritis hospitalizations and emergency visits of 39%, 81%, and 95% after 1, 2, and 3 doses respectively. When limiting analysis outcome to gastroenteritis episodes between doses (e.g., between dose 1 and 2), vaccine efficacy was 83% after dose 1 of RotaTeq®. Insufficient data from the large Rotarix® trial is available in the public domain.

Faecal shedding of vaccine virus: For RotaTeq®, vaccine virus shedding was limited with 9% shedding after dose 1, none after dose 2 and only 0.3% after dose 3. The latest shedding was 15 days post dose 1 and one subject shed 4 days after dose 3. All infants had “low” quantities of virus

in the stool. In the Rotarix® trials, 54% of the infants shed the vaccine virus after dose 1 and 13% after dose 2. However, culturing the antigen positive stools revealed that only 26% of the infants were shedding live virus after dose 1.

Vulnerable groups: WHO requested that clinical trial data be generated in vulnerable populations, and the following data are available.

- *Malnourished infants:* for Rotarix®, no difference in vaccine efficacy was noted in malnourished infants compared to well-nourished infants; no data exists on efficacy of RotaTeq® in malnourished infants.
- *Premature infants:* In a sub-analysis of the large phase III trial with RotaTeq®, no difference in fever, vomiting, diarrhoea or irritability was noted between premature and full-term infants. A similar analysis is ongoing for Rotarix®.
- *HIV positive infants:* Published clinical trials with either vaccine excluded children known to be HIV positive at time of enrollment; however, HIV positive infants are included in the ongoing phase III efficacy trials in Africa with both vaccines.³

Update on rotavirus vaccine studies in Africa and Asia (K Neuzil, PATH)

Dr Kathy Neuzil provided an update on the progress of the Rotarix® and RotaTeq® phase III clinical trials that are currently ongoing in Africa and Asia. PATH's Rotavirus Vaccine Programme is working in partnership with both Merck and GSK Biologicals, respectively, to evaluate the use of their rotavirus vaccines in Asia and Africa.

- Studies of GSK Biologicals' Rotarix® vaccine are ongoing in South Africa and Malawi. No Rotarix® phase III trials are being conducted in Asia by the public sector.
- In Africa, efficacy trials for Merck's RotaTeq® are being conducted in Mali, Ghana and Kenya. In addition, efficacy trials for RotaTeq® are also ongoing in Bangladesh and Vietnam.

³ A clinical study to assess the immunogenicity and safety trial of Rotarix® in HIV-infected infants in South Africa is completed and results should be available mid-2008. A RotaTeq® safety and immunogenicity trial is scheduled to begin in second quarter 2008.

Results from these trials will be critical in enabling global and national policymakers to make evidence-based decisions about the introduction of rotavirus vaccines in developing countries.

Trials of both vaccines have similar eligibility criteria and are being given with routine EPI vaccines including OPV. Of note, HIV status is not an exclusion criterion in these trials. Primary and secondary outcome measures were selected based on consultations with many international experts and public health institutions. These trials are scheduled to be completed in 2008. An interim analysis for the Rotarix® trial will be conducted in first quarter of 2008. For RotaTeq®, analysis of the study will likely be completed in 2009.

These studies will provide clinical trial data of protective efficacy within the next 1-2 years that will be available for SAGE and other decision-makers to review. The trials will provide a framework for how the currently available rotavirus vaccines perform in some of the most impoverished regions of the world. Several crucial questions will need to be considered by SAGE and international donors with regard to vaccine introduction in Asia and Africa. Two questions of substantial relevance for vaccine introduction in Asia and Africa might include:

- 1) Will the data from these trials sites be applicable to other GAVI-eligible countries? What criteria should be used to extrapolate results from these sites to countries in other regions, such as EMRO (e.g., under-5 mortality, per capita GDP)? According to the WHO mortality strata, the current clinical trial sites are representative of countries from all of these strata. In particular, some of the countries in the clinical trials (e.g., Bangladesh, Mali) represent the most impoverished regions according to the WHO strata. Selection of the most impoverished regions for the trials was based on the rationale that an effective vaccine in these settings would be sufficiently effective in countries under WHO strata representing less impoverished regions.
- 2) What is an acceptable efficacy for the population of these regions with high rotavirus mortality and is there an absolute “cut-off” for efficacy below which a vaccine is deemed to have failed? To address this issue, other factors need to be included in addition to absolute efficacy, such as cost effectiveness of the vaccine and DALYs averted. For example

preliminary data with varying efficacy and current DTP3 coverage rates in Asia and Africa, suggest that rotavirus vaccines with moderate efficacy of 50-60% would still substantially reduce mortality and be potentially cost-effective.

Within the next 1-2 years, evidence will be available for decision-makers to assess the introduction of rotavirus vaccines in regions of the world with the highest rotavirus mortality.

Discussion of the presentations

One participant commented that the issue of intussusception will continue to be a barrier for the acceptance of rotavirus vaccines in the developing world. Despite the reassuring data that currently licensed vaccines do not carry the same risk of intussusception as Rotashield®, a finite risk of smaller magnitude cannot be excluded without data on a substantially larger number of vaccinated children. The safety of the current two vaccines with regard to administration of the first dose of the vaccine to infants aged >12 weeks has not been studied and intussusception among children receiving dose 1 after 12 weeks of age should be monitored closely. Dr Parashar responded that very few (<10%) of the US children were receiving dose 1 at age >12 weeks and for this reason, potential risk in this age group after dose 1 would be difficult to assess in the short term from the US rotavirus vaccine data base.

The potential protective effect in the clinical trial of the Rotarix® vaccine against intussusception was brought to attention by one participant and the question was raised whether post-licensure efforts have been undertaken to assess for a protective effect. In response to the Rotarix® trial data, another participant noted that a protective effect while intriguing was only noted in one of the two cohorts (the safety cohort and not in the efficacy cohort) suggesting that it could potentially be a chance occurrence. No current post-licensure data assessing temporal trends pre- and post-vaccination exist.

What questions will remain at the conclusion of the clinical trials? (M Santosham, JHU)

Dr Mathu Santosham elaborated on his experience in the developing countries with the HiB initiative, particularly based on introduction and dialogue with decision-makers. It was noted that inadequate communication between researchers and decision-makers was a major barrier to new vaccine introduction. Under-staffing of the immunization systems in country and the substantial burden of work with existing vaccines was identified as another potential barrier. For example, in Uttar Pradesh, India, coverage for existing EPI vaccines decreased as OPV coverage increased. There are many new vaccines that are being presented to countries with differing competing priorities, including other health sector needs and intervention strategies.

The clarity and consistency of messages from international donors, public health institutions, and researchers is of utmost importance in the successful introduction of a new vaccine. Consultation between decision-makers and those involved in the delivery process is critical. Communication and awareness should be enhanced and incorporated in the vaccine introduction plans. Considerably more resources are needed to achieve communication goals than typically anticipated. It was recommended that researchers use absolute numbers of deaths averted, for instance, as opposed to rate reductions when discussing with decision-makers issues related to vaccine benefit and introduction. In addition, identifying “local champions” is also crucial.

The effectiveness of non-vaccine interventions for the prevention of diarrhoeal disease are well known in countries, and the suggestion was made that vaccine introduction should be seen in the context of ongoing improvements in hygiene and sanitation levels, and the use of oral rehydration therapy, zinc supplementations, and other proven effective therapies. Vaccine introduction should not compete against, or try to replace, these effective interventions.

Finally, unresolved research and public health questions for rotavirus vaccines need to be considered. Mortality reduction needs to be considered as a priority for improved outcomes as a result of vaccine introduction in resource poor settings. No rotavirus vaccine trials to date, have studied mortality as an end-point, partly because of the large sample sizes that would be necessary and in part due to the close follow-up of participants in clinical trials, which makes death an

unlikely outcome in a clinical trial setting. Nevertheless, these studies need to be conducted to influence decision-makers of the value of rotavirus vaccines.

Other issues that need further study might include:

- comparison of rotavirus vaccines against traditional therapies (ORT, Zinc, hygiene) which would be difficult to undertake;
- laxity in dosing schedule to mimic real world situation (i.e., dose one at older age);
- trial of rotavirus vaccines in step-wedge design (cluster) which might be limited in interpretation but would provide the intervention to all members of the community;
- public health impact of viral shedding with regard to immuno-compromised children and possible herd immunity;
- possibility of viraemia after rotavirus vaccination and its potential impact;
- interchangeability of rotavirus vaccines under routine use;
- impact of a strict schedule on rotavirus vaccine coverage and impact on administration of vaccine outside recommended administration schedule;
- vaccine effectiveness when co-administered with OPV;
- vaccine efficacy in developing countries;
- long-term sustainability of vaccine administration in poor nations—what will happen when GAVI funding diminishes?

The need for demonstrating mortality reduction through vaccination and having an effective communication plan when discussing vaccine introduction issues with key decision-makers was highlighted.

Discussion of the presentation

Many participants concurred with the recommendation for identifying local champions but also raised the issue of how to identify effective champions in country. One participant highlighted that identifying and nurturing local champions was the driving force behind the regional rotavirus surveillance networks that have resulted from collaborations among academia, ministries of health, CDC, WHO, and PATH. Such networks are particularly relevant to decision-makers as they generate local and regional data and are supported by highly effective local champions. These networks when established prior to vaccine introduction also provide crucial data for assessing

impact after vaccine introduction. It was also emphasized that local champions are important not only for communicating effectively with decision-makers but also with citizens using sound culturally appropriate language which in turn reduces misperceptions about vaccines and builds trust. Lastly, the issue was raised that investigators have to be careful about the fine line that exists between being local champions and being misperceived or misrepresented as being biased towards specific vaccines.

Recommendations for rotavirus vaccines for consideration (T Vesikari, Tampere University)

Dr Timo Vesikari opened the discussion by presenting the current rotavirus vaccines in historical context through a review of data from previous rotavirus vaccine trials in developing countries. Although the early vaccine candidates had a lower efficacy in developing world settings, many trials demonstrated some degree of success even under these settings. The risk is allowing the good to become the enemy of the best, in the process of comparing data from clinical trials in developing countries against those trials in developed countries. The vaccines and the trials discussed included the following:

- *RIT4237*: the first rotavirus vaccine, this was a bovine strain (with a G6 serotype which is not found in human rotaviruses), demonstrated good efficacy (>80%) in Finland against severe rotavirus disease, but lower efficacy was observed in clinical trials conducted in developing countries such as Peru, Brazil, Rwanda and The Gambia.
- *WC3*: was another bovine strain (G6), which performed well in trials in the US but a trial in Central African Republic reported no efficacy.
- *RRV-TV (eventually licensed as Rotashield®)*: this reassortant vaccine has a rhesus rotavirus (G3) parental strain, into which the VP& genes of G1, G2 and G4 serotypes are reassorted. RRV-TV was tested in various low socioeconomic status settings and demonstrated good efficacy. These included Venezuela (efficacy of 88%), Brazil (46%), and a US trial among a

low-socioeconomic rural population of Native Americans (64%). In addition, an unpublished WHO-supported trial in Myanmar was conducted where efficacy was ~50%.

The risk-benefit ratio of RRV-TV (Rotashield®) was discussed when many global experts at a WHO meeting in 2000 recommended that the vaccine be considered for developing world where the benefits of mortality reduction would far outweigh risk of intussusception. However, withdrawal of the vaccine from the US was tremendously influential for the global community. This lesson needs to be remembered should a similar situation arise with one of the new rotavirus vaccines being rejected in the US or Europe.

The concept of what an “acceptable” level of efficacy would be with regard to a beneficial vaccine for the developing world was discussed. As the epidemiology of rotavirus disease is so different in developing world and the mortality is substantially higher than in developed countries, a vaccine with lower efficacy might still be of marked benefit. Participants all agreed that a gradient of lower efficacy existed for all previous rotavirus vaccines when tested in developing countries. However, it would be important for SAGE and other public health partners to be informed that even vaccines with lesser efficacy in developing world would lead to substantial public health benefits including absolute mortality reduction.

Acceptable standards for vaccines for developing countries should not be that different than industrialized countries; thus while vaccines with lower efficacy might still be beneficial, this should not preclude researchers from modifying vaccines to find better solutions. For example, the potential for designer vaccines with multiples strains might improve efficacy as was the case when the monovalent rhesus vaccine was modified to its tetravalent construct.

It was also emphasized that discussions of anticipating a lower efficacy would be useful in terms of engaging researchers to quickly identify reasons why efficacy was lower so that, if possible, interventions to enhance efficacy can be undertaken. For example, it might be possible that breast-feeding at the time of vaccination interferes with vaccine take and perhaps withholding of breast-feeding for 30 minutes before and after vaccination would improve efficacy. If such an intervention were to improve efficacy by 10-20%, it might be sufficient data to enhance the acceptability of a vaccine with lesser efficacy.

The issue of serotype-specific protection was also discussed. Both vaccines provide good cross-protection against all circulating strains, with the possible exception on limited current data for P[4]G2 strains. The strain replacement analogy between rotavirus vaccines and the that which is observed with pneumococcal vaccine is inappropriate and needs to be corrected. As indicated previously, “new” human rotavirus strains have emerged and spread globally in the absence of national or global rotavirus vaccine introduction, in the mid 1990s (G9) and the early 2000s (G12). Given that natural shift in rotavirus strains will continue to occur in the vaccine era (*i.e.* independent of the use of vaccine), the public health community must be cautious not to misinterpret the shift as being related to vaccination and strain replacement.

Finally, as most infants in the developing countries of Asia and Africa are often older than 12 weeks of age when receiving their first dose of routine EPI vaccines, the age limitation on the use of rotavirus vaccines needs careful consideration. On one hand, the currently recommended age windows of administering dose 1 at 6-12 weeks of age, and the complete course by 24-32 weeks of age, may prevent a substantial number of children from being vaccinated. In addition, it may be that these specific children with delays in vaccination are those at the greatest risk for dying from rotavirus disease and would likely benefit the most through vaccination. On the other hand the safety concerns of giving the vaccine at a slightly older age, when the natural occurrence of intussusception occurs in infants is worrying. This dilemma is likely to be answered only by continued well executed post-marketing surveillance for safety.

Session 2: The Programmatic Perspectives

The role and potential interference of breastfeeding (R Glass, FIC, NIH)

Dr Roger Glass provided an overview on the challenges for live oral rotavirus vaccines in the developing world focusing on the theme of “*what if*” the vaccines performed at a lower efficacy than anticipated. The biggest questions for the current live oral rotavirus vaccines are:

- Will the current rotavirus vaccines work in the developing world?
- How well will they work in impoverished populations?
- What is the goal-post for success?

Prior experience with live oral vaccines in the developing world has focused the need for determining potential reasons for lower efficacy in these populations, and this should be a priority so that simple solutions to improve vaccine take can be evaluated. Potential disappointment with the impact of new live oral rotavirus vaccines might be avoided by planning research now to address key questions.

A decade ago, WHO recommended that efficacy trials be conducted in Asia and Africa and encouraged simultaneous testing of vaccines in the least developed countries to avoid delays in introduction⁴. There are many reasons why oral vaccines might perform less optimally in developing country populations, and include substantial epidemiological differences in the epidemiology of rotavirus disease between the industrialized world and developing countries. In developing countries, rotavirus disease occurs year-round; ~80% of the children are infected by one year of age; rotavirus strains are diverse; mixed infections with other enteric agents are common; and case-fatality is high. In contrast, in industrialized countries, rotavirus disease is very seasonal; only ~40% develop rotavirus disease during first year of life; only 5 serotypes predominate; mixed infections are relatively uncommon; and case-fatality is low. These epidemiologic criteria should be considered when extrapolating vaccine trials data to other countries.

⁴ Future Directions for Rotavirus Vaccine Research for Children in Developing Countries.

In addition, there are necessary biological steps for an oral vaccine to overcome to be able to induce an immune response in the host, with many hurdles to an effective vaccine take. For example, the vaccine must retain its titre. Potential hurdles to successful immunization for a live oral rotavirus vaccine include factors that lower viral titre (*e.g.* stomach acid, breastmilk, high maternal antibodies) or factors that impair the host immune response (*e.g.* malnutrition, interfering microbes, other infections such as HIV/malaria/TB). Key hurdles that might impair vaccine take, but which could potentially be modified include the following:

Maternal antibodies: Preliminary existing data do suggest that the geometric mean titres (GMT) of transplacental maternal IgG to rotavirus, is higher among children in developing countries compared those in industrialized countries, at the age of immunization. The question remains whether circulating maternal antibody titres inhibit the immune response to a vaccine. If so, then delaying immunization (*e.g.* by 4-6 weeks), or increasing the vaccine dose could improve efficacy.

Breastfeeding: Are the neutralizing titres of breastmilk different among women from the US and Europe and other less developed countries? What is the interval between breastfeeding of the infant and administration of the oral rotavirus vaccine? Previous studies have revealed inconsistent results with regard to these questions but a meta-analysis of studies prior to 1990 suggests that breastfeeding may inhibit response to rotavirus vaccines. If neutralizing antibody titres in breastmilk do impair efficacy, then perhaps one solution could be to withhold breastfeeding at the time of immunization (*e.g.* 30 minutes before and after vaccination).

Interfering microbes: Enteric viruses, vaccine viruses (OPV), enteric bacteria and parasites are commonly present in the intestinal systems of children living in the developing world. These factors may play a role in interfere with viral adherence, cell entry and immune response. One solution to this might be co-administration of probiotics with the vaccine, although this has never been evaluated.

Pre-existing conditions: Chronic diarrhoea, underlying medical conditions (malnutrition, HIV, malaria, TB), and rotavirus strain diversity are other factors that could impair the efficacy of rotavirus vaccines in developing countries. Experimenting with different buffers, higher titres of

vaccine, and co-administration with zinc or Vitamin A are examples of research to identify pragmatic solutions that could improve vaccine efficacy and improve outcomes.

Discussion of the presentation

Participants acknowledged the need for additional research into many of these topics. However, vigorous debate ensued whether withholding breast-feeding was a pragmatic consideration in most countries. Several participants noted that programmes globally are strongly supporting breastfeeding and withholding, even transiently, would not be feasible or advisable.

The question of addressing this in a research setting to better understand the potential for interference from breastmilk to impair vaccine take was discussed; and it might be performed in the laboratory or in a clinical trial setting. Most available data on breastfeeding interference was with the older generation vaccines that were tested at lower titres. With the new rotavirus vaccines, no data exists that breastmilk suppresses immune response and good immune responses were described in the studies to date, although no differentiation was made between infants who were breastfed and those who were not. One manufacturer noted that data on maternal antibodies or immunogenicity after breast feeding did not exist but noted that in the RotaTeq® trials no difference in efficacy existed between breastfed and non-breastfed infants.

With regard to immunogenicity to rotavirus vaccines and the role of maternal antibody, studies with Rotarix® in Mexico, Finland and South Africa, have indicated that high circulating maternal antibody is inversely correlated with the GMT of the vaccine response. RotaTeq® has not been examined in this way, because the serum immune response is not seen as a strong correlate of protection. Some of these issues will be addressed by the current phase III clinical trials in Africa and Asia with both vaccines – immunogenicity data will be available; the vaccines are given with OPV, and information on HIV, the weights of the children, and malaria status is being recorded.

The OPV experience was highlighted — studies by Jacob Johns demonstrated that administration of OPV at an older age and increasing the time interval between doses improved immunogenicity, although delaying breastfeeding for 4 to 6 hours did not improve this response. However, giving rotavirus vaccines at later ages may be more challenging, given the intussusception concerns noted above.

In summary, many of these topics are research questions that could be evaluated to anticipate what would enhance vaccine take in the event that efficacy is found to be lower. However, these are unlikely to be prove to pragmatic solutions for the programmatic use of rotavirus vaccines.

Timing of vaccination in 45 low & middle income countries (A Clark, LSTMH)

Dr Andrew Clark presented an analysis undertaken for WHO, of the demographic and health surveys from 45 low and middle-income countries and summarized their immunization schedule data from 1996-2005. Twenty-seven of the 45 countries were from Africa. The data were identical for DTP3 and OPV3.

For BCG, a majority of infants were vaccinated at birth as scheduled, although some were vaccinated later, with 25% of children receiving their BCG dose after 2.8 months. For DTP, the overall median delay for dose 1 was 2.4 weeks, and the overall median delay for dose 3 was 6.9 weeks. For DTP, cumulative coverage by age reveals that 58% received dose 1 by 12 weeks of age and 81% by 24 weeks of age. Assessment of country-specific data suggests that delays vary substantially. Within countries, factors related to timeliness of vaccination include rurality, birth order, age of the mother, mother's education and place of delivery.

The implications of these findings for the introduction and use of rotavirus vaccine was evaluated. The WHO recommendation to administer the first dose of rotavirus vaccines between 6-12 weeks of age, and no later than 12 weeks of age; and the need to complete the course of vaccination by 24-32 weeks of age¹ will impact the vaccine coverage achievable. For instance, in Bolivia with the current timing of vaccination, a rotavirus vaccine would be expected to result in only a 34% reduction of rotavirus disease compared to 60% if routine vaccination was given on time. In many countries, more than 50% of children would be denied rotavirus vaccines based on WHO's strict age adherence recommendations. Many of these countries have the highest rotavirus mortality rates, and given the factors associated with delayed vaccination noted above, the highest risk infant populations might be at an increased disadvantage. Furthermore, the situation is even worse if we exclude those infants receiving the second dose after 6 months of age. In the 25% of countries with

the worst timeliness for immunization, 25% of the infants receive the DTP1 vaccine >2 months late, and this extends to >4 months late for DTP3.

The introduction of rotavirus vaccines may present an opportunity to improve timing of EPI schedules in many countries, and optimise the administration of other vaccines at same time (pertussus, polio *etc.*)

Discussion of the presentation

It was noted that although delays in immunization existed, many countries did adhere to the EPI age recommendations and that rotavirus vaccines could be administered within a strict schedule. This was unlikely to be true in countries with the highest rotavirus mortality, and that those infants not adhering to the EPI age schedule are perhaps those with delayed vaccination, are at the highest risk of severe disease. It was noted that the strict age-adherence recommendations for rotavirus vaccines were largely driven by the perception of an association of intussusception with rotavirus vaccines with a “catch-up” schedule based on the higher background rates among children older than 12 weeks of age. A risk-benefit analysis with a strict versus a free immunization schedule in developing countries is critically needed.

Working Groups: To develop recommendations for WHO on the clinical studies in Africa and Asia

Drs. Neuzil and Steele provided guidance remarks and a framework of discussion for the two working groups, elaborating on three main themes emerging from the day's discussions. These themes included the following:

- 1) To identify if a lower level of efficacy of rotavirus vaccines would still be beneficial in Asia and Africa
- 2) To determine criteria that could be used to extrapolate data to other countries or regions not included in the trials to date
- 3) To define data-gaps in rotavirus research particularly in special populations, including HIV-positive infants, malnourished infants, and premature babies, either in post-marketing surveillance or in ongoing or new studies.

Efficacy in developing countries:

The general consensus emerging from both working groups was that an absolute point estimate of efficacy below which vaccine is deemed to have “failed” is not appropriate. There was a recommendation that an absolute reduction in morbidity and mortality can indeed be notable, even with less efficacious interventions and would ultimately vary depending on the many regional factors. A single point estimate of efficacy should not be a pre-requisite for making a recommendation on vaccine introduction. It was suggested that perhaps a range of efficacy and regional impact on mortality and morbidity (*e.g.*, hospitalizations, cost-savings) would more effectively convey the full potential of a vaccine. It was also emphasized that SAGE and WHO recommendations should be broad because specific recommendations take the decisions out of the hands of the country-level decision makers.

The groups also concurred that more important than identifying lower limits of acceptable vaccines might be anticipating and identifying reasons for lower efficacy in developing countries, so that if the results of trials are less than ideal, focus can be shifted towards modifying vaccine delivery to optimize efficacy. Potential areas of research with policy implications for vaccine delivery were identified and included the following:

- The role of breast-feeding immediately before or after receiving oral vaccines;
- Whether delaying immunization by 1-2 months when maternal antibodies are lower, might improve vaccine “take;”
- To determine the characteristics of the children that escape vaccine protection and why?

Nevertheless, although consensus existed with regard to need for anticipating and identifying reasons for less than ideal vaccine efficacy, it was noted that attempting to modify vaccination delivery (especially if within the current EPI schedule and practice) would not be pragmatic. Investigators of current trials were encouraged to assess whether these data are being gathered and could be made available in a timely manner to assess potential ways to optimize vaccine efficacy.

Criteria for extrapolating efficacy data:

Participants discussed the WHO position on the need for vaccine safety and efficacy data from Asia and Africa prior to recommending global inclusion of rotavirus vaccines into national immunization programmes. It is acknowledged that regional differences in efficacy are likely to exist, and that not every region is likely or required to have large efficacy study data available. Therefore, the question arises of whether the data from the current clinical trial sites for both rotavirus vaccines could be extrapolated to other countries in other regions. The discussion predominantly focused on the possible criteria that could be used by WHO and SAGE to extrapolate the data from the ongoing clinical trials in Africa and Asia to a global recommendation for rotavirus vaccine introduction.

One such criteria might be the WHO Mortality Strata. The clinical trials are being conducted in countries that fall under the WHO strata with the highest under five mortality. The meeting participants noted that extrapolation of efficacy data from clinical trials conducted in different populations, on the basis of the WHO mortality strata would be simple and acceptable as the population and socio-economic parameters would also likely be similar. Although other criteria were discussed, it was proposed that for the purposes of SAGE to evaluate the clinical trial results when available, and to enable SAGE to make further recommendations, the current trials across these strata would provide the appropriate information required.

It was discussed that even among countries that fall within the same WHO mortality strata, epidemiological differences in rotavirus disease are different such that efficacy might also differ.

These epidemiological differences may in fact be manifestations or proxies of biological factors that could impair or facilitate vaccine “take.” For example, robust data for the Asian Regional Rotavirus Surveillance Network has revealed marked differences in age at first rotavirus infection and seasonality of rotavirus disease among the participating countries. These differences may in part be due to factors such as different modes of transmission, force of infection, pre-existing maternal antibodies, or variations in breast feeding practices. With regard to the trials in Asia, it was noted that sample size calculations were based on pooling data from Bangladesh and Vietnam, countries with different under five mortality and socio-economic conditions. It was unclear whether sufficient power would exist if Bangladesh data were considered separately from Vietnam, however investigators agreed to hold subsequent discussions addressing this topic.

It was agreed that, in addition to WHO mortality strata, gathering and comparing epidemiologic data on rotavirus disease might provide additional criteria for extrapolation of efficacy data of rotavirus vaccines in Asia and Africa. As for any vaccine, not all of these data would be needed prior to a recommendation, and post-licensure effectiveness studies would be additional important sources of information on public health benefit.

Data on special populations:

Discussion on this topic was brief, as there is not a significant amount of data available for the current licensed vaccines. WHO had requested that data be generated in vulnerable populations as discussed above. The need for safety and efficacy data in HIV-positive infants was stressed; this is ongoing with Rotarix® currently and a study is planned with RotaTeq®. Data in malnourished infants and in premature infants, either thorough post-marketing surveillance or ongoing or new studies was requested.

Session 3: Defining the future research agenda for current vaccines

Post-marketing surveillance - the realistic way forward? (S Evans, LSTMH)

Dr Stephen Evans provided an overview of the objectives of post-marketing surveillance (PMS) for adverse events. These included: detecting problems; evaluating harms; demonstrating safety; completing the map of knowledge on the topic; and being sure of benefits. The most common safety focus is on time immediately after exposure when an effect is seen and the frequency of that occurrence. However, other dimensions such as age, sex, genetic disposition and other risk factors might be important to consider. Clinical trials show relatively frequent events, within relatively short time periods, in relatively good environments and arte often in industrialised countries. Within those boundaries safety is known and efficacy is demonstrated. Efficacy does not usually change direction dramatically outside the boundaries, but “harms” may appear after licensure.

For rotavirus vaccines, large safety and efficacy clinical trials have been conducted and post-marketing studies and surveillance are ongoing. Advantages and limitations of PMS approaches and methods were presented with the recommendation that epidemiologic methods are used more frequently and the usefulness of the relatively novel self-controlled case-series method⁵.

Safety is the demonstrated absence of harm, and it should be noted that the “absence of evidence” is not “evidence of absence”. Demonstrating safety often requires studies, of large enough size, which would have detected a “harmful event” as statistically significant. Most importantly, all risk-benefit discussion in public health should be in terms of absolute risks. Relative risk may be high but absolute risk may be substantially lower. If the incidence of the disease being prevented is high in relation to the absolute risk, than “harm” may be tolerated.

Dr Evans noted that the WHO Global Advisory Committee for Vaccine Safety is drafting PMS framework and guidelines after a meeting on the subject, hosted in Geneva on December, 2006.

⁵ Whitaker HJ, Farrington CP and Musonda P. Tutorial in Biostatistics: The self-controlled case series method. *Statistics in Medicine* 2006, 25: 1768-1797

Can we change the rotavirus vaccine schedule? (A Kapikian, NIAID, NIH)

Dr Albert Kapikian presented a perspective on the use of a neonatal rotavirus vaccine dose schedule and the potential how this can offer important advantages to some of the questions of rotavirus vaccination.

As background, the development of an alternative second generation bovine vaccine (UK strain) was discussed. This development programme began prior to the withdrawal of Rotashield®, and both strains were initially developed by the NIH. The parallel development of two reassortant vaccines, one based on a rhesus rotavirus parental strain (which is G3 serotype) and the second on the bovine rotavirus strain (G6), was in part due to the finding that the UK strain was characteristically non-reactogenic in comparison to rhesus rotavirus vaccine tetravalent vaccine (RRV-TV, which was eventually licensed as Rotashield®) and which was associated with a transient fever in up to one-third of vaccines. The studies with bovine-human rotavirus reassortants were reviewed and it was noted that the reassortant UK vaccine was equally efficacious against severe rotavirus diarrhoea as Rotashield®.

The risk of rotavirus vaccine associated intussusception, whether perceived or with an actual potential for risk, clouds the future of all other live rotavirus vaccines. A strategy of vaccine delivery derived from lessons learned from Rotashield® and supported by epidemiologic studies has the potential to eliminate the risk of intussusception. It was proposed that the administration of new rotavirus vaccines at 0-4 weeks of age for dose 1 and at 4-8 weeks (dose 2), without “catch-up” vaccination beyond 8 weeks could eliminate the risk of intussusception. This is based on the natural history of intussusception which tends to occur in infants between 3-12 months of age.

The challenge will be to demonstrate if a rotavirus vaccine works at this young age. Evidence exists from studies in Australia, India, and Mexico that naturally-occurring rotavirus infection neonatally or in early infancy can induce protection against a subsequent rotavirus illness. Questions on this approach include whether there is evidence for the effectiveness of a single neonatal dose of rotavirus vaccine; or whether the immunologic immaturity of the neonate and high levels of circulating maternal antibodies would prohibit effective rotavirus vaccination during the neonatal

period. Encouraging signals for the feasibility of this approach does exist from rotavirus vaccine studies in neonates in Finland, Israel, and Venezuela.

Overall benefits of neonatal vaccination for rotavirus might include the following:

- Neonatal rotavirus vaccination may prove to be the safest time to administer an oral, live, attenuated vaccine to infants.
- A single dose of rotavirus vaccine may at least yield adequate protection versus severe diarrhoea due to rotavirus.
- The protection of vulnerable infants in developing countries during the first two months of life, who are now excluded by the conventional schedule starting at ~2 months.
- That infants are more likely to have exposure to a health-care provider during neonatal period.

Discussion of the presentation

It was observed that the primary rationale for neonatal dosing schedule was based on the premise that the risk of intussusception could exist with the currently licensed vaccines when administered on the current EPI schedule. However, the safety data with the new vaccines are reassuring and no signal of risk has been identified so far. There may be many other reasons for a neonatal vaccination strategy, such as neonatal dosing reaching a greater number of at-risk children. Administration of BCG at birth has high coverage and is more of a demanding reason to study neonatal dosing for rotavirus vaccines, and would be a stronger rationale for researching this topic rather than introduction based on a potential better safety profile.

Maternal antibodies are high in neonates and may prevent “take” of a neonatal vaccine, especially for one that is derived from human rotavirus strains. The question was posed whether a bovine rotavirus strain may “take” better than a human rotavirus vaccine and if this might explain the good immune response observed after neonatal dosing with a bovine vaccine. No data exist to support or deny this hypothesis. With the current human rotavirus vaccine (Rotarix®), it is clear that without an IgA response, viral replication is not likely, which does suggest that a human strain vaccine may be less likely to “take” with neonatal dosing. Nevertheless, human rotavirus vaccines based on neonatal strains which are adapted to this host environment might also be better suited to neonate dosing.

How much disease could be prevented in first 2 months? Several commented that data on incidence rates were sparse but existing data suggest marked variability in the amount of rotavirus disease in this very young age. For instance, in Philadelphia, attack rates are flat from birth to 8-9 months of age, whereas in some parts of Venezuela, severe disease begins at 2 months and peaks at 5 months of age and up to 10% of rotavirus-positive children may be less than 3 months of age in parts of Venezuela. In Bangladesh, severe disease is rarely observed before 6 months of age and peaks at 11 months. However, in longitudinal studies in South Africa, 17% of infants hospitalized with moderate to severe rotavirus gastroenteritis were <3 months of age. This was 6% in Malawian infants less than 3 months of age.

On the other hand, even the data with Rotashield® introduction were sparse with regard to kids < 60 days of age and could not exclude risk in that group. This was also noted by the GACVS previously. Several meeting participants emphasized that attributable risk should be a more important consideration than the relative risk of intussusception after vaccination and that attributable risk would increase with age despite stable relative risk.

Several recommendations were made:

- The need for a risk-benefit model for the developing countries, was urgently required.
- The need for data on the co-administration of OPV and rotavirus vaccines and potential interaction at birth since OPV is administered at birth in many countries;
- The role and interaction with breast-milk (nearly universal at birth in developing countries);
- The risk of intussusception with neonatal dosing would need assessment;
- WHO guidance/lead and support for studying neonatal schedule in developing countries.

Session 4: The new rotavirus vaccines under development

Lessons learnt for the new live rotavirus vaccines (M Levine, CVD)

Dr Levine summarized the differences in immune responses in populations living in developed versus developing countries. For oral vaccines, the immune response is greater in industrialized countries whereas the opposite is observed with parenteral conjugate vaccines. These oral vaccines include OPV, rotavirus, cholera and Shigella vaccines.

Some factors that may affect “take” of oral vaccines in children in developing countries include:

- for live viral vaccines, competing enteric viruses;
- for live bacterial vaccines, competing bacterial flora;
- placentally transferred maternal serum antibody;
- age at time of first dose;
- interval between doses;
- antibodies and other components of breast milk;
- active immunity from prior antigenic contact;
- the “normal” gut is different in developing country versus industrialized country residents;
- formulation (e.g., ratio of strains in multivalent vaccine).

Data from the development and use of live, oral cholera vaccines and focusing on different immune responses in developing countries can help elucidate this discussion. Robust data exists indicating the presence in developing country young children of an “*environmental enteropathy*” where the small bowel bacterial overgrowth diminishes the vibriocidal responses to cholera vaccine. It is not known whether this is true for rotavirus vaccine as well. Overcoming the intestinal barriers to the “take” of an oral vaccine in developing countries might necessitate increased antigenic content per dose of oral vaccine; extra doses of vaccine; co-administration of zinc, vitamin A and other agents that affect gut integrity; antibiotics prior to oral immunization; and withholding breast milk for hours before and after oral immunization.

Finally, evidence was presented from the HiB vaccine introduction experience in Mali, which had a dramatic impact on HiB disease, hospitalizations and under 5 mortality. It was concluded country-specific and credible disease burden and impact estimates and local champions are critically necessary for generating political will and influencing decision makers to introduce a new vaccine.

Bovine-human reassortant rotavirus vaccine (UK strain) (J Boslego, PATH)

Dr John Boslego summarized the construction of the UK bovine strain-based rotavirus reassortant vaccine (which is a G6 serotype) with the VP7 genes for serotypes G1, G2, G3, G4, G8, and G9 specificities derived from human rotavirus strains. The bovine-human rotavirus reassortants with G1 (DxUK), G2 (DS-1xUK) and G3 (PxUK), serotype specificities were produced at the NIH in 1984, and the G4 (ST-3 x BV) serotype specificity in 1986. Two additional serotype specificities of bovine-human reassortants with G9 (AU32-VP7 serotype 9 x UK) in 1997 and G8 (HRV 1290-VP7 serotype 8 x BV) were produced at NIH in 2000.

The clinical development of the reassortant UK vaccine by NIH was summarized. The quadrivalent vaccine (G1, G2, G3 and G4) grown in *FRhL-2* cells was evaluated and demonstrated safety and immunogenicity in adults, children (6-60 months) and infants (6-24 weeks). In 1997, the quadrivalent vaccine (G1, G2, G3 and G4) was compared to RRV-TV in infants in Finland by Vesikari *et al.* The trial demonstrated safety and immunogenicity of quadrivalent vaccine (*FRhL-2* cell line) in infants at 2 months of age. RRV-TV was associated with transient and generally low-grade fever in up to one third of vaccinees. In contrast, bovine rotavirus based vaccine was characteristically non-reactogenic.

With regard to licensing, the license was returned back to NIH as was the manufacturing technology. The Office of Technology at NIH has further awarded licensing rights to eight vaccine manufacturers; seven of which are developing country vaccine manufacturers and one is an USA-based vaccine manufacturer. Manufacturing technology is being transferred from the NIH to UK bovine-human rotavirus vaccine manufacturers in developing countries.

The need for a “designer” rotavirus vaccine for developing countries was raised because the serotype G9 strain has emerged as an important serotype in various parts of the world (*e.g.* India, Brazil), whereas serotype G8 appears important in Africa. One or both of these two serotypes could be added to the quadrivalent rotavirus vaccine, thus formulating a pentavalent or a hexavalent rotavirus vaccine. Potentially, coverage of all the important the VP7 serotypes could eliminate the need to protect against the various VP4 specificities associated with the various VP7 serotypes. Reassortants for these emerging VP7 serotypes – such as G9 and G8 - are available.

The widespread use of rotavirus vaccines could save up to 225,000 deaths a year by 2025. However, achieving this will require improving the availability and affordability of rotavirus vaccines. Delays in access to rotavirus vaccines will severely hamper efforts to reduce childhood suffering and death from rotavirus. The potential supply landscape includes the currently two rotavirus vaccines, manufactured by GSK Biologicals and Merck & Co, with a current combined capacity estimated at 60-80 million doses, much of which will go to developed countries. These manufacturers can only supply 7-15 million doses to the developing world, a fraction of the projected demand of 160 million doses.

PATH is involved in advancing rotavirus vaccine development with alternative candidates. The bovine-human rotavirus reassortant vaccine project objectives include supporting the process and clinical development of the human reassortant rotavirus vaccine through Phase 2 at two selected manufacturers — one in India and one in China. In addition, PATH provides a platform of technologies, training, and common technical support that will be made available to the seven developing country manufacturers developing the rotavirus vaccine.

At the end of the five-year project, it is projected that at least two manufacturers of the NIH bovine-human rotavirus vaccine will have completed Phase 2 clinical development of a product that is appropriate for use in low-income countries around the world.

Neonatal rotavirus vaccine (116E) (S Prasad, BBIL)

Dr Prasad provided an overview of the neonatal rotavirus vaccine candidate, 116E. The strain was isolated and characterized at the All India Institute for Medical Sciences (AIIMS) led by Dr. M.K. Bhan. Neonates born at AIIMS, New Delhi, were commonly infected with a rotavirus strain before discharge from the hospital. Those infants infected were observed to remain asymptomatic and experienced 46% fewer attacks of rotavirus diarrhoea than a cohort of babies born at the same hospital but not infected with this strain of rotavirus. In addition, greater reduction in the severity of rotavirus diarrhoea was observed in the infected neonates than in the non-infected neonates. This suggested the possibility that the strain 116E may be an avirulent strain, which nevertheless induces protective immunity and offers clinical protection. Characterized as P[11]G9, the strain is a naturally occurring reassortant with the VP4 gene of bovine rotavirus origin, and all other RNA segments of human rotavirus origin. 116E is a live, naturally attenuated vaccine candidate that was sent for vaccine development to the NIH by DBT-India, under the Indo-US joint VAP programme.

Phase 1 safety studies in adults and children have been completed in US and India. The vaccine was non-reactogenic and without any serious adverse events observed in these studies. Immunogenicity was defined as a 4-fold or greater raise in serum IgA and was observed to be 20% in the placebo group versus 73% in the 116E group. Virus shedding in stool samples collected on day 3 and 7 post-dose was demonstrated in 6% in the placebo group versus 40% in 116E group.

A phase Ib/IIa dose-escalation study in 360 infants in India is ongoing and completion is expected in the first quarter 2008. Other Phase II and possible Phase III Efficacy study are being planned to start in 2008.

It is noted that an efficacious rotavirus vaccine has the ability to save 150,000 infant lives per year in India alone.

Human neonatal rotavirus vaccine (RV3) (R Bishop, MCRI)

Dr Ruth Bishop provided an overview of the development and status of the neonatal rotavirus vaccine candidate, RV3. The RV3 strain was isolated from faeces excreted by a normal healthy full-term male infant on days 4 and 5 of life in Royal Children's Hospital, Melbourne in 1977. The infant was artificially fed from birth and had no diarrhoea during first 14 days of life. The neonatal strain RV3 is a P[6]G3 strain and carries antigenic epitopes which are cross reactive with G1 and G9 strains. A follow-up birth-cohort study in Melbourne, revealed that neonatal infection with RV3 provided 100% protection against severe rotavirus disease later. This provided the basis for further development of RV3 as a candidate vaccine.

Early phase II trials demonstrated an immune response in 46% of the infants and 54% protection against severe disease. Although the sero-response was low, those subjects who developed an immune response were protected against severe rotavirus infection. Subsequently the viral titre was increased to enhance the vaccine immunogenicity, and the cell line for cultivation was modified to the WHO suggested Vero cells. New development with the increased viral titre of vaccine virus is planned with phase I and II vaccine trials targeted in New Zealand and Indonesia. The trials will include an arm with neonatal dosing.

The potential strengths of the RV3 strain as a suitable rotavirus vaccine are:

- this is a human neonatal rotavirus strain;
- the strain is stable, naturally attenuated and adapted to the infant gut;
- natural infection is asymptomatic and protective; and the protection is heterotypic;
- the strain was safe and well tolerated in phase I and II trials;
- higher titre of the vaccine has been achieved in Vero cells;
- this may be an ideal candidate for neonatal administration

Alternative approaches to rotavirus vaccination (Dr R Ward, Cincinnati)

All human vaccine trials to date, have tested live rotaviruses including the new candidate vaccines now being investigated. Their development is based on the excellent protection elicited by natural rotavirus infections, particularly against severe rotavirus disease. However, the problems with the early, live rotavirus vaccine candidates were that animal rotaviruses provided inconsistent protection, particularly in developing countries; the first neonatal rotavirus vaccine (M37) provided no protection in one study; and the first licensed (reassortant) vaccine (Rotashield®) was associated with intussusception. Ongoing concerns about the safety and efficacy of live oral vaccines in developing countries has been a major impetus to develop and test alternative candidates.

This presentation focused on “non-living” or alternative rotavirus vaccine candidates. None of the alternative vaccines have been evaluated in humans; several have been developed and tested in animal models including:

- Inactivated rotavirus particles (triple-layered and double-layered)
- Virus-like particles (VLPs)
- DNA vaccines
- Vectors expressing rotavirus proteins
- Rotavirus proteins VP4, VP7, VP6, NSP4
- Peptides from rotavirus proteins

These non-living candidate vaccines have been primarily evaluated either in the gnotobiotic piglet illness and shedding model or the adult mouse shedding model. The conclusions obtained with these models have not been identical and it is not clear which model will be more applicable to humans.

The gnotobiotic piglet model (developed by Dr Linda Saif at Ohio State University) has advantages and disadvantages. Pigs are clearly more similar to humans than mice, and especially at the level of the intestinal system, which suggests this model is more applicable to man. Also, this is an illness model and the mouse model is dependent on protection against intestinal virus shedding only. However, gnotobiotic animals are known to have abnormal intestinal immune responses which could greatly alter the conclusions obtained with this model. This model is also limited due to

complexity and cost, the lack of inbred animal strains, and the lack of strains with specifically-induced genetic defects.

The adult mouse model was developed by Dr M McNeal and Dr R Ward at Cincinnati Children's Hospital. The outcome for this model is protection against virus shedding only. The model includes inbred strains for consistency and genetic knock-out mice to define mechanisms of protection. This has become the model used worldwide for most mechanistic studies on active immunity to rotavirus. Mice are given the vaccine and subsequent shedding after viral challenge is the outcome (*i.e.* how much shedding can be reduced through vaccination). Both parenteral or intranasal administration of inactivated virus (especially with adjuvant) diminishes shedding in mice.

Studies in gnotobiotic piglets where the oral inoculation of piglets with a live human rotavirus vaccine was protective against illness and shedding after a subsequent challenge with the same virus. However, oral or parenteral inoculation (with or without adjuvant) with this virus after its inactivation provided no protection. Protection was induced by intranasal immunization of mice with inactivated virus particles and adjuvant; this protection remained intact in B-cell deficient mice and after depletion of CD8 T-cells. Thus, neither antibody nor CD8 T-cells were required for protection, which was a very different conclusion than suggested from studies in gnotobiotic piglets

Other candidate inactivated rotavirus vaccines include a formaldehyde-inactivated, purified rotavirus vaccine candidate, prepared from a P[4]G1 strain as well as a candidate vaccine prepared from P[8]G1, P[4]G2 and P[6]G9 strains. No data has been published on these candidate vaccines.

Studies with virus-like particles (VLPs) in mice have been conducted using various routes of administration, and various constructs of VLPs, including combinations of the VP2, VP4, VP6 and VP7. For instance, VLPs provided 90% protection against murine rotavirus shedding when administered intranasally with adjuvant, although oral immunization was not effective. This strategy may be an alternative using a prime-boost approach. Two intranasal inoculations with 2/6 VLPs and adjuvant given after a single oral dose of live, attenuated human rotavirus augmented protection in piglets. No significant clinical progress with this or any other rotavirus VLP vaccine has occurred even though studies in animal models have continued

A review of studies with a VP6 based vaccine, which when fused with maltose-binding protein and administered intranasally with LT(R192G), induced nearly complete protection in mice. Subsequent studies indicate that CD4 T-cells rather than antibodies were required for protection after VP6 immunization.

The “non-living” rotavirus vaccines would not have the same potential safety problems as live rotavirus vaccines, and may well overcome the concerns about efficacy with live oral vaccines for children in developing countries. Evidence from animal studies, particularly mice, suggests that non-living vaccines can be effective. These vaccine candidates now need to be evaluated in humans, to determine if at least one of these approaches would work to protect infants from severe rotavirus diarrhoea, and especially if the efficacy or safety of the other rotavirus vaccines is problematic.

Working Group: The clinical development expectations for the new rotavirus vaccines (Convenor - H Greenberg)

The safety concerns associated with live oral rotavirus vaccines have influenced the clinical development of these vaccines. The development of new alternative live oral rotavirus vaccines in collaboration with emerging manufacturers, and the discussions held at an earlier WHO meeting in April 2006 (*Upstream Rotavirus Vaccines and the Role of Emerging Manufacturers*) prompted the discussion on clinical development for new rotavirus vaccines in less developed countries.

1. How large should safety trials for new rotavirus vaccines be to provide appropriate safety from the risk of intussusception?

Participants agreed that the answer to this question has to be assessed in the context of the regional value, need, and benefit of the vaccine. The group also agreed that WHO/IVB and GACVS should provide recommendations on the excess rate of intussusception that should be assessed for, in post-licensure studies, but emphasized that such a recommendation should not impede licensure or be a pre-requisite for clinical trials with unrealistically large sample sizes prior to licensure.

From a regulatory perspective, the expectation may be to have similar large trials (i.e. in excess of 60,000 subjects) for new rotavirus vaccines that are biologically different from the current two licensed vaccines, and thus may have a different safety profile with respect to intussusception. However, pre-licensure clinical trials would need to enroll a large number of infants to detect even a reasonably large magnitude association within week of vaccination. In general, the consensus of the meeting was that the mandate to assess the safety (particularly rare adverse events) of new rotavirus vaccines should not be placed on large pre-licensure trials but rather on post-marketing surveillance - possibly at designated sentinel sites using standardized protocols. The rationale for this consensus was that even the large 60,000 – 70,000 subject clinical trials conducted for Rotarix® and RotaTeq® are insufficiently powered to confidently rule out rare adverse events and such a requirement on future vaccines would be take the issue of safety out of the context of efficacy. Neither aspect should be discounted and the candidate vaccines, the meeting recommended the need for good efficacy trials in various settings. For safety, the recommendation was that emphasis should be focused on close monitoring post-licensure.

2. *What should be the clinical endpoints for efficacy, and are they the same irrespective of dose number or age?*

Demonstrating reduction in mortality would be the ideal outcome of interest. In clinical trials, however, mortality is an unusual occurrence given that enrollees are closely monitored and the best standard of medical care is available. It was recommended that post-licensure studies on mortality although challenging, should be considered.

For these reasons, hospitalization - as a surrogate for severity, cost, and clinic visits have typically been used as efficacy endpoints for rotavirus vaccines. It was noted that because of the variability in treatment and admission practices, a standardized severity score might serve as a meaningful end-point. Using severe rotavirus gastroenteritis, based on a standardized definition, as an endpoint would follow the recommendations set forth in the WHO “*Guidelines to Assure the Quality, Safety and Efficacy of Live, Attenuated Rotavirus Vaccines (Oral)*”⁶, and have the additional benefit of consistency with the recently completed and on-going rotavirus vaccine efficacy trials.

3. *Should demonstration of serotype cross protection be required and if so, which serotypes?*

Meeting participants agreed that this issue is a relatively low priority for clinical trials given the past evidence on heterotypic protection observed, and that fact that exposure to the various serotypes cannot be controlled. In addition, the ongoing clinical trials in various settings across the world should tease out this issue further, if it exists.

4. *Regulatory oversight of clinical development by vaccine manufacturers*

Currently four countries are manufacturing rotavirus vaccines. In the US and in Europe, the pharmaceutical manufacturers typically consult with the FDA or the EMEA before the clinical trial development. In addition, the clinical trial development is reviewed critically by the regulatory authority on an ongoing basis. The question was raised whether the new rotavirus vaccines in development will have a rigorous process of regulatory review, and whether the WHO or regulatory agencies in developing countries consult with emerging manufacturers pre-licensure.

WHO has programmes to strengthen the national regulatory authorities (NRAs) of developing countries. One such is the Developing Country Vaccine Regulators Network (DCVRN) which is

⁶ Technical Report Series, 2005

providing close support and joint review of clinical trial dossiers and post-marketing surveillance in collaboration with local national regulatory agencies.

Other questions were identified and briefly discussed and included the following:

- *How useful would it be for a vaccine not to require buffering?* This would have immense benefit as it would help logistically in developing countries, would have a positive influence on the cold-chain capacity and potentially reduce waste.
- *Potential single-dose rotavirus vaccine.* Previous rotavirus vaccine candidates have not performed well with one dose, but meeting participants agreed that this would be a benefit if feasible. Post-licensure studies of the current vaccines will be needed because in clinical trials, partial dose-series participants are rare.
- *Spread of vaccine virus to non-inoculated children.* This may be worth investigating, as the possibility of indirect effects of vaccination are being increasingly recognized and need to be evaluated for new vaccines. Cluster-randomized introduction are important to study potential indirect effects.
- *Does shedding need further investigation prior to licensure of new vaccines or should it be conducted post-licensure?* The WHO Technical Series, “Guidelines to Assure the Quality, Safety and Efficacy of Live, Attenuated Rotavirus Vaccines (Oral)”⁶ indicates that shedding does need to be evaluated. A transmission observation study is ongoing with Rotarix® in the Dominican Republic in twins.

Conclusion of the Meeting

The meeting report will be submitted to WHO and to SAGE for review. It was anticipated that the meeting report could serve as a framework for evaluating the clinical trial data as it became available. In addition, the meeting report could be a guideline for future research needs in the field of rotavirus vaccine development.



WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTÉ
INITIATIVE FOR VACCINE RESEARCH

Minutes and Summary

ROTAVIRUS VACCINES: EVALUATING CLINICAL TRIAL DATA
AND GUIDING FUTURE RESEARCH

CDC Conference Centre, Atlanta -28-29 November, 2007

Draft Agenda

Moderator - Jon Abramson
Rapporteur - Mannish Patel

Wednesday, 28 November

8:30 Registration

9:00 Objectives of the Meeting D. Steele
*Objectives and current WHO position - SAGE recommendations,
pre-qualification and rotavirus position paper*

Session I - The Global Priority for Rotavirus Vaccine Development

09:15 An update on the introduction and safety of rotavirus vaccines U. Parashar
*Including the available results of rotavirus vaccine introduction in
in the USA and Latin America*

09:45 Challenges to rotavirus vaccine introduction in developing countries D. Steele
*Including programmatic issues (age of administration, OPV, cold chain)
and specific questions for developing countries such as strain diversity,
maternal antibody and the hard-to-reach populations*

10:00 Status of the studies of the licensed vaccines P. Dennehy
*In regard to developing country issues and studies in vulnerable groups
(such as malnourished, HIV positive) and strain cross protection, less-than-
full dose protection etc)*

- 10:30 Status and timelines for rotavirus vaccine safety and efficacy studies in Africa and Asia K. Neuzil
What studies are ongoing to address the questions listed above

11:00 Coffee / Tea

- 11:30 What questions will remain at the conclusion of the clinical trials? M. Santosham
Would data in addition to the clinical trial data be helpful in informing global recommendations for Africa and Asia? If so, what are the critical questions and how can they best be answered? (e.g. effectiveness data)

- 12:00 Discussion Group on SAGE recommendations for consideration T. Vesikari
- *What level of protective efficacy would be considered beneficial in Africa and Asia?*
 - *What criteria should be used to extrapolate data to other countries or regions not included in the trials to date?*
 - *What further data might be gathered on special populations, including HIV-positive infants, malnourished infants, and premature babies, either in post-marketing surveillance or new studies?*

13:00 Lunch

- 14:00 Working Groups breakouts to develop recommendation for SAGE and WHO

15:30 Coffee / Tea

Session 2 - The Programmatic Perspectives

- 16:00 The role and potential interference of breast feeding R. Glass
16:15 Discussion

- 16:30 The age of administration of rotavirus vaccines A. Clark
17:00 Discussion

- 19:00 RVP-hosted dinner at Houston Mill House

Thursday, 28 November

Session 3 - Defining the future research agenda for current vaccines

- 08:30 Post-marketing surveillance - the realistic way forward? S. Evans
GACVS report and background on the WHO post-marketing surveillance meeting (12/2006) and current situation

- 09:00 Can we change the schedule? A. Kapikian
The case for a single dose
A neonatal dose schedule for rotavirus vaccines

09:30 Discussion on the safety of the currently available vaccines

10:30 Coffee / Tea

Session 4 - The new rotavirus vaccines under development

11:00 Lessons learnt for the new live rotavirus vaccines M. Levine

11:20 Bovine human reassortant rotavirus vaccine (UK) J. Boslego

11:40 Neonatal rotavirus vaccine (116E) S. Prasad

12:00 Human neonatal rotavirus vaccine (RV3) R. Bishop

12:20 Alternative approaches to rotavirus vaccination R. Ward

12:40 Discussion

13:00 Lunch

14:00 Discussion group H. Greenberg

The clinical development expectations for the new rotavirus vaccines

- *standardization of the international expectations of rotavirus clinical trials*
- *how large should the safety trials for new rotavirus vaccines be?*
- *What should be the clinical endpoints for the efficacy studies?*
- *Should demonstration of serotype cross protection be required?*

15:00 Closed Session to draft recommendations to WHO

This session is closed to industry and the vaccine manufacturers

16:00 Coffee /Tea and Close of the meeting