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PATH

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The Tenth International Rotavirus Symposium, held in Bangkok, Thailand, drew together over 350 delegates from 53 countries. The theme, “Fulfilling the Promise of Rotavirus Vaccines,” highlighted the unprecedented global opportunity to significantly lower childhood deaths and disease caused by rotavirus. This opportunity flows from the availability of two safe and effective vaccines; the commitment of increased resources to fund vaccination in low-income countries; and from growing awareness and political will in support of rotavirus vaccination.

The vaccines, which became available only six years ago, are now used in 38 countries. Today, most of these are in the Americas and Europe, however, more than a dozen countries in Africa and Asia are preparing to introduce rotavirus vaccines.

Nonetheless, the Symposium also recognized that fulfilling the promise would require intensified work on many fronts. Vaccine efficacy is considerably lower in low-income countries than in middle- and low-income countries, and the reasons for this remain unclear. In order to increase vaccine use and impact, research is needed to understand and address the reasons for this reduced efficacy. While some research is underway—including the development of new vaccines—the Symposium also underscored the need for additional studies.

The Symposium focused on sharing experiences and lessons learned, and on moving forward the research agenda.

The Organizing Committee thanks all presenters and participants, many of whom travelled long distances to contribute their insights and share their work. In particular, we thank our hosts in Bangkok, who remind us through their diligent efforts and partnership, that with patience and perseverance we can together fulfill the promise of rotavirus vaccines.

THE SCIENTIFIC PROGRAM COMMITTEE

Dr. Mary Agocs, World Health Organization

Dr. Ciro de Quadros, Sabin Vaccine Institute

Dr. Roger Glass, Fogarty International Center

Dr. Kathy Neuzil, PATH

Dr. Umesh Parashar, US Centers for Disease Control and Prevention

Dr. Mathuram Santosham, Johns Hopkins University

Dr. Duncan Steele, Bill & Melinda Gates Foundation

Dr. Piyanit Tharmaphornpilas, Ministry of Health Thailand
Twenty years ago, rotavirus was a silent killer. Now it is known, and 38 countries are using rotavirus vaccines to prevent deaths and disease caused by dehydrating diarrhea in children. The Tenth International Rotavirus Symposium, held in Bangkok, Thailand, highlighted the ongoing progress in combatting this notorious killer of children that is responsible for 37 percent of all diarrheal disease and 5 percent of all deaths in children under five.

“Fulfilling the Promise of Rotavirus Vaccines,” was an apt theme for the meeting, and presenters emphasized the meaning of that promise: preventing the deaths of some 230,000 children in Africa and 188,000 children in Asia every year.

Although primarily in middle- and high-income countries, current vaccines are already making an enormous difference. Speakers presented data from a range of these countries: In Mexico, vaccine use has lowered rotavirus deaths by 40 percent. In the first two years following rotavirus vaccine introduction, Brazil had 1,500 fewer deaths and 130,000 fewer hospital admissions for diarrhea in children. In the United States, vaccine use lowered the reported incidence of disease by 60 to 80 percent.

“We’re at a new age of fulfilling the promise,” said Dr. Roger Glass, with the Fogarty International Center at the U.S. National Institutes of Health. “We’re in a decade when child and maternal health have come to the fore again... Rotavirus vaccine is part of that.”

While two new WHO-approved rotavirus vaccines have been available for only six years, the experience of early adopter countries is already yielding new insights: into herd protection, vaccine efficacy, and vaccine safety.

Presenters summarized a new safety evaluation of the two vaccines, which finds that the risk of vaccine-associated intussusception is just one or two per 100,000 – far less than 1 per 10,000 first indicated with Rotashield.

“That is a real victory for our safety surveillance,” said Dr. Kathy Neuzil with PATH. “It’s amazing that we could detect these rare events, and we should feel very reassured by that data.”

Throughout many of the presentations, two consistent messages emerged. Firstly, vaccines are having the greatest impacts in low-income settings, where rotavirus is most common and most severe.

Secondly, vaccine efficacy varies among countries that are richer and poorer: in high-income settings it typically exceeds 90 percent; in middle-income settings it ranges from 75-85; and in low-income settings it reaches about 40 to 50 percent.

Bangladesh provides an example of a low-income country where a rotavirus vaccine could make an enormous difference. Khalequz Zaman, PhD, with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), reported on the situation in his country and a recent clinical trial for Rotarix. Every year, there are approximately 2.4 million cases of rotavirus diarrhea in children under five, and 15,000 deaths. Therefore, an efficacy of even 40 percent would avert an enormous amount of disease and save the lives of many children.

Researchers examined some of the possible explanations for the disparity in vaccine efficacy. Several studies investigated—and ruled out—the
likelihood that unique circulating genotypes were to blame. Other research conducted by Dr. Duncan Steele, Bill & Melinda Gates Foundation found that adding a third dose of Rotarix vaccine would be a simple and direct way to increase vaccine impact in Africa. A modeling study by Ben Lopman, with the US CDC found that the biggest gains in VE would come by improving the natural immune response of children, which could possibly be accomplished by improved nutrition. Meanwhile, a study by Dr. Gagandeep Kang, with the Christian Medical College in India found that repeated rotavirus infections could cause a significant increase in malabsorption in malnourished children.

Anecdotal evidence points to a wide range of possible factors affecting vaccine efficacy in low-income settings, from interference of maternal antibodies to the role of multiple gastrointestinal infections, but rigorous studies have yet to be carried out.

As Glass emphasized, “We have to do the research now because this could substantially improve the performance of this vaccine.”

In the meantime, the World Health Organization’s recent recommendation to lift the age restriction on rotavirus vaccination—allowing children over 32 weeks of age to be vaccinated—could potentially prevent another 40,000 deaths a year.

Speakers also updated the Symposium on the rotavirus vaccine pipeline, noting that it has a number of promising new candidates in various stages of development. These include live human oral vaccines, a neonatal vaccine, human-animal reassortants, and inactivated vaccines. Vaccine developers and manufacturers from China, India, Indonesia and Vietnam were among those who presented.

Continuing research into rotavirus pathogenesis, immunity, and correlates of protection challenged some long held ideas. Dr. Harry Greenberg with Stanford University discussed the role of rotavirus protein NSP1 in viral pathogenesis and host range restriction. Dr. B.V. Prasad with the Baylor College of Medicine identified a new host cell target of rotavirus. Several presenters evaluated the utility of Immunoglobulin A as a correlate of protection, and Dr. Manuel Franco, from the Javeriana University in Colombia presented fresh insights on potential alternative correlates, including B cells that express intestinal homing receptors.

As delegates discussed the promise of new technologies for combating rotavirus, they also reviewed plans for accelerating the introduction of existing vaccines, particularly in countries that bear the greatest burden of disease. Thirty-eight countries have introduced rotavirus vaccine into their Expanded Program on Immunization system, most of them in the Americas, and six in Europe. Only a smattering is in Africa and Asia, but with GAVI support, another 15 nations are planning to introduce the rotavirus vaccine, 12 of them in Africa.

Asia remains the one region where the vaccine has yet to be widely accepted. Despite the fact that surveillance for the disease first began in Asia, and robust data shows the high toll of the disease in the region, only one Asian country has introduced the vaccine.

Several speakers noted that surveillance data is necessary, but not usually sufficient to prompt vaccine introduction. Advocacy is essential, and the Symposium’s final session addressed the question of how to translate science into policy.

“How can we as scientists be better advocates for rotavirus vaccine?” Neuzil asked. “No one knows the issues better than the people in this room. You are the experts, the most compelling messengers are passionate...” The challenge, then, is “to channel our passion into action,” she added.
Dr. Supamit Chunsuttiwat, a senior medical adviser in the Department of Disease Control of the Government of Thailand, opened the Tenth International Rotavirus Symposium—the first to be held in Asia.

He recognized the seminal contribution of Dr. Ruth Bishop and her colleagues at the University of Melbourne, Australia. Their role in discovering rotavirus four decades ago was recognized in 2011, when Bishop received the prestigious Prince Mahidol Award, established in honor of Prince Mahidol, the father of the present king of Thailand. The award recognizes lifetime achievement in promoting medicine and public health.

He noted that the global effort to develop vaccines against rotavirus sprang from the scientific observation that initial infection by rotavirus is followed by protective immunity to reinfection. This observation prompted years of research and disease surveillance, creating a baseline of knowledge for eventual vaccine introduction.

Chunsuttiwat noted that the Asian Rotavirus Surveillance Network has been active for more than a decade, and that Thailand had been a member since the beginning. Network surveillance has shown that rotavirus causes half of all cases of severe childhood diarrhea in any country in the region. However, the vaccines remain unavailable in most Asian countries. Chunsuttiwat identified the main barrier as vaccine cost.

He reported that Thailand recognizes diarrhea caused by rotavirus as a significant public health problem. This led the National Advisory Committee on Immunization Practice of Thailand to recommend phased introduction in 2010 of a vaccine in the national immunization program. A phased pilot program is now underway, and will be rigorously analyzed to assess the cost-effectiveness and impact of rotavirus vaccine.

“Symposium data, information and experiences will be crucial for driving further decisions on implementation of vaccination to maximize the benefit of rotavirus vaccine for children worldwide.”
On behalf of the organizing committee, Professor Mathuram Santosham, of the Johns Hopkins Bloomberg School of Public Health, announced the establishment of the Roger Glass Lectureship, to be delivered every two years at the convening of the International Rotavirus Symposium.

“I always think of Ruth Bishop as the mother of rotavirus and Roger Glass as the father of rotavirus,” Santosham said. “It is indeed a fitting tribute that Roger Glass is being honored with the Roger Glass Lectureship.”

In his lecture, Dr. Roger Glass presented the history of rotavirus research, vaccine development and delivery up until the present day, and the challenges still ahead. As Glass has been central to this history, his story was both personal and reflective of the role of many of the scientists present at the conference.

Glass’ own interest in rotavirus began with his work at the International Center for Diarrheal Disease Research, Bangladesh in 1979. At the time, 90 percent of diarrheal episodes were of unknown cause—and diarrhea was a major public health issue. Glass’s wife, Dr. Barbara Stoll, set up a sentinel surveillance system in a hospital that reported 100,000 cases a year. Screening of just four percent of affected patients showed that rotavirus was the most common cause of diarrhea. This revelation led to Glass’ life-long commitment to ending the terrible burden of rotavirus disease.

Milestones in Rotavirus Research
Glass reviewed a number of the milestones in rotavirus research, vaccine development and advocacy. The decade of the 1980s saw huge advances in the science of rotavirus, including an understanding of rotavirus genetics and reassortment. The first real vaccine breakthrough came in the late 1990s, when Dr. Albert Kapikian at the US National Institutes of Health developed the rhesus rotavirus vaccine, which was recommended for use in the US in 1998.

“We were incredibly excited,” Glass recalled. “It gave us an opportunity to think about taking a vaccine back to Bangladesh and seeing if we could stop the deaths from diarrhea there and in the low-income countries of the world.”

Then, “We hit the iceberg,” Glass said. The finding of 15 cases of intussusception (IS) associated with Rotashield led to its withdrawal from the market in 1999. “It was a terrible outcome, when we thought that the world could benefit from this vaccine.”

But Glass and the vaccine community remained focused on the promise of rotavirus vaccines and the importance of disease surveillance. Work by the Asian Rotavirus Surveillance Network, launched in 1999, soon revealed that 40 to 50 percent of hospitalizations for diarrhea were due to rotavirus, rather than the 20 to 40 percent previously estimated.

And vaccine R&D ultimately led to success. In January 2006, The Lancet published two articles establishing the efficacy and safety of two new oral rotavirus vaccines that had been tested in over 60,000 children each.

Rotavirus Vaccine Benefits
What followed was the rapid uptake of the rotavirus vaccines in national EPI programs, beginning in many countries of the Americas. Post-introduction studies soon began to reveal the vaccines’ impact in preventing deaths, disease and hospitalizations.
Studies in the US, Australia, Belgium, and other countries showed that the vaccines reduced diarrheal hospitalizations from between 60 and 90 percent, depending upon population coverage. In the US, overall hospitalizations for diarrhea were reduced by 40-45 percent. Data from low- and middle-income countries have also revealed significant impacts. In Mexico, vaccine use lowered all-cause diarrhoea deaths by 40 percent.

The benefits also appeared to extend to unvaccinated children, older siblings and parents. This decreased hospitalizations in older age groups and “added another 25 percent to the value of the vaccine,” Glass said. In addition, there was negligible evidence of vaccine-associated intussusception. “The ratio of benefit to possible risk is huge and compelling,” Glass said.

After PATH-sponsored studies demonstrated vaccine efficacy and public health impact in seven low-income countries, WHO recommended global use of rotavirus vaccine.

Glass noted that today there is much to celebrate. “We now have 38 countries with rotavirus vaccine—about 20 percent of the world’s total. The impact of these vaccine introductions has been enormous, and the herd effects really were unanticipated.”

Challenges Ahead
Glass stressed the need to evaluate the impact of the vaccines as they go forward. “We need to do the research to know how well they would work and what we could do to improve their performance,” Glass said.

He noted differences between high- and low-income countries that could influence vaccine efficacy: disease epidemiology; circulating serotypes; rates of mixed infections; malnutrition; interference from high maternal antibody titer; and different gastrointestinal infections that could interfere with vaccine take.

“We have to do the research now, because understanding this could substantially improve the performance of these vaccines,” and prevent hospitalizations and deaths, Glass said.

Reviewing the map of countries that have introduced rotavirus vaccines, Glass commented, “It’s a very interesting picture.” By world region, the biggest gap in coverage is Asia. “And yet this is where we started surveillance, this is where we had the most data,” Glass said. This issue is that data do not make decisions, the community makes decisions, Glass said.

“It’s all about people,” he concluded. “We’re all here because we have a common vision of how we could use these vaccines in our own countries... We have the knowledge, we have the financial support, and we have the motivation. We have incredible people, and those people are you. And while many challenges remain, the goal is clear. It’s compelling, and it’s doable in a decade.”

“We now have 38 countries with rotavirus vaccine—about 20 percent of the world’s total. The impact of these vaccine introductions has been enormous, and the herd effects really were unanticipated.”

Roger Glass, National Institutes of Health, United States
Vaccine Introductions to Date:
38 Countries that have Introduced Rotavirus Vaccines to Date

*National introductions by geographic region, as of 1 Sept 2012
WHO Rotavirus Vaccine Update 2012
In April 2012, WHO’s Strategic Advisory Group of Experts on Immunization (SAGE), after reviewing the existing evidence, concluded that the risk benefit analysis continues to favour early immunization but the current age restrictions for the first dose (<15 weeks) and last dose (<32 weeks) are preventing vaccination of many vulnerable children. By removing the age restrictions, programmes will be able to immunize children who are currently excluded from the benefits of rotavirus vaccines and this is likely to include some of the children most vulnerable to severe rotavirus disease. Many more deaths could be averted, but with a small additional increase in intussusception cases. Dr. Fatima Serhan of the World Health Organization explained both the reasoning of the experts, and the significance of the change. Serhan also reviewed the latest global data from WHO on rotavirus epidemiology.

The World Health Organization estimates that globally 453 000 (420 000 - 494 000) child deaths due to rotavirus infection occurred during 2008. Five countries (India, Nigeria, the Democratic Republic of the Congo, Ethiopia and Pakistan) accounted for more than half of all rota deaths under age five in 2008. Globally, rotavirus deaths accounted for approximately 5 percent of all child deaths.

The WHO global rotavirus surveillance network includes 64 countries and 185 sentinel sites. WHO has adopted a layered approach for surveillance which involves global, regional and national laboratories collaborating together to improve laboratory capacities in countries. The network has 10 regional reference labs spread over the world, and a global reference lab at the US CDC.

WHO Rotavirus Surveillance Network, 2011
Source: WHO/IVB New Vaccines database
Data collected from WHO/Regions.
SAGE reviewed epidemiology data in young children from more than 30 countries: studies about vaccine efficacy and effectiveness under a variety of immunization schedules; new estimates of the benefits and risk of intussusception following immunization, and data on the age of first infections.

A review (Sanderson C et al 2012) estimated that the median age at infection for rotavirus for all the studies was 43.5 weeks (inter-quartile range 38 to 52 weeks). This review reported that of all the cases of rotavirus diarrhoea in children less than 3 years old that are severe enough for hospital admission, about 3 percent will occur before the child is 9 weeks old. About 6 percent will occur before 13 weeks, about 10 percent before 17 weeks, and only 32 percent before they are 32 weeks old. For example, in a sub-Saharan African country, 14 percent of rotavirus cases occur before 15 weeks of age. Ideally vaccination schedules should be designed to provide benefits to those at highest risk.

Both rotavirus vaccines are efficacious, but data show that they are more efficacious in low child mortality settings (vaccine efficacy ~ 90 percent) than in high child mortality (vaccine efficacy ~ 60 percent). Observational studies have reported similar findings. The potential of administering a rotavirus vaccine before rotavirus gastro-enteritis (RVGE) cases occur depends on providing each vaccine dose in time and in achieving high coverage with each dose before the peak of the disease incidence occurs. As the potential of preventing RVGE deaths is a function of vaccine effectiveness, age specific distribution of deaths and coverage and timeliness, unless high coverage is achieved by the age when the peak of disease incidence occurs the impact will be lower than anticipated.

Currently, there is only limited data on the risk of intussusception in children receiving rotavirus vaccines and there is very little evidence about the risk of IS after each vaccine dose. Most RCTs lack precision to examine the impact of RV1 and RV5 on intussusception with different schedules. From
thirteen observational studies reporting on specific surveillance for intussusception, the majority did not provide risk estimations or comparisons of results with unvaccinated children. Results from a case-control study reported an increased risk after RV1 doses one and two in Mexico and after the second dose of RV1 in Brazil up to 14 days after vaccination, and a surveillance study from Australia showed an increased risk after the first RV5 dose in children aged one to three months up to 7 days and up to 21 days after vaccination. Studies were performed mainly in countries with low or medium overall mortality rates. Trade-offs exists when considering various rotavirus vaccine schedule options. A model analysis by the CDC, LSHTM and WHO assessed the potential number of vaccine-associated deaths from intussusception and the estimated number of rotavirus deaths that could be averted by removing age restrictions in view of the above findings.

A rotavirus vaccination programme under the previous age-restricted schedule would prevent almost 33 percent or 148,600 of the global deaths (5th–95th centiles, 103,600–193,800) if delivered at the same ages at which the DTP vaccine is currently being delivered in these countries. Without the age restrictions, a RV programme would prevent 48 percent or 196,900 deaths of all rotavirus deaths (138,700–252,900). A rotavirus vaccination program limiting vaccination to children < 15 weeks of age would result in about 285 intussusception deaths (98–678).

Without age restrictions it would cause 618 intussusception deaths (318–1,148). The median incremental benefit-risk ratio in all mortality strata was estimated to be nearly 145 lives averted for every death caused, ranging from 119-258 lives averted for every death caused across the different mortality settings.

Therefore, in order to maximize rotavirus vaccine impact, WHO recommended that the first dose of vaccine should be administered as soon as possible after 6 weeks of age, along with DTP vaccine. It also noted that, in view of the age distribution of rotavirus disease, providing vaccines to children older than 24 months of age would be of little benefit. A summary of SAGE discussions and recommendations can be found at the following link: http://www.who.int/entity/wer/2012/wer8721.pdf.

“By removing age restriction, programs will be able to immunize children who are currently excluded from the benefits of rotavirus vaccines, and this is likely to include some of the children most vulnerable to severe rotavirus disease.”

Fatima Serhan, WHO

**Does timing really matter?**

Dr. Colin Sanderson, of the London School of Hygiene & Tropical Medicine, estimated the public health impact of the age at which children receive rotavirus vaccine, and how vaccination at a slightly older age might impact vaccine efficacy.

To tackle this question, Sanderson’s team reviewed data on the age of natural infection with rotavirus and on vaccine coverage (from 69 countries). They combined these two data sets to produce estimates of the impact of the delays. In some cases, there was sufficient country data to allow analysis of the proportion of rotavirus cases that would have been prevented if infants had received their first dose of rotavirus along with DTP.

Results differed significantly among countries. Malawi, for example had a very early peak in diseases, while the peak in Bangladesh was much later. Coverage data also varied enormously among countries. Iraq, for example, had started vaccination at a fairly late age, and coverage increased slowly from there. Laos and India had strong initial coverage, but never reached very high coverage overall.
Sanderson’s team then used the data to estimate vaccine impact using different vaccine schedules, and assuming relatively low vaccine efficacy (protection of 45 percent with the first dose, 55 percent with the second).

“In some places like Bangladesh,” Sanderson noted, “it doesn’t make a lot of difference whether you use a 6, 10, 14 schedule, or a 2, 4, 6 schedule, and that’s because the peak is relatively late. On the other hand, in Malawi, it does make a difference, and that’s because the peak is earlier.”

The team also analyzed the data by economic status. In India, this showed a large disparity in coverage between the poorest (40 percent coverage) and richest quintiles (more than 80 percent coverage).

In conclusion, Sanderson noted, “Shifting schedules or reducing delays only has a material impact in countries in which either the ages at RVGE (are) young, or the ages at vaccination (are) old, or both.”

Even after an extensive review of the data, “It’s unclear where the balance between these earlier and later schedules should lie, but the key point is that it is going to vary between populations. So it needs to be looked at on a country by country basis,” Sanderson said.

“**It’s unclear where the balance between these earlier and later schedules should lie, but the key point is that it is going to vary between populations. So it needs to be looked at on a country by country basis.**”

Colin Sanderson, London School of Hygiene & Tropical Medicine, United Kingdom
Rotavirus burden by world region

Dr. Jacqueline Tate, with the US Centers for Disease Control and Prevention, recently updated the analysis of global mortality due to rotavirus, finding that in 2008 it caused 453,000 deaths, or 37 percent of all deaths from diarrhea, and five percent of all child deaths. While still unacceptably high, this reflected a decline in both diarrheal mortality and rotavirus mortality over the past 30 years.

To conduct the assessment, Tate’s team started with the estimated 1.3 million deaths attributed to diarrhea in 2008, and determined the proportion caused by rotavirus. An extensive review of PubMed literature and surveillance network data yielded 131 different usable studies, encompassing 151,172 specimens. Study methodology was similar to that used in 2004, enabling easy comparison.

Hospitalization for severe rotavirus was used as a proxy for rotavirus deaths, based on the assumption that the proportion of severe hospitalizations and deaths were similar. Such an assumption was necessary because there are few studies in low-income countries—where the majority of deaths occur— that can attribute a diarrhea-associated death to a particular disease.

Tate analyzed the data based on five mortality strata:

- **Strata A**: All countries with very low child mortality
- **Strata B and C**: All countries with low child mortality
- **Strata D: Asia**: All countries in Asia with high child mortality
- **Strata D: Americas**: Countries in the Americas with high child mortality
- **Strata D & E: Africa**: Countries in Africa with high child mortality

For each stratum, the research team calculated the proportion of diarrhea hospitalizations that were due to rotavirus, and used those numbers to estimate the number of deaths caused by rotavirus.

### Number of Diarrhea and Rotavirus Deaths by Strata

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Mean Detection Rate (95% CI)</th>
<th>No. of Diarrhea Deaths</th>
<th>No. of Rotavirus Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>49 (34-64)</td>
<td>&lt;1,000</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>B&amp;C</td>
<td>40 (36-44)</td>
<td>67,000</td>
<td>27,000</td>
</tr>
<tr>
<td>D: Asia</td>
<td>42 (35-48)</td>
<td>452,000</td>
<td>188,000</td>
</tr>
<tr>
<td>D: America</td>
<td>42 (37-47)</td>
<td>13,000</td>
<td>5,000</td>
</tr>
<tr>
<td>D&amp;E: Africa</td>
<td>33 (28-38)</td>
<td>704,000</td>
<td>232,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1,236,000</strong></td>
<td><strong>453,000</strong></td>
</tr>
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</table>

37 percent of Diarrhea Deaths and 5 percent of all Deaths in Children <5 of Age are Due to Rotavirus
Stratum A had the highest mean detection rate, but lowest number of deaths. Although African nations showed the lowest mean detection rate (33 percent), they recorded the highest number of deaths caused by rotavirus.

Over half of global rotavirus deaths—232,000—were in Africa. Asia’s burden was also high, with 188,000 deaths.

Ten countries accounted for 67 percent of all deaths from diarrhea. India alone accounted for 100,000 deaths—one-fifth of the global toll. Five of the nations with the highest burden of disease were located in Asia; the remaining five were in Africa.

### Ten Countries with the Greatest Number of Rotavirus Deaths - 2008

<table>
<thead>
<tr>
<th>Country</th>
<th>Deaths</th>
<th>% Is Percent Of Total Global Rotavirus Deaths</th>
<th>% Is Percent Of Total Global Rotavirus Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>98,621</td>
<td>98,621</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>41,057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>39,144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR Congo</td>
<td>32,653</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>28,218</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afghanistan</td>
<td>25,423</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>10,637</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>9,970</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>9,857</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angola</td>
<td>8,788</td>
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</tr>
</tbody>
</table>

Based on the research, “One out of every 260 children born each year will die from rotavirus by their fifth birthday,” Tate said. “The highest prevalence occurred in children hospitalized for diarrhea in developed countries, but the majority of deaths occurred in developing countries in Africa and Asia.”

The analysis shows that while deaths from diarrhea have been declining, there has not been a corresponding decline in deaths from rotavirus. “The proportion of severe diarrhea cases that are due to rotavirus have been increasing over time, from 29 percent in 2004 to 37 percent in 2008,” Tate said.

Going forward, Tate’s team will reassess this burden based on recent findings that place the total number of childhood deaths from diarrhea at 800,000 per year (12 percent of all childhood deaths). They will also begin assessing the impact of rotavirus vaccines on the mortality estimates in countries that have introduced the vaccine, particularly in countries where the death toll is highest.
Decreasing diarrhea mortality over time

- 1986: an estimated 3.5 million deaths from diarrhea in children; 25 percent, or 873,000 annually due to rotavirus between 1975 and 1985.
- 2003: an estimated 2.1 million deaths from diarrhea; 22 percent, or 444,000 annually due to rotavirus between 1986 and 1999.
- 2004: an estimated 1.8 million deaths from diarrhea; 29 percent, or 527,000 due to rotavirus between 1990-2004.
- 2008: an estimated 1.3 million deaths from diarrhea; 37 percent or 453,000 due to rotavirus.

Surveillance in Action in Africa

Dr. Jason Mwenda, with the African Rotavirus Surveillance Network, reported on progress in surveillance since the establishment of the Africa Rotavirus Surveillance Network in 2005 with support from WHO and partners.

Since 2005, the number of countries in the surveillance network has increased from 4 to 19. So far this year, hundreds of laboratory samples from hospitals reporting cases of acute diarrhea have shown a mean detection rate for rotavirus of about 40 percent. That rate has been consistent over time and across countries, Mwenda reported.

Rotavirus Sentinel Surveillance Sites and Regional Reference Labs (RRLs)

- Built on framework and experience of surveillance for other Vaccine Preventable Diseases (VPDs)
- Some components of Rota surveillance are integrated with surveillance for other VPDs eq IBD

“Over 200,000 kids are dying in the Africa region due to rotavirus diarrhea. And when you look at the top ten countries for mortality, you can see most of these countries are actually in Africa,” Mwenda said. He described how the data is being used to inform policy in the African WHO region, and discussed current challenges.
He noted that only eight African countries are on track to meet Millennium Development Goal 4 (MDG4), which focuses on the reduction of child mortality.

“We should tell the Ministers of Health that the rotavirus vaccine is one of the most effective interventions that can contribute to attainment of the MDG4,” Mwenda said. He called this “the advocate’s message.”

As of September 2012, across the region, the vaccine has been introduced in five countries, South Africa (2009); Zambia (January 2012 as a demonstration project); Ghana (April 2012); Rwanda (May 2012), and Botswana (August 2012).

Meanwhile, other nations in Africa, among them Malawi, Tanzania and Ethiopia, are ready to introduce the vaccine, but have been hindered by lack of supply of vaccine, Mwenda reported.

The Africa Rotavirus Surveillance Network is working with the CDC and other partners to design vaccine impact studies. Three are underway already in South Africa, Rwanda and Zambia, while a fourth is being prepared in Ghana.

“We have come a long way in terms of establishing the surveillance and using the data to support the introduction of the rotavirus vaccines,” Mwenda concluded. “But it is actually important to continue the advocacy and to keep emphasizing the value of the sentinel surveillance data for decision-making, and to increase investments to support rotavirus vaccine introduction.”

**Surveillance in Action in Nepal**

Dr. Jyoti Ratna Dhakhwa, Nepal Pediatric Society, reported on findings from hospital-based surveillance of children under five, which began in Nepal in 2010.

One study was carried out in 2010-2011 at the Kanti Children’s Hospital, a 300-bed hospital with a 30-bed unit for diarrheal cases. The samples were processed at the Public Health Research Laboratory.

“The major finding is that one-fourth of the diarrheal cases in the sentinel site tested positive for rotavirus,” Dhakhwa said. Rotavirus infection peaks from December to April in Nepal, and is most common among children less than 21 months of age. The most common genotype was G12P6 (32 percent).

A second study was carried out in Patan Hospital, a missionary hospital. It looked at children under three years of age who presented with non-bloody watery diarrhea over a three-month period. Out of 119 samples, 53 percent were rotavirus positive.

Taken together, Dhakhwa said that the studies reveal, “One-in-four children suffer from rotavirus diarrhea in Nepal.” Most of the children are below 24 months of age.

Dhakhwa stressed the need to generate more evidence through surveillance and to improve rotavirus control measures such as case management. Although more than half the burden of diarrhea among Nepalese children is caused by rotavirus, Dhakhwa noted the need for more information on circulating strains in order to support introduction of rotavirus vaccines.

“**The value of the African rotavirus network is growing but the funds to continue this important work are limited.**”

Jason Mwenda, African Rotavirus Surveillance Network

“**One-in-four children suffer from rotavirus diarrhea in Nepal.**”

Jyoti Ratna Dhakhwa, Nepal Pediatric Society, Nepal
Nepal at a Glance
Nepal is a small South Asian country with a population of 26.6 million. The child mortality rate is 54 per 1,000, down by 64 percent since 1991. The neonatal mortality rate is 33 percent. To achieve the MDG4, the neonatal mortality rate would need to drop to 17 percent. The maternal mortality rate is 281 per 100,000.

Diarrhea is the second-most common cause of death among children under five years of age, after deaths from acute respiratory infections. Rotavirus causes a significant percentage of cases of diarrhea among Nepalese children.

Surveillance in Action in China
Dr. Zhao-jun Duan, with the China Centers for Disease Control, described the public health system in China, and reported the results of rotavirus surveillance in his country.

He first noted the complexity of the four-level public health agency known as the Center for Disease Control and Prevention (CDC). The agency is composed of the national-level China CDC, the Provincial CDC, the Prefectural/Municipal CDC, and the County CDC. There are also a number of township hospitals and village clinics that are part of the larger network.

Within the China CDC there is a National Institute of Viral Disease, and three systems associated with viral diarrheal surveillance. The Viral Diarrhea Surveillance system uses a common case definition of rotavirus, and uniformly collects and stores demographic information and information on clinical symptoms. Data compiled monthly by the provincial CDCs is sent to the China CDC every six months, which in turn reports the results to WHO. Stool specimens are collected within 24 hours of hospital admission, and every Provincial hospital is asked to collect and test 400 specimens per year, sending about one-third of them to China CDC for retesting.

Field Sites for Viral Diarrhea Surveillance

Rural: LLH, XHC, LCC
Urban: Other 14 Sentinel Hospitals
Now in its third stage of development, the surveillance system in China now cooperates globally on efforts aimed at introducing vaccines against rotavirus into the Expanded Program of Immunization (EPI).

“This year, we got much support from the WHO Western Pacific Regional Office, and also the US CDC, and now we have a basic network,” Duan said.

Surveillance data from 2009-2011 reveals that:
- Among children under five hospitalized for diarrhea, 30 to 40 percent test positive for rotavirus
- The highest rotavirus positive rate is in age group 9-17 months; 90 percent of cases are in children under two
- The rotavirus peak season is October to February, and the positive rate during the peak season is 56 percent
- The most common G/P combination in 2009-2010 was G3P[8] and in 2011 was G9P[8]

The Lanzhou Lamb rotavirus vaccine
Is the only vaccine in use in China, and about thirty million doses have been used. Four rotavirus vaccines are in clinical trials in China, including two produced locally, as well as RotaTeq and Rotarix. Other vaccines are in development, and Chinese manufacturers of a vaccine that covers genotypes 1, 2, 3, 4, 8, and 9 are applying for permission to test their vaccine in a clinical trial.

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<thead>
<tr>
<th><strong>Rotavirus Vaccines in China, 2012</strong></th>
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<tr>
<td><strong>Vaccine</strong></td>
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<td>---------------------------------------</td>
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<tr>
<td>Lanzhou Lamb rotavirus vaccine</td>
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<td>Lanzhou reassortment rotavirus vaccine</td>
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<td>Shenzhen reassortment rotavirus vaccine</td>
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<td>RotaTeq</td>
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<td>Rotarix</td>
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Natural History Lessons from a “Small town” in India

Dr. Gagandeep Kang, with the Christian Medical College, described the rotavirus work being done in an urban slum in Vellore, a relatively small town in southern India. “The nice thing about being in a small town is that you work with the community, and you can do the kinds of studies that can’t always be done in larger towns,” Kang said.

Vellore has a population of about 400,000 people, and Kang’s team works in an area of 40,000 people. The area has large numbers of urban poor, and lacks adequate sanitation and clean water.

Kang focused on two issues: 1) nutrition and intestinal permeability, and 2) measurement of IgA responses in natural infection and vaccination.

The birth cohort study followed 373 children for the first three years of life. Some mothers were enrolled while still pregnant, enabling researchers to collect maternal blood, and cord blood at the time of birth. Regular collection and testing of children’s stools revealed an incidence of severe rotavirus diarrhea of 4.9 per 100 child years.

The researchers compared their results with that of a similar cohort followed in Mexico. One striking difference was in the degree of protection afforded by natural rotavirus infections. In Mexico, one prior infection offered 87 percent protection against severe rotavirus; two natural infections provided 400 percent protection. In the Indian children, one infection offered 18 percent protection; two infections provided 57 percent.

“In Mexico, no child had moderate or severe diarrhea after two prior rotavirus infections, whereas for us, 22.4 percent of third or later rotavirus diarrheas were moderate to severe,” Kang reported.

This led to the question of whether nutritional status was affecting susceptibility to rotavirus infection in the Indian cohort.

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**Factors Affecting Responses to Enteric Vaccines**

- Impaired gut function
- Concurrent infections
- Impaired nutrition
- Aberrant microbiota
- Impaired immunity
- Poor performance of vaccines for gut or gut-acquired pathogens
- Intense exposure
- Genetic factors
- Other environmental factors

To answer this question, the researchers compared the nutritional status of children who had repeated infections with rotavirus and those who had fewer infections. They conducted intestinal permeability studies with children enrolled in the study, using a single sugar absorption test.

The study found that the odds of mal-absorption were doubled in malnourished children:
- If children had had at least one rotavirus diarrhea, and
- If the children had had two asymptomatic rotavirus infections, independent of any rotavirus diarrheas.

The findings show that “Rotavirus infection does affect the gut,” Kang said.

Kang’s team then analyzed the implications for vaccine response. Based on analysis of anti-rotavirus IgA from study samples, they found that 95 percent of children sero-converted following vaccination. However, children receiving the vaccine didn’t seem to reach anything like the geometric mean that occurs with natural infection, according to Kang.

In addition, rather than boosting after a second dose of vaccine, almost every child tested had a rapid drop in IgA antibodies.

The researchers are now studying what seroconversion means in terms of protection. “If there is a serological correlate of protection, we have the sera and the infection data to test it,” Kang said.

When is it vaccine failure? Telling the difference with diagnostics

Dr. Eric Houpt, with the University of Virginia, described a new molecular diagnostic that can quickly and affordably diagnose an array of enteropathogens that cause diarrhea in the developing world.

He noted that a complete stool workup using conventional methods is really never complete, is costly, and is qualitative, not quantitative. Houpt’s team has been developing diagnostics that are sensitive, practical and at least semi-quantitative in testing for a comprehensive number of enteropathogens.

Houpt explained that because mixed infections with a number of pathogens are the norm in developing country settings, quantification of the different pathogens could provide a more precise diagnosis. In addition, it may reveal that apparent cases of vaccine failure are actually infections due to other diarrheal pathogens.

Houpt’s diagnostics detect over two-dozen pathogens, including E. coli, other bacteria, viruses and protozoa. The tool, which is considerably less expensive than conventional methods, has been tested at five sites around the world.

Results in one of those studies, of a birth cohort in Dhaka, Bangladesh, revealed that during their first year of life children in the community have about five enteropathogens present in their stool. In contrast, children in Virginia have an average of less than one pathogen present per specimen.
To infer which of the pathogens in a specimen contributed the most to diarrhea, the researchers measured the load. A pathogen was considered a probable contributor if it was present at a higher load than in any of the previous surveillance stools for that individual. It was considered less likely to contribute to infection if it had been found previously at a similar or higher level. It was considered dominant if it occurred at the highest load relative to other likely pathogens in the specimen.

Rotavirus featured prominently in the results, Houpt reported. In an analysis of moderate or severe cases of diarrhea, it was dominant more often than any other pathogen.

Nonetheless, diarrhea was clearly associated with multiple dominant or probable enteropathogens. “Multiple pathogens appear to be reacting as a gang,” he said.

“Rotavirus is clearly one of or the most important pathogen. But it occurs with other probable or dominant pathogens as well, and this may have implications for how much diarrheal burden can be reduced with a single-pathogen vaccine. It really depends on how dominant rotavirus is in that context of the GI tract.”

Eric Houpt, University of Virginia, United States
Severity

- The majority of diarrhea episodes were mild in this community study.

<table>
<thead>
<tr>
<th>% of probable/dominant detections</th>
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<tr>
<td>1. EAEC (10.9%)</td>
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<tr>
<td>2. Campy (10.5%)</td>
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<tr>
<td>3. EPEC (9.7%)</td>
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<tr>
<td>4. Rotavirus (7.6%)</td>
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<tr>
<td>5. E. histolytica (6.6%)</td>
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- Only 39 (9.3%) were moderate or severe (Ruuska score > 6).

<table>
<thead>
<tr>
<th>% of probable/dominant detections</th>
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<tbody>
<tr>
<td>1. Rotavirus (13.2%)</td>
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<tr>
<td>2. E. histolytica (10.1%)</td>
</tr>
<tr>
<td>3. EAEC (9.4%)</td>
</tr>
<tr>
<td>4. Campylobacter (8.4%)</td>
</tr>
<tr>
<td>5. Cryptosporidium (7.9%)</td>
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Intussusception in Asia: What Is Known

Dr. Julie Bines, with the University of Melbourne, noted that the most recent data from countries that were early adopters of rotavirus vaccines suggest that there is a signal, albeit small, of an increased risk of intussusception, “of the order of an incidence of 1-2 per 100,000 vaccinated infants in some settings.”

While some countries, including Australia, have determined that the benefits of the vaccination far outweigh the risks of intussusception, Bines pointed out that this might not be the case in countries where the incidence of intussusception in the unvaccinated population is high or not known.

Baseline rates of intussusception have been reported to vary considerably in countries where studies have been conducted. For example, low rates appear to prevail in Indonesia (18 per 100,000 infants less than 1 year old), while much higher rates are found in Japan (180-190 per 100,000 infants), South Korea (236 per 100,000 infants less than 2 years) and Vietnam (302 per 100,000 infants less than 1 year). In other countries, including China, an accurate estimation of the baseline incidence has not been well documented.

Bines reviewed possible explanations for regional differences in reported intussusception rates. Factors could include genetic, cultural or environmental differences; exposure to infection; therapeutic practices, methods of diagnosis and access to healthcare services.

The clinical presentation of intussusception in children in Asia reflects that described in other regions. A significant proportion of infants have been reported to have a prior history of either respiratory infection or acute gastroenteritis. Bines reported a variation in treatment methods preferred in Asian countries. In countries with low baseline incidence of intussusception, surgery tends to be the preferred method of treatment. However in China and Vietnam, hydrostatic reduction under ultrasound guidance or air enema is often used. In a paper from China, over 6,000 cases of intussusception were reported during a 13-year period at Shanghai Children’s Hospital, including 13 cases in just one day. In this experience ultrasound was used for diagnosis and very few deaths occurred despite a huge number of babies presenting with intussusception.

If diagnosed and treated promptly intussusception is usually associated with good outcome. However delayed diagnosis and surgery can be associated with both death and morbidity from surgery. Mortality is ten times higher in babies that arrive at the hospital more than 48 hours after the onset of symptoms. A new study from Indonesia reported a mortality rate of 20 percent.

Across the region, a number of pathogens have been associated with intussusception. “Studies in Taiwan and Vietnam suggest that adenovirus is a very important pathogen in association with intussusception,” Bines said. In Korea, 88 percent of intussusception cases are in patients older than two years.

Also of interest for Asia is a US study that found a dramatic increase in the risk of intussusception (40 times more likely) in infants and small children who had experienced bacterial enteritis in the preceding six months.

“Intussusception occurs in children throughout Asia in the absence of a rotavirus vaccine, it is going to continue to be with us, so we need to understand it, not to be fearful of it.”

Julie Bines, University of Melbourne, Australia
Why is intussusception important today?
A brief review of the links rotavirus vaccines and intussusception

Rotashield, the world’s first vaccine against rotavirus, had an unusual and rare association with intussusception, a form of bowel obstruction in which one part of the bowel telescopes into another part. Symptoms in babies frequently include abdominal pain, intestinal obstruction, vomiting, irritability, shock and pallor, and bloody stool.

Intussusception can be deadly if not treated. However, it can also be transient and asymptomatic, occurring as a normal part of bowel contractions.

After being launched in the US in 1998, Rotashield, a human rhesus reassortant vaccine, was associated with intussusception. After more than 500,000 infants had received at least one dose of the vaccine, the associated risk was determined to be an estimated at 1 in 10,000 to 30,000. The vaccine was voluntarily withdrawn from the market.

Bines noted that the Rotashield experience had a tremendous impact on the development of subsequent vaccine candidates, necessitating very large clinical trials (over 60,000 infants) of the two current rotavirus vaccines. Those trials showed no association with intussusception. However, WHO recommended routine post-marketing surveillance.
Intussusception data from early adopter countries has shown that:

- **United States:**
  - Vaccine Safety Datalink study reviewing 786,725 doses of RV5 found no association with increased incidence of intussusception, but was unable to rule out a risk of 1-2 in 100,000
  - Vaccine Adverse Events Reporting System found a small increase in intussusception reported at 3-6 days, following dose 1 of RV5
- **Europe:**
  - A manufacturer-sponsored study of RV1 showed a small increase of intussusception in the seven days following Dose 1
- **Brazil:**
  - Active surveillance found no increase in intussusception following the first dose of RV1, but an increased risk of 1 in 76,000 after the second dose.
- **Mexico:**
  - Two studies have shown a small increase in intussusception in the first week following dose 1 of RV1.
- **Australia:**
  - Active surveillance found a small increase in the risk of intussusception following dose 1 of both commercially available vaccines.

Bines reported that the risk in Australia was 1 case of intussusception per 200,000 doses of vaccine. “And it was the decision of the Australian regulator (TGA) that the potential risks of intussusception were far outweighed by the benefits achieved with the rotavirus vaccine program.

“This should be considered a success for post-marketing surveillance. We should be reassured by the fact that such a rare risk, of the order of 1 in 100,000 vaccines, can be detected within 1-2 years of the introduction of a new vaccine”

**Modeling Change: Explaining Reduced Vaccine Efficacy in Low-Income Countries**

Dr. Ben Lopman, with the US CDC explained a dynamic mathematical model used to predict vaccine efficacy (VE) in different socio-economic settings, and reported the insights gleaned from its findings.

According to the premise of the study, rotavirus vaccines, like all live enteric vaccines, are less immunogenic and less effective in certain populations in low-income settings. In the highest income settings, rotavirus vaccine efficacy is upwards of 90 percent. In middle-income settings, it ranges from 75-85 percent, and in low-income settings, it ranges from about 40 to 50 percent.

The model interprets rotavirus clinical trial data in high-, middle- and low-income settings, using data inputs of natural protection, immunogenicity and local incidence. The output is vaccine efficacy. The model can then be used to illustrate how changing any one input may impact efficacy.

**Model Results and Implications**

The result is a prediction of vaccine efficacy, and of efficacy against severe rotavirus in the 6-23 month age group (roughly the age group followed in the clinical trials). The model predicts vaccine efficacy of 93 percent in high-income settings, 86 percent in middle-income settings, and 51 percent in low-income settings.
“The model is doing a pretty good job capturing the range of efficacies we see,” Lopman noted.

The model highlighted two significant features: efficacy is higher against severe disease, and vaccine efficacy reduces with age, but only in low-income settings.

“Again, this is consistent with what has been observed in clinical trials,” Lopman said. “In the US and Europe, efficacy remains high in the second, even third year. It’s pretty similar in the first and second year in Latin America, whereas in the African trials, efficacy drops off really sharply in the second year of life.”

After confirming that the model was a good fit to reality, the modelers went on to change one input parameter at a time to see how each one might be altered to improve vaccine efficacy. The biggest boost in vaccine efficacy came as a result of increasing the natural immunity parameter.

Lopman noted that the model suggests a few potential areas for real-life gains in vaccine efficacy, and sets some realistic expectations about what can be achieved with different strategies.

While improving the immunogenicity of the vaccines would make a difference, “The bigger gains in vaccine efficacy are to be had by improving the natural immune response,” Lopman said. For example, he suggested that the use of probiotics or nutrient supplementation might overcome micronutrient deficiencies and boost immune response.

Lopman emphasized another consistency between the models and observed data: “The number of cases prevented in low socio-economic settings – despite the lower efficacy – is greater than the number of cases prevented in high-income settings. The disease burden is greater in low-income settings, and so are the potential benefits of vaccination, and, again, the models are consistent with that.”

Challenging paradigms of rotavirus immunity and host range restriction

The two surface proteins VP4 and VP7 are classically considered the most important for stimulating an immune response, said Stanford University’s Dr. Harry Greenberg. But he noted that each of the 11 rotavirus genes is important. Greenberg focused his talk on the fifth gene, which encodes the NSP1 protein. He related this gene to host range restriction and innate immunity.
According to Greenberg, host range restriction is the idea behind Merck’s vaccine, RotaTeq. It is also the basis of RotaShield and the Chinese Lamb vaccine. Host range restriction assumes that an animal rotavirus will not typically make a human sick. Because of host range restriction, rotavirus “can cross species barriers but they tend not to stick. And the infectious dose to cross a species barrier is very big,” Greenberg said.

For example, there is about a 100,000-fold difference in infectivity when a mouse rotavirus infects a mouse, and when a simian rotavirus infects a mouse.

To take advantage of host range restriction, vaccines harness a process called reassortment, in which the different strains of rotavirus infecting the same cell shuffle their RNA segments, giving rise to genetically distinct progeny. Reassortment can be used to create live rotavirus that combines genes from bovine, simian, human and other rotaviruses. To better understand how these vaccines work, Greenberg examined the nature of the relationship between the species barrier and the innate immune system.

“We’ve learned more and more and more about what happens with the host and the pathogen when the infection first occurs, and what the host does to squash the pathogen, and what the pathogen does to squash the host. And it is an incredibly complicated dance,” he said.

In this dance, rotavirus stimulates two different host cell pathways—IRF and NF Kappa B (NF-kB)—which in turn stimulate interferon. Interferon can both suppress the replication of a virus, and stimulate the acquired rotavirus-specific immune response. But the virus has strategies to stop the host from making interferon.
Greenberg argued that, contrary to common assumptions, host range restriction is at least partly the result of a species-specific antiviral response of the innate immune system.

He described a series of experiments in which mice were infected with both mouse rotavirus and simian rotavirus and recombinants of the two. Analysis showed that host range restriction tracked with the NSP1 gene: “If the virus had gene five from the simian parent, it was simian-like irrespective of any other gene,” he said. “So gene five plays a huge role in coding for host range specificity.”

In other words, any recombinant virus that had simian gene five was greatly limited in its ability to infect a mouse, even if every other gene in the virus came from a mouse rotavirus.

Greenberg hypothesized that gene five was involved with the regulation of interferon, the key early actor in an innate immune response. Additional studies using a mouse model with the interferon signaling knocked out proved this to be the case. The story became far more complicated however, as Greenberg set out to determine the mechanism by which the homologous (100 percent) mouse virus blocks the interferon system.

Greenberg summarized his conclusions to date as:

• Efficient homologous rotavirus replication paradoxically induces interferon and antiviral genes in bulk intestinal tissues.
• Intestinal type I interferon induction at bulk levels occurs primarily in intestinal hematopoietic cells.
• In villous epithelium, the target cells for rotavirus infection, the murine rotavirus replicates despite transcription of a variety of antiviral genes, and it replicates preferentially in cells that are turned on to express the highest basal interferon levels.
• Rotavirus-infected villous epithelium is unable to induce type I interferon genes, and this defect correlates with a defect in the NF-kB pathway.
• Interferon secreted by plasmacytoid dendritic cells in a mouse helps enhance the acquired immune response. Therefore, the ability of a heterologous virus to stimulate this response is associated with its immunogenicity.
All is not equal: Benefits and Cost-Effectiveness of Rotavirus Vaccination

Dr. Rick Rheingans, with the University of Florida, described two studies that assess the impacts and cost-effectiveness of rotavirus vaccination within low-income countries, looking at disparities among wealth quintiles.

“The purpose of this work is to examine whether immunization programs in low-income countries reach vulnerable and high-risk children; and then to determine what this tells us about where we can redouble our efforts and increase impacts,” Rheingans said.

A 25-country study, published earlier in the journal Vaccine, looks at the benefits and costs of vaccines within each country based on economic status, geography and vulnerability. The study used proxy data to estimate rotavirus mortality, and used quintile-specific information on DPT1 and DPT2 coverage to estimate the distribution of benefits and costs.

Going from the poorest 20 percent to the richest 20 percent of children, it estimated the impact and cost-effectiveness of the vaccine. It then examined what would happen if the level of coverage of all quintiles could be raised to that of the richest quintile.

“What’s the health cost of these disparities?” he asked.

The results varied considerably, as countries had different levels of disparity in terms of both mortality and coverage.

Some countries, such as Bangladesh, had very high levels of coverage across all of the wealth quintiles. Therefore, it would not make a huge difference if all quintiles had the same protection as the richest. However, in countries such as India, equal coverage would increase benefits among the poor by 80 percent, and by 35 percent overall.

The study found that while rotavirus vaccination is cost-effective at a national level, there is great variability within countries.

“What’s the health cost of these disparities?” he asked.

However, current vaccine delivery systems disproportionately benefit wealthier children, who are at lower risk in a number of countries, which reduces both the impact and the cost-effectiveness of vaccination.

As an example, Rheingans discussed a study in Nigeria that combined individual child risk factors with published meta-analysis estimates of relative risk in order to estimate each child’s risk. It found a three times higher mortality risk for the poorest quintile compared to the richest. Even within wealth quintiles there was large disparity.

In conclusion, Rheingans said, “All this points out the importance of redoubling efforts to invest in getting vaccines to those who are most vulnerable. Doing so is both impactful and is likely to be very cost-effective, at least as cost-effective as vaccination itself.”

Among the strategies that could be deployed: geographically targeting areas with high impact and low coverage; socioeconomic targeting, targeting poor children through strategies like conditional cash transfers, which have been effective in places like India; and potentially vulnerability targeting, targeting individuals or areas with high level of vulnerability, for instance those who are already involved in feeding programs.
Age Restrictions Reconsidered

In 2006, as it prepared for the licensing of two new commercial vaccines for rotavirus, the World Health Organization (WHO) recommended that the first dose of vaccine be given within the first 12 weeks of life. In 2009, with more clinical data available, the recommendation was revised to a first dose by 15 weeks. And, in 2012, the WHO recommended removing the age restriction entirely, to improve access to rotavirus vaccination.

Dr. Manish Patel, with the US CDC, explained the thinking behind these changes. The initial 12-week recommendation represented a “conservative approach” to dealing with the issue of intussusception, raised by the experience with RotaShield in 1999. The risk of intussusception with RotaShield was about one in 10,000, but in a child of three months or older the risk was higher. Health authorities recorded a sharp increase in intussusception rates in the first three-to-six months of life.

The recommendation limiting the first dose to children 12 weeks of age and under was intended to reduce any increased risk of increase in intussusception rates from vaccination.

However, by 2009, initial safety data was available from the US and Latin America, and clinical trial data was available from Africa and Asia. A re-evaluation of the age guidelines led to the recommendation of expanding the first dose to children 15 weeks of age, in order to improve coverage, Patel said.

Since then, substantially more safety data has come available on vaccine use in Latin America, the US, Europe and Australia. It indicates the risk of intussusception is about 1-2 cases per 100,000 vaccinated children—a rate 5 to 10 times lower than the risk with Rotashield.

Therefore, WHO conducted a benefit/risk analysis to quantify what would happen if the age restriction were lifted and children older than 15 weeks of life could get the vaccine. It asked how many more cases of intussusception could possibly occur.

“Now there are tradeoffs for that,” Manish said. “If you were to lift the restriction, obviously you would see more intussusception cases. But you would also reach more children and you would improve coverage. You already have a vaccine that’s moderately efficacious in poor settings. And if you have an age restriction, you’ve limited the delivery of vaccine to those particularly in need with the highest risk of dying.”

The model took vaccine coverage data from UNICEF’s Demographic Health Surveys from 45 countries and extrapolated it to all of the WHO regions. WHO divides the regions based on levels of child mortality into A (very low), B and C (low), D Americas (high), D Asia (high), and D & E Africa (high).

It found that with an age restriction of 15 weeks in B and C countries, approximately 63 percent of children are reached. If there is no age restriction, and all children may receive their vaccine when they come in for their routine DPT1 vaccine, then 91 percent of children are reached by the end of their first year of life.

“If there is no age restriction, in Africa and Asia, you improve the coverage from 63 and 64 percent to 88 and 86 percent. It’s a very simple concept,” Patel said.

The global picture is just as dramatic. The model found that lifting the age restriction would lead to an absolute increase in vaccine coverage of about 24 percent.

“With the lifting of the age restrictions, you would have averted approximately 47,000 additional rotavirus deaths while causing an additional 300 or so intussusception deaths,” Patel said. “This comes to 154 lives saved for every death caused.”
In its April 2012 recommendation, WHO also noted that removal of the age restriction might be especially important in countries where mortality is high and delay in vaccination is common.

"If there is no age restriction, in Africa and Asia, you improve the coverage from 63 and 64 percent to 88 and 86 percent. It’s a very simple concept."

Manish Patel, Centers for Disease Control and Prevention, United States

Third dose for Africa and Asia?

“The experience we have with multiple oral vaccines for enteric infections are beset by problems when given to children in developing countries,” said Dr. Duncan Steele, with the Bill & Melinda Gates Foundation. The problems appear to be related to number of issues: host-related issues such as nutrition and maternal antibody, and vaccine characteristics such as the antigen used and the number and frequency of doses.

Steele presented the results of several clinical studies that shed light on whether or not a third vaccine dose could significantly improve vaccine effectiveness for children in developing countries.

The first was an immunogenicity study in South African infants designed to examine the interaction of the Oral Polio Vaccine (OPV) and the live human monovalent rotavirus vaccine. By chance, it evolved into a study that also looked at two age regimens for giving the vaccine (two doses delivered at 6 and 10 weeks of age, versus two doses delivered at 10 and 14 weeks of age).

The results showed that only 13 percent of children seroconverted when receiving the first dose at six weeks of age, while 43 percent showed a similar immune response when given the first dose at ten weeks. Maternal antibody titres are likely to play a role in this difference by age, and, in addition, OPV seemed to interfere with the rotavirus immune response after the first dose in both regimens.

The second study, also WHO mandated, looked at the immunogenicity of a more concentrated version of the GSK vaccine, delivered either in two doses (at 10 and 14 weeks) versus three doses (at 6, 10 and 14 weeks) in healthy infants. The vaccine was given concomitantly with OPV.

The results showed that the concentration of the vaccine had little impact on seroconversion at six weeks of age, and that the older the children were when they got the rotavirus vaccine, the better the immune response. Seroconversion two months after the last dose was similar in the 2- and 3-dose arms, and infants getting the first dose at a later age (10 weeks) had three-fold higher vaccine shedding in their stools, then infants receiving the vaccine at a younger age.

“And, obviously that’s an indication of the replication in those infants,” Steele said.

A study conducted in Malawi and South Africa compared the immunogenicity and efficacy of the vaccine when administered in a three-dose schedule that received Rotarix at 6, 10 and 14 weeks of age or a two-dose schedule at 10 and 14 weeks of age, both given with OPV. In both studies, with varying efficacy, the 3-dose arm showed higher levels of immune responses. Three-doses also showed improved efficacy in South Africa by about 10 percent, but seemed to have little impact in Malawi.

More recent results from the study assessing second-year efficacy of the vaccine trial has demonstrated a dramatic difference in the protective efficacy in the second year of life in the three-dose versus the two-dose arm, Steele reported.
Protecting against rotavirus disease from birth
Dr. Julie Bines, from the University of Melbourne, addressed two questions: How to improve vaccine efficacy and protection for small babies, and whether a human neonatal rotavirus vaccine could protect infants from rotavirus disease from birth.

The questions are important to developing countries, Bines said, given the significant burden of disease, lower vaccine efficacy, and heightened challenges to vaccine delivery.

Bines focused on birth as the best immunization opportunity, when mothers and babies are more likely to be in contact with health care workers. “It’s an established EPI time point for many developing countries for OPV and BCG administration. And it is also a time when intussusception is extremely rare,” Bines said.

“We’re not going to affect the environment in the immediate short-term that these children are living in,” Steele said. “It’s really important that we do understand and try and manipulate the things we can change. And we can change today the number of doses. There’s a lot of promise with that.”

Duncan Steele, Bill & Melinda Gates Foundation, United States
She noted that a birth vaccine would also avoid possible interference with maternal IgA antibodies transferred across the placenta and maternal antibodies in breast milk.

In addition, neonatal rotavirus strains could offer intrinsic advantages for newborn vaccination. Neonatal rotavirus strains are adapted to and replicate well in the neonatal gut, are often asymptomatic, and natural infection has been associated with protection against rotavirus disease in later infancy.

The Rotavirus Group at Murdoch Children’s Research Institute, Australia has worked with a single human neonatal rotavirus strain, G3P6, to develop the RV3-BB vaccine. This unique strain was isolated from healthy newborns in Melbourne in 1975. Naturally occurring G3P6 appears to be 100 percent protective against severe rotavirus, and is asymptomatic. Natural infection also appears to offer protection against a range of rotavirus strains, including G1, G3 and G4.

She reported that Phase I/II trials of a low-titer RV3 vaccine found no associated adverse events. A higher titer vaccine has now been developed at Murdoch Children’s Research Institute and Phase I studies showed it was well tolerated with a vaccine take in 89 percent of infants after a single dose.

Phase II trials are currently underway in New Zealand (in collaboration with the University of Otago) and Indonesia (in collaboration with Gadjah Mada University and BioFarma, Indonesia). The Indonesia trial is assessing the efficacy of three doses of the RV3 vaccine against rotavirus gastroenteritis. The RV3-BB vaccine is now under development at BioFarma, Indonesia.

“Our aim is to develop an affordable human neonatal rotavirus vaccine to provide protection from rotavirus disease from birth, and we feel we have an ideal strain to do that.”

Julie Bines, University of Melbourne, Australia

Rationale for a Birth Dose Strategy for a Rotavirus Vaccine

- **First** rotavirus infection
  - most severe
  - produces a strong immune response that limits disease on re-infection
- **Younger** age at first infection in developing countries
  - Is a first dose at 6-8 weeks with completion of course (max protection) at 5-6 month of age too late to protect some infants?
  - Gap in the first 6-8 weeks — no protection
- **Birth is “best” immunization opportunity**
  - Established EPI time-point in many developing countries (OPV, BCG)
- **Intussusception is extremely rare**
  - improved safety profile
All-Cause Diarrheal Mortality Reduced in Mexico

The rotavirus vaccine program represents Mexico’s most recent effort to reduce deaths due to acute diarrhea. Dr. Edgar Sanchez-Uribe, with Mexico’s National Center for Child and Adolescent Health, reported that four continuous years of rotavirus vaccination has significantly lowered deaths due to all causes of diarrheal mortality, as well as the number of the hospitalizations and medical visits due to acute diarrhea.

“Even though acute diarrhea still occupies one of the top places in the list of the leading causes of mortality in children under five, there have been important improvements in preventing mortality due to this cause,” Sanchez-Uribe said. In the 1980s, acute diarrheal disease was the leading cause of under-five mortality in Mexico; by 2010 it was the sixth leading cause.

“Nowadays, it has been surpassed by prenatal diseases, congenital malformation, pneumonias, and accidents,” Sanchez-Uribe said.

Rotavirus vaccine was introduced in Mexico in February 2006 in poor, high-risk municipalities, and introduced nationally in 2007. Monovalent vaccine was used initially, with a switch to the pentavalent vaccine in 2011.

To evaluate the impact of the rotavirus vaccination program, researchers calculated the frequencies of death, hospitalizations and first medical encounters due to acute diarrhea. They obtained mortality data from all Mexican states through the death certificate registry. Hospitalization data was obtained from 346 Ministry of Health hospitals where diarrhea was regularly reported. Data on new cases of rotavirus were taken from approximately 1,770 health units, generating the cumulative incidences during the rotavirus season. Then they compared the pre- and post-vaccination period.

“While the initial analysis demonstrated a greater impact among infants, today this effect has also been documented in all the children under five,” Sanchez-Uribe said. Furthermore, “The reduction of under-five mortality due to diarrhea is sustained for four continuous years,” Sanchez-Uribe reported.

Study results included:

- 46 percent fewer deaths from acute diarrheal disease in children under five;
- Approximately 1,000 childhood deaths averted every year;
- About 17,800 diarrhea-related hospitalizations averted in rotavirus season since 2008;
- Within primary care settings a 39.5 percent reduction of acute diarrheal cases in children under one year of age—the age at which disease is concentrated;
- 675,515 averted medical visits in the rotavirus season.

“While the initial analysis demonstrated a greater impact among infants, today this effect has also been documented in all the children under five. The reduction of under-five mortality due to diarrhea is sustained for four continuous years.”

Dr. Edgar Sanchez-Uribe,
Ministry of Health, Mexico
A view across Latin America and the Caribbean

Before the introduction of the vaccine in Latin America and the Caribbean, there were an estimated 15,000 deaths due to rotavirus, 75,000 hospitalizations, two million clinical visits, and ten million cases of rotavirus diarrhea a year.

Rotavirus vaccination programs have begun to change those numbers, said Ms. Lúcia Helena de Oliveira, with the Pan American Health Organization (PAHO). She reported on the rotavirus surveillance network, policy development, and lessons learned through rotavirus vaccine introductions in the region.

“The Latin American countries were the first countries in the world to introduce the rotavirus vaccine into the public health section,” beginning with Panama in March 2006, de Oliveira said. Currently 17 countries across the region have introduced rotavirus vaccine.

PAHO’s directing council paved the way for this rapid introduction during its annual meeting in 2006, when the Ministers of Health passed a resolution to mobilize funding for new vaccines like rotavirus, pneumococcus, and human papillomavirus.

Across the region, national governments finance 93 percent of the cost of the program’s vaccines, de Oliveira reported. Of the region’s 35 countries, 33 purchase vaccines through PAHO’s Revolving Fund. Although the fund lowers vaccine price, the new vaccines are still more expensive than earlier vaccines. This makes it crucial that vaccine introductions are grounded in evidence.

PAHO works with countries to gather that evidence using a tool called ProVac. It employs a uniform surveillance guideline and a system of sentinel hospital surveillance that spans 95 sites in 16 countries.

In the early years of rotavirus vaccine introduction, there was a huge gap in coverage between the basic childhood pentavalent vaccine and rotavirus vaccine. Rotavirus lagged far behind. But that coverage has evened out, and rotavirus vaccines are now helping to boost the coverage of the other vaccines.
De Oliveira shared data on vaccine effectiveness across a number of countries in the region. Among the findings:

- **Brazil**: 1,500 fewer deaths and 130,000 fewer hospital admissions for diarrhea in children under five after the introduction of the rotavirus vaccine (2007-2009);
- **El Salvador**: diarrhea decreased 48 percent during the rotavirus season period in 2008, and 35 percent in 2009 compared to the pre-vaccination period;
- **Nicaragua**: In 2007, the number of gastroenteritis decreased 23 percent during the rotavirus season in children no more than 11 months old;
- **Panama**: Diarrhea-caused hospitalizations decreased 22 percent in 2007 and 37 percent in 2008.

De Oliveira highlighted a number of lessons learned during the long period of rotavirus vaccine introduction. She noted that a major challenge has been limited cold-chain storage capacity, as rotavirus vaccine takes up a much greater volume than most other vaccines. De Oliveira urged countries to plan ahead to ensure adequate cold chain capacity before vaccine introduction.

Other lessons included the importance of strengthening the integration between epidemiological surveillance and laboratory surveillance; assuring quality and affordable prices for all countries; and introducing new vaccines at a universal level across a country, allowing for better impact evaluation, reliable vaccination coverage and equity with regards to vaccination access.

“The lessons learned support PAHO’s strategic vision for the new vaccine introduction, which is grounded in the sustainability of political, technical, operational, and financial support.”

Lúcia Helena de Oliveira, PAHO
Rotavirus Vaccines in the USA

Umesh Parashar, with the US CDC, reported on the impacts of rotavirus vaccines over the six years since they were introduced. The pentavalent vaccine RotaTeq was introduced in 2006, and the monovalent vaccine Rotarix was introduced in 2008. Both remain available through the national vaccination program.

A nationwide system of laboratory surveillance that includes 67 laboratories scattered across the country provide weekly data on the number of rotavirus tests conducted and the number of positive results.

“After vaccine introduction there was a 60 to 80 percent reduction in rotavirus positive detections—a remarkable and striking impact on disease reduction,” Parashar said.

Vaccination also has a major impact on the seasonality of rotavirus. Previously, there was a clear winter seasonal pattern, with increased rotavirus activity beginning in the West in November and December, and then migrating over time to the East Coast. After vaccine introduction, that pattern disappeared, replaced with sporadic dispersed disease activity.
In addition to its passive surveillance system, the CDC has used an active surveillance system in three counties to track vaccine impact. Not only did it find a great reduction in rotavirus cases among vaccinated children, but also a decline in disease in unvaccinated older children and adults—a result of herd immunity.

Surveillance and strain monitoring have revealed strain changes, and increase in G3 in particular. “But we’ve seen these strain changes happen without vaccine too, and the data that we have doesn’t support a role for vaccine in producing these changes,” Parashar said.

Strain monitoring has revealed that a small number of infections in children were caused by a new rotavirus strain that is a reassortant made with strains included in the RotaTeq pentavalent vaccine. “We have had few of these cases so it’s clearly something to continue to look at,” Parashar said.

Two surveillance systems have been tracking intussusception in the United States: an active surveillance platform called the Vaccine Safety Data Link (VSD), and VAERS, a passive surveillance system. Focusing on the first dose of vaccine, VSD data detected only one case of intussusception in the first week after the delivery of 310,000 vaccines—ten times the number of children who were given the vaccine in the Phase III clinical trial. “So there is no evidence of increased risk, with a good number of doses given,” Parashar said.

However, Parashar also noted a recent study based on the passive reporting system that detected peaks in increase in intussusception rates in the three- to five-day period after vaccination. “Is it some kind of a real risk that we have not yet picked up in active surveillance or something related to reporting?” Parashar questioned.

“We still cannot exclude a very low risk. But for all outcomes—from deaths to hospitalizations, emergency visits, and outpatient visits, the benefits of the vaccine are clearly far greater than the small risk of intussusception,” Parashar said.

“After vaccine introduction there was a 60 to 80 percent reduction in rotavirus positive detections—a remarkable and striking impact on disease reduction.”

Umesh Parashar, Centers for Disease Control, United States

Impact in South Africa
Dr. Nicola Page, with South Africa’s National Institute for Communicable Diseases (NICD), recounted how rotavirus was first detected in South Africa in cultured monkey kidney cells in 1963; the first reported cases in human infants came in 1976. Duncan Steele and other researchers studied the epidemiology of rotavirus disease throughout the 1980s and 90s, and analyzed the burden of disease in the early 2000s. They found that rotavirus was responsible for between 17,600 and 25,600 rotavirus cases every year in children under two.

Clinical trials later established the safety and efficacy of Rotarix vaccine in South Africa, and it was introduced into the South African Expanded Program on Immunization (EPI) in August 2009. Currently, the vaccine is given at six and 14 weeks as a two-dose schedule.

Rotavirus surveillance was initiated in April 2009 to monitor trends in the number of diarrhea and rotavirus hospitalizations, and in the serotype distribution.
The country’s sentinel surveillance system is composed of four sites, covering areas that are urban and rural, temperate and sub-tropical. “Any children who presents to those sites for the treatment of diarrhea and are admitted for treatment, are invited to enroll in the study,” Page said.

April 2010 data shows coverage of 50 percent and 60 percent for the first dose, and between 40 percent and 45 percent for the second. The figures for April 2011 are slightly better, with vaccine coverage for one dose ranging from 66 percent and 84 percent at the four sites, and between 56 percent and 88 for two doses. Low coverage at one site was due to vaccine stock-outs during part of the year.

Over several years, from 2009 through 2011, the surveillance found significant reductions in rotavirus disease.

“In the under-one age group, we saw between 60 percent and 64 percent reduction in rotavirus cases,” Page reported. In addition, there was a 31 percent to 34 percent reduction in overall diarrhea admissions over two years.

However, when looking at the proportion of children who tested positive for rotavirus over time, there was a slight increase in the number of rotavirus cases among the 12 to 23 month old group and the 24 to 35 months age group, possibly due to waning immunity, according to Page.

![Graph](image-url)
“Despite our moderate vaccine coverage, we’ve seen consistently fewer numbers of rotaviruses year on year, and we’ve seen a decrease in all cause diarrhea. We’ve seen a roughly 50 percent decline in rotavirus disease in children under five, with the greatest reduction in kids under one.”
Nicole Page, National Institute of Communicable Diseases, South Africa

A Tale of Two Israels
Dr. Ron Dagan, with Israel’s Ben-Gurion University reported on a study in Southern Israel that is home to ten percent of the country’s population. One hospital with one emergency room serves the entire region, and the 15,000 women who give birth every year. About half the births are of Jewish children, who track socio-economically with more high-income countries, and half are Bedouin children who more closely resemble a developing country population. The Bedouins live in more crowded conditions, have a higher birth rate, and experience greater rates of respiratory and gastrointestinal disease.

More than 95 percent of the children who are born in the region are treated in the same hospital, which has enabled calculation of disease incidence.

Dagan reported on a prospective sentinel study on the impact of rotavirus vaccine implementation in the National Immunization Program (NIP). The study began in April 2006 and is ongoing. Health workers record all pediatric emergency room visits and hospitalizations of children under five years caused by respiratory infections and gastroenteritis. All children under five years of age, presenting with vomiting or diarrhea, are offered participation in the study. ELISA tests are used to determine infection with rotavirus and PCR was used for serotyping.

Dagan reported that, prior to vaccine introduction, rotavirus gastroenteritis was common in both Jewish and Bedouin populations in Southern Israel, and was responsible for a high rate of emergency room visits and hospitalization in children under two years.

However, research revealed that incidence varied between the two groups. In the first year of life, about 1.5 percent of Jewish children in the region presented with rotavirus gastroenteritis, and about 2.5 percent of the Bedouin population. The Bedouin population also had much higher rates of hospitalization, whereas the Jewish population had higher rates of outpatient treatment. One of 78 Jewish children and one of 43 Bedouin children were hospitalized for RVGE.

In 2008 both Rotarix and RotaTeq became available in Israel and were reimbursed ~50 percent for complimentary health insurance. However, the vaccine was used by ~25 percent of the Jewish children but none of the Bedouin children. This resulted in 37 percent reduction in RVGE in the Jewish population in first year of life, in the presence of no reduction among the respective Bedouin population.

In January 2011, the pentavalent rotavirus vaccine became available through the National Immunization Program (NIP). Within one year, there was an 81 percent reduction of hospital use due to rotavirus during first year of life among the Jewish population (compared to the pre-rotavirus period), and a 70 percent reduction among the Bedouin population. During the second year of life, this disparity widened, with a 70 percent reduction in hospital use for rotavirus among Jewish children, and a 27 percent reduction among Bedouin children.
The effectiveness after two doses or more of rotavirus vaccine was 79 percent for Jewish children and 57 percent for Bedouin children, which came to 60 percent overall. The impact of three doses is still being evaluated.

Late Breaker: Vaccine Impact in Bangladesh

“It has been estimated that in Bangladesh there are about 2.4 million cases of rotavirus diarrhea in a year in children under five, resulting in about 15,000 deaths in a year,” reported Dr. Khalequz Zaman, with the International Centre for Diarrhoeal Disease Research (ICDDR,B).

He summarized the first results from a Rotarix clinical trial in a GAVI-eligible country. The study was the result of collaboration between the ICDDR, B and the global nonprofit PATH, the result of a call by the WHO for efficacy data in Africa and Asia.

The study was conducted in Matlab, where the ICDDR, B has conducted health research and provided health services since 1966, working in 67 of the area’s 142 villages. The other 75 villages are the government comparison area, in which normal government health services are available. Matlab has a central hospital and satellite clinics that treat about 12,000 to 15,000 diarrhea patients in a year.

The study used a cluster randomized trial design that saw Rotarix introduced into half of Matlab

“Before vaccination, 2.7 percent of all outpatient visits during the entire year were children with rotavirus gastroenteritis. It went down to 1.5, and then went to 0.5 percent. Altogether we had an 81 percent reduction in the relative importance of RVGE compared to other causes. And for the Bedouin population it was 54 percent.”

Ron Dagan, Ben-Gurion University, Israel
villages, administered along with other EPI vaccines, at 6 and 10 weeks of age. Introduction was initiated in November 2008 in half of all government villages, and in April 2009 in half of ICDDR, B service area villages. Vaccination and monitoring continued until March 31, 2011, after which Rotarix was introduced into all remaining Matlab villages through a donation from GSK.

Through the course of the trial, there were 7,112 children in the Rotarix villages, and 6361 children in non-Rotarix villages. Zaman reported that about 68 percent of children in the Rotarix villages received dose one at a mean age of 8.4 weeks. About 65 percent of children received dose two, at a mean age of 13 weeks.

The results showed an incidence rate of 6.8 diarrhea episodes per 100 person years in the Rotarix villages, compared to 7.5 episodes per 100 person years in the non-Rotarix villages. In Rotarix villages about 15 percent of cases were very severe, compared to about 17 percent of cases in non-Rotarix villages. Mortality was low everywhere, due to high use of Oral Rehydration Solution both at home and in the clinic.

Overall, vaccine effectiveness was a significant 28.4 percent, Zaman reported. When stratified according to age, a somewhat different picture emerged. In children less than 12 months of age, the adjusted vaccine efficacy of 42.3 percent was significant. In children from 12 to 24 months, vaccine efficacy was 15.3 percent, which was not significant.

ORS Use in Trial

ORS use in this population is very high, both at home and in the clinic, contributing to low mortality from diarrhea

<table>
<thead>
<tr>
<th>ORS use prior to clinic attendance (%)</th>
<th>Rotarix Villages</th>
<th>Non-Rotarix Villages</th>
</tr>
</thead>
<tbody>
<tr>
<td>All episodes</td>
<td>564 (71%)</td>
<td>572 (74%)</td>
</tr>
<tr>
<td>ARD episodes</td>
<td>276 (83%)</td>
<td>311 (82%)</td>
</tr>
<tr>
<td>ORS use at treatment facility (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All episodes</td>
<td>694 (88%)</td>
<td>676 (87%)</td>
</tr>
<tr>
<td>ARD episodes</td>
<td>303 (91%)</td>
<td>346 (91%)</td>
</tr>
<tr>
<td>IV use at treatment facility (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All episodes</td>
<td>31 (4%)</td>
<td>43 (6%)</td>
</tr>
<tr>
<td>ARD episodes</td>
<td>12 (4%)</td>
<td>21 (6%)</td>
</tr>
</tbody>
</table>

ORS—Oral Rehydration Solution
ARD—Acute rotavirus diarrhea
IV—Intravenous

“"This is the first study to assess the effectiveness of human rotavirus vaccine in a GAVI-eligible country in Asia. It significantly reduced severe rotavirus diarrhea. We found moderate vaccine effectiveness, similar to other high-rotavirus burden areas. These data support WHO’s recommendations for use of rotavirus vaccines in Asia.”

Khalequz Zaman, ICDDR,B, Bangladesh
SESSION V: CURRENT AND FUTURE ROTAVIRUS VACCINES

Rotavirus Vaccines – Pipeline 2012

Dr. Georges Thiry, Director of the Advance Rotavirus Vaccine Program (ARVAC) at PATH, reviewed the rotavirus vaccine pipeline from the three vaccines now on the market to those into clinical trials, and in pre-clinic. The vaccine pipeline includes a range of approaches: live oral vaccines either as human strains or reassortants (bovine-human, Rhesus-human and ovine-human reassortants), and non-replicating vaccine candidates in pre-clinical as inactivated or sub-units.

Update by the Current Rotavirus Vaccine Manufacturers

Merck
Dr. Michelle Goveia with Merck presented an overview of the history of RotaTeq, from its licensure in the United States in 2006, to today, when it is licensed in more than 105 countries. As of June 2012, more than 77 million doses had been distributed worldwide, with about 49 million of those in the US.

In addition, “We've had two very exciting events recently,” Goveia said. “In May of this year, Rwanda introduced RotaTeq into their national schedule. And in July of this year, RotaTeq became available in Japan.”
Three Phase III pre-licensure studies that evaluated 71,725 subjects had paved the road for RotaTeq, establishing the safety and efficacy of the vaccine. In high-income settings, the vaccine showed 98 percent efficacy against severe rotavirus, and 74 percent efficacy against any severity of rotavirus. In low-income settings in Ghana, Kenya and Mali it had 64 percent efficacy against severe rotavirus in the first year of life; in Bangladesh and Vietnam it had 51 percent efficacy.

Vaccine Effectiveness of 3-Dose Regimen (2,4,6 Months) Against Severe Rotavirus in Nicaragua: 2 Years of Follow Up

- Matched case-control study
  - Hospital-based prospective surveillance at 6 hospitals from February 2007 to October 2009
  - Cases: 300 children with severe RGE resulting in hospitalizations or ED visits
  - 2 age-matched control groups: community controls, hospital controls

<table>
<thead>
<tr>
<th>Age</th>
<th>Community Controls (N=851&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Hospital Controls (N=792&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>Combined (N=1643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months&lt;sup&gt;d&lt;/sup&gt;</td>
<td>93% (62, 99)</td>
<td>78% (49, 91)</td>
<td>85% (66, 93)</td>
</tr>
<tr>
<td>≥12 months&lt;sup&gt;d&lt;/sup&gt;</td>
<td>85% (69, 93)</td>
<td>55% (22, 74)</td>
<td>71% (51, 82)</td>
</tr>
<tr>
<td>All ages</td>
<td>87% (74, 93)</td>
<td>64% (44, 78)</td>
<td>76% (63, 84)</td>
</tr>
</tbody>
</table>

<sup>a</sup>n=225 <12 months; n=626 ≥12 months.
<sup>b</sup>n=233 <12 months; n=559 ≥12 months.
<sup>d</sup>Age at time of disease on set, defined as the age between the birthdate of the case until the symptom on set date of the case. Median age was 14 months.


Since the introduction of rotavirus, more recent studies have documented vaccine impact in a number of countries. Findings include:

- Nicaragua: vaccine efficacy of a 3-dose regimen against severe rotavirus of 85 percent for children under one, based on two years of hospital surveillance;
- Southern Australia: an 83 percent reduction in rotavirus hospital admissions in the three years following vaccine introduction in 2007;
- Finland: adjusted vaccine effectiveness of 98 percent in children over six months of age and fully vaccinated;
- United States: A 74 percent decrease in overall seasonal average peak rotavirus incidence since 2006.

“With two years of follow-up in Nicaragua, we see a combined vaccine effectiveness of 85 percent in the children who are less than 12 months; and for those who are older than 12 months of age, the combined effectiveness was 71 percent. Across all ages, across this study, there was 76 percent effectiveness.”

Michelle Goveia, Merck, United States
GlaxoSmithKline

Dr. Bernd Benninghoff of GSK Vaccines reported on the experience with Rotarix. He described its short, two-dose schedule, which allows “completing the course at the earliest possible age, preventing morbidity and mortality from rotavirus gastroenteritis regardless of the circulating strains.”

Benninghoff reported that Rotarix, a live attenuated human virus based on the G1P8 strain, is now in more than 130 countries worldwide, and more than 130 million doses have been administered. The first dose can be delivered as early as six weeks. Summarizing some of the vaccine’s key clinical features, Benninghoff noted that it has demonstrated efficacy against several heterotypic strains, and shown sustained high efficacy protection over three years with minimal waning of immunity.

Post-licensure vaccine effectiveness and observational studies have found:

- Significant protection against rotavirus-associated hospitalization in four of six studies, ranging from 76 to 85 percent;
- In Belgium, two doses of Rotarix offer an overall vaccine effectiveness of 91 percent (ranging from 75 to 97 percent);
- Reductions rotavirus-associated hospitalizations ranging from 35 percent to 93 percent in a 4-country study (Belgium, Australia, Brazil, South Africa);
- In South Africa, a 67 percent decline in rotavirus gastroenteritis in children aged five years.

Most notably, Rotarix has been associated with a 22 to 33 percent reduction in diarrhea-related deaths.

“It is fantastic to see the reduction in gastroenteritis-associated death,” Benninghoff said. “It is a great achievement that the vaccine can show this kind of thing.”

Additional findings on Rotarix from numerous studies include decreased rates of hospital-acquired rotavirus infection: 67 percent reduction in Austria, and an 87 percent reduction in urban Australia after mass vaccination. Furthermore, there is increasing evidence that widespread vaccination can result in herd protection, Benninghoff said.

Summarizing the value of Rotarix, Benninghoff stressed the importance of being able to complete the full course of the vaccine by ten weeks of age. This is particularly important in regions of the world where infants are exposed to rotavirus very early in life. A global seropositivity study shows that whereas there is 0 percent seropositivity prior to first vaccination in the United States and Finland, there is 25 percent seropositivity in India, and 12 percent in Africa.

“Post-licensure vaccine effectiveness and observational studies have found:

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Bernd Benninghoff,
GlaxoSmithKline, Belgium
Update by the New and Future Rotavirus Vaccine Manufacturers

An Oral Live Rotavirus Vaccine in India

Dr. Sai Prasad with Bharat Biotech, described development of the ORV116E rotavirus vaccine. Pointing out that rotavirus vaccine could save 100,000 infant lives a year in India alone, Prasad noted his company’s focus on “the number of lives that we could potentially save, irrespective of how efficacious this vaccine is.” Nonetheless, their goal is to develop a safe and highly efficacious vaccine.

The 116E strain was originally isolated from an infant with asymptomatic mild diarrhea in India in the All India Institute of Medical Sciences in 1988. Follow-up with the infants showed that the strain conferred protection for up to two years.

Further characterization of 116E showed that it was a reassortant with the VP4 gene of bovine origin. The strain was sent to the US National Institutes of Health for production of seed lots, which were later transferred back to Bharat Biotech and used as the vaccine starting material.

ORV116E is a live, naturally attenuated vaccine. A series of clinical trials have been conducted in both the United States and India, and a Phase III clinical trial is currently underway. It involves 6,800 infants in India and uses a three-dose regimen of 116E, given together with other childhood vaccines.

The estimates for Vaccine Efficacy seem to be different in various regions of the world; probably due to the high level exposure early during the first months in developing countries.

Early protection in UMV is important to help reduce the number of infections.

Htay Htay Han, PV Suryakiran, Serge Debrus, Bernd Benninghoff WSPID - November 18-22, 2009, Buenos Aires, Argentina.
Based on prior results, Prasad reported that researchers expect the vaccine to be safe and to offer a protective efficacy of 60 percent or higher. The trial is being conducted at three different sites, where a range of rotavirus strains circulate.

Planned trials include EPI interference studies, and global safety and immunogenicity studies.

In terms of vaccine introduction, “Our Chairman, Dr. Krishna Ella, has made a commitment to supply our rotavirus vaccine at $1/dose to all public sector entities worldwide,” Prasad announced.

The company has established a manufacturing capacity of about 250 million doses, and is targeting the first quarter of 2014 for licensure in India.

“Our Chairman, Dr. Krishna Ella, has made a commitment to supply our rotavirus vaccine at $1/dose to all public sector entities worldwide.”

Sai Prasad, Bharat Biotech, India

Indonesia and Australia partner to create a neonatal vaccine

Dr. Adriansjah from Bio Farma and Dr. Margie Danchin, a pediatrician at the Murdoch Children’s Research Institute, each presented on the neonatal RV3 vaccine.

RV3 is based on the human neonatal rotavirus strain G3P6, which was isolated in the mid-seventies in Melbourne from healthy newborns in obstetric hospitals. It causes a natural asymptomatic infection that offers a high degree of protection against rotavirus over the first three years of life.

“The aim of the RV3 rotavirus vaccine program is to develop a low-cost oral vaccine to protect infants from birth, particularly in developing countries,” Danchin said.

Bio Farma is collaborating with the Murdoch Children’s Research Institute to develop and commercialize the vaccine in Indonesia. Bio Farma is a state-owned enterprise established in 1890, and the only vaccine manufacturer in Indonesia. It currently produces a number of vaccines included in the Expanded Program of Immunization: TT, DT, DTP, DTP-HB, BCG, Td, Polio, Measles, Hepatitis and Seasonal flu vaccine.

“In Indonesia, the rotavirus infection occurs for about 60 percent of hospitalized children with acute gastroenteritis, and is most common in the children between 7-23 (months),” Adriansjah said.

Introduction of a rotavirus vaccine into the national immunization program would require a recommendation from the Indonesian Technical Advisory Group on Immunization, an independent body appointed by the Ministry of Health. To do so, the advisory group would need to take into account a number of factors, including the epidemiological status of rotavirus in Indonesia and an analysis of cost-effectiveness.

Bio Farma would be responsible for the manufacture of the RV3 rotavirus vaccine. Once manufacturing begins, “The initial goal would be for us to fulfill the national capacity in relation to the immunization program of Indonesia,” Adriansjah said.

Currently, Bio Farma is working on the production of experimental lots, coordinating with Indonesia’s regulatory authorities to comply with standards and norms.

“We anticipate some trials in the years 2014 through 2016 where, finally, we have the timeline for commercialization will be somewhere in 2017.”
Meanwhile, a Phase I safety trial for the RV3 vaccine has been successfully conducted in Australia. Dr. Margie Danchin reported on the trial and its results.

The RV3-BB vaccine was prepared in WHO prequalified vero cells under Good Manufacturing Practices at Meridian Life Sciences in Memphis, US. Danchin said that it represents the culmination of almost four decades of research in Australia by the Murdoch Children’s Research Institute.

In Indonesia, the rotavirus infection occurs for about 60 percent of hospitalized children with acute gastroenteritis, and most common in the age of 7-23 months of age,” A. Adriansjah, BioFarma, Indonesia

The Phase I trial, completed in March 2011, assessed the safety, tolerability and immunogenicity of a single oral dose. There were 60 participants: 20 adult men aged 18 to 50 years; 20 children aged 3 to 8 years, and 20 infants, 6 to 8 weeks of age, with 10 vaccine and 10 placebo recipients in each age cohort. The infants were between 10 and 12 weeks when they finished the study. All received a full three-dose schedule of RotaTeq following the study.

It found that a single dose of the vaccine was well tolerated in all age cohorts. There were no adverse events that were considered associated with the vaccine. Vaccine take, which was measured as the combined serologic response and feces replication following a single dose, occurred in eight out of nine infants in the vaccine group or 89 percent, and in two out of ten infants in the placebo group. Those 2 infants both had wild-type rotavirus detected by RT-PCR in their stool.

### Results: Immunogenicity – Infants

<table>
<thead>
<tr>
<th></th>
<th>VACCINE TAKE</th>
<th>SEROLOGICAL RESPONSE</th>
<th>RV3-BB IN STOOL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(combined serological response and faeces replication following a single dose of RV3-BB)</td>
<td>(≥3X increase in serum IgA and/or Neutralising Ab at day 28)</td>
<td>(day 3-6 post vaccination)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>8/9 (89%)</td>
<td>5/9 (56%)</td>
<td>7/9 (78%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2/10 (20%)*</td>
<td>2/8 (25%)</td>
<td>0/10 (0%)</td>
</tr>
</tbody>
</table>

* Wild-type rotavirus detected
Since the successful completion of the Phase I trial, Phase II trials have begun in New Zealand and will soon commence in Indonesia, Danchin reported. The trials will assess the immunogenicity and efficacy of the vaccine with the first of three doses, delivered either at birth or at 6 to 8 weeks of age.

“**In this Phase I study of a neonatal vaccine, the vaccine was well tolerated in all age cohorts. It was immunogenic with a vaccine take identified in 89 percent of infants.**”
Margie Danchin, Murdoch Children’s Research Institute, Australia

**New human-bovine vaccine in India**

Dr. Mandeep Singh Dhingra from Shantha Biotechnics Limited in Hyderabad, India, discussed development of a human-bovine reassortant vaccine based on the UK-Bovine strain.

He reported on a recent burden of disease study in India. The study was based on analysis of more than 2,000 stool samples from hospitalized children less than five years of age with severe diarrhea from 12 sites across India.

“We are seeing around 26.4 percent average rotavirus positive diarrhea with the peak high as 52.5 percent in December and a minimum positivity of around 10.3 percent in May,” Dhingra reported. Positivity rates peak in the 7- to 12-months age group.

Genotype analysis reveals the top three strains are G1, G2, and G9. In addition, G12 is emerging.

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**Burden of Disease Study**

<table>
<thead>
<tr>
<th>% Positive for Rotavirus in Stool</th>
<th>Genotyping of Rotavirus positive stool samples from severe diarrhea cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>Others 16%</td>
</tr>
<tr>
<td>7-12 months</td>
<td>G1 37%</td>
</tr>
<tr>
<td>13-24 months</td>
<td>G2 18%</td>
</tr>
<tr>
<td>25-59 months</td>
<td>G9 19%</td>
</tr>
<tr>
<td></td>
<td>G12 10%</td>
</tr>
</tbody>
</table>

Others 16%
Shantha Biotechnics was the first company to develop and manufacture a recombinant human product in the Indian market. “We’ve been there since 1993, and in 2009, we became a part of Sanofi group,” Dhingra said. Their vaccine portfolio includes hepatitis B, pediatric combination vaccines, and a cost-effective bivalent oral cholera vaccine, which is now being used in Haiti.

The company has been working with the U.K.-bovine rotavirus strain since 2005 to develop a tetravalent vaccine that includes G1, G2, G3, and G4.

“We are developing an oral liquid rota vaccine which basically contains the buffer and the virus in the same formulation,” Dhingra said. “The company has invested in the infrastructure for developing a quality vaccine, the target being WHO prequalification, which is the target for all the vaccines that Shantha develops.”

A Phase I/II study is currently underway in India. It is a randomized controlled safety and immunogenicity study working with one cohort of 20 adults and one cohort of 100 infants, administered in three doses at 6, 10 and 14 weeks of age. The infant study is comparing the effects of three different antigen concentrations, to RotaTeq and a placebo.

Looking to the future, Dhingra says his company has planned Phase III and EPI vaccine interference studies.

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Return of Rotashield in Ghana

Dr. George Armah, with the Noguchi Memorial Institute for Medical Research reported on the first results of a Phase IIb clinical trial of the tetravalent rhesus reassortant rotavirus vaccine, also known as Rotashield. The trial was conducted in rural Northern Ghana.

RotaShield was originally licensed in 1998 in the United States and then voluntarily withdrawn due to a rare association with intussusception, which occurred disproportionately in infants receiving the first dose at more than three months of age.

“We in Ghana and South Africa actually were involved in the immunogenicity studies of this vaccine when we were asked to put it on clinical hold,” Armah recounted. “It’s a shame we couldn’t complete it.”

Rotavirus is common in Ghana. It is reportedly responsible for more than 40 percent of cases of diarrhea in children, and 60 percent of cases among children hospitalized for diarrhea.

The two currently licensed rotavirus vaccines, RotaTeq and Rotarix, are given at a mean age of 68.6 and 57.4 days, respectively, and are not licensed for use in newborns. However, studies in Africa show a high burden of rotavirus disease in the first weeks of life, leading to recognition of the need for a neonatal vaccine. A recent study of burden of disease suggests that within one month of birth, 35 percent of children have already been infected, Armah reported.

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“The company has invested in the infrastructure for developing a quality vaccine, the target being the WHO prequalification.”

Mandeep Singh Dhingra, Shantha, India

“Protection of infants against rotavirus gastroenteritis at an earlier age will help reduce the high burden that we showed in this age. It’s not only in Ghana but it’s all across Africa, I am sure across developing countries.”

George Armah, Noguchi Memorial Institute, Ghana
For the Phase IIb clinical trial of Rotashield, the first dose was administered at an average age of 11 days. The study was designed as a double-blind data, placebo-controlled trial, with two doses of the vaccine given between zero and 28 days, and the second at 30 and 59 days of age. Children are immunized against rotavirus along with the routine EPI vaccines, including oral polio vaccine where possible.

Blood samples were taken immediately before the first dose and 14 days following the second dose. Health care workers followed up with the children, two days and then four days after the first dose, and then weekly until the children received their second dose. After that, children were assessed once a month, until they were 12 months old. The vaccine efficacy analysis encompassed 447 infants. In terms of safety, the vaccine group and the placebo group had very similar reactions following immunization. Looking at the vaccine, “It was safe—there was really no big issue,” Armah said.

The results showed an efficacy against any serotype in severe gastroenteritis of 57.6 percent; efficacy against vaccine serotypes was 60.5 percent.

Armah summarized a number of lessons from the study: “We’ve shown that, yes, it is feasible to have immunization in neonates. We can protect them,” he said. “The vaccine is safe and immunogenic, and significantly reduces rotavirus gastroenteritis in African children through the first year of life with an efficacy comparable to that of vaccines given at older ages.” In addition, the research showed that the use of a vaccine in newborns significantly reduces the risk of rotavirus vaccine-associated intussusception, because it is delivered before the infant reaches a higher-risk period of time.

A Vaccine Made in Vietnam
Dr. Nguyen Trang from the National Institute of Hygiene and Epidemiology, presented the development of the Rotavin-M1, a human monovalent vaccine, developed to serve Vietnam’s national birth cohort of 1.5 million infants.

Started in 1998, surveillance has shown that rotavirus is still the major cause of diarrhea in hospitalized children, with a prevalence of over 50 percent. In a 2006 study, the disease was found to cause 122,000-140,000 hospitalizations and close to 3,000-5,500 deaths a year. More updated numbers find close to 200,000 hospitalizations a year.

The Rotavin-M1 strain was originally from a stool of a child with the acute diarrhea in 2003, and the strain was attenuated through about 40 passages in cell culture. After six years of development, the vaccine went through Phase I, IIa and IIb clinical trials in the country.

“I think the position of the government is to try to encourage the introduction of vaccine, recognizing the disease burden of rotavirus, while, in the meantime, Rotarix and RotaTeq are still too expensive for the people.”
Nguyen Trang, National Institute of Hygiene and Epidemiology, Vietnam

“The then gladly, in April 2012, the vaccine was licensed in Vietnam, and now it’s in distribution,” Trang said.

He described the clinical trials, which were supported by the Ministry of Science and Technology of Vietnam and the US CDC. The Phase IIa trial enrolled 200 infants, divided into five groups to compare different concentrations of antigens and dosing regimens (two or three doses, delivered either one or two months apart). It found that the higher concentration of antigen, delivered through two doses two months apart had the greatest impact on seroconversion, with a rate of 73 percent.

In the Phase IIb trial, 600 infants received the new candidate vaccine and 199 received a placebo.
After one year of follow-up, the trial showed the vaccine to be safe and immunogenic, with a seroconversion rate very similar to that of Rotarix: 81 percent for Rotavin-M1 and 81.5 percent for Rotarix.

There were few adverse events, with no difference between the vaccine and the placebo groups, and no cases of vaccine-associated intussusception.

### Immunogenicity and Efficacy of Rotavirus Vaccines in Vietnam

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Schedule</th>
<th>Seroconversion- Vaccine (95%CI)</th>
<th>Seroconversion- Placebo (95%CI)</th>
<th>RV-IgA GMT- Vaccine</th>
<th>RV-IgA GMT- Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix</td>
<td>2 doses, 1 month apart</td>
<td>63.3 (54.3 - 71.6)</td>
<td>7.8 (2.6 - 17.3)</td>
<td>77 (55, 109)</td>
<td>&lt;20</td>
</tr>
<tr>
<td>N=375</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 doses, 2 months apart</td>
<td>81.5 (73.4 - 88)</td>
<td>15.4 (7.6 - 26.5)</td>
<td>176 (124, 251)</td>
<td></td>
</tr>
<tr>
<td>Rotavin - M1</td>
<td>2 doses, 2 months apart</td>
<td>81 (77 - 84)</td>
<td>14 (9 - 19)</td>
<td>82 (71, 96)</td>
<td>7.6 (6.4, 8.9)</td>
</tr>
<tr>
<td>N=680</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavin - n=80</td>
<td>3 doses, 1 month apart</td>
<td>56 - 63</td>
<td></td>
<td>71 (35, 141)</td>
<td></td>
</tr>
</tbody>
</table>

Analyzing antibody response, the study found that prior exposure to rotavirus infection made a big difference. The seroconversion rate in the children that had not been exposed to rotavirus was 83 percent, compared to 50 percent in children that had been exposed to rotavirus.

Mathematical modeling of the immunogenicity data (IgA and IgG) suggested that maternal antibody directly correlates with seroconversion, while age is a confounding factor. The researchers therefore concluded that the improved immunogenicity found when giving vaccine at a later age might be primarily affected by the waning of the maternal antibodies.

Looking ahead, Trang noted that the vaccine has been licensed for only one year, and renewal will require clinical effectiveness data and post-marketing safety data (including surveillance for intussusception), as well as demonstration of non-interference with Oral Polio Vaccine. Only then will Rotavin be considered for integration into the national immunization schedule.

“This vaccine induced very good immune response in the Vietnamese children using the two doses at two-month intervals. We think that rotavirus M1 is safe to use in our children,” Trang concluded.
Killed vaccine coming to life
Dr. Baoming Jiang from the US CDC summarized work with an Inactivated Rotavirus Vaccine from inception to proof of concept. "We have two wonderful live oral vaccines," he pointed out. "So the question is, why do we need a killed vaccine, an inactivated vaccine?"

The reason, he said, is that the two available vaccines are much less effective in developing countries. Furthermore, the best strategies to improve this efficacy, "will probably take years to sort out," Jiang said.

Therefore, Jiang has been investigating the potential of inactivated rotavirus vaccine (IRV). He enumerated the expected advantages, including improved efficacy and safety, easy combination with other childhood vaccines, ease of delivery, lowering of administration cost and greater vaccine coverage.

Because the vaccine would not be administered through the digestive track, efficacy would not be compromised by other infections in the gut, as may be the case with live oral vaccines that are swallowed. Nor would it likely pose the same risk of intussusception.

However, because it is delivered parenterally, an inactivated vaccine would induce an IgG immune response, rather than an IgA response. This raises the question of whether IgG would be protective. Jiang described primate studies that indicate IgG can mediate mucosal immunity.

“So we believe we have proof of concept for parenteral vaccines,” Jiang said.

Proof of Concept
Serum IgG Can Mediate Mucosal Immunity/Protection

Westerman et al, PNAS 102:7268-7272, 2005
His group has identified a human strain that can be grown to high titer and that is a triple-layered particle—two characteristics important for a killed vaccine. The strain, called CDC-9, is a reassortant of G1P8, and contains a VP3 gene from G2P4. This allows it to cover more than 80 percent of circulating serotypes, Jiang reported.

Preclinical studies in guinea pigs have shown that an inactivated strain can induce broad cross-reacting neutralizing antibodies. A preclinical study in piglets – the first in a large animal model – also induced effective immunity with an inactivated strain.

One challenge with a killed vaccine could be cost. But different strategies could keep cost low, including the use of skin immunization. Jiang discussed a new technology called NanoPass MicronJet, an intradermal microneedle device for skin immunization, approved by US FDA. “There’s no pain, no needle.” It also requires a much smaller dose, making it cheaper. "We plan to use this technology to test our IRV in preclinical, and hopefully, clinical trials as well," he reported.

“We believe we have established technology. We have strains and method. We have proof of concept in clinical studies in animals. Our expectation is greater than 80 percent efficacy for low-income countries.”

Baoming Jiang, Centers for Disease Control & Prevention, United States
New insights into infectivity

Dr. B.V.V. Prasad, with the Baylor College of Medicine described an emerging new paradigm for understanding rotavirus infectivity, host specificity and pathogenesis, based on the interaction between a binding site on the rotavirus particle known as VP8 and host cells.

As background, Prasad reviewed the drivers of rotavirus’s enormous genetic and strain diversity. Point mutations, gene rearrangements and genetic reassortment contribute to expanding diversity. This diversity is classified based on variations in the virus’ VP7 protein, which determines its G serotype, and variation in its VP4 protein, which determines its P serotype. Further classification is based on genetic variability, and variation in VP4 genetic sequences yields more than 35 P genotypes.

Some of this variation determines the precise shape of a particular site on the VP4 protein, known as V8, and it is responsible for binding to host cells. Until now, scientists have believed the V8 site uniquely binds to sialic acids on glycan molecules on or in the host cell. Rotavirus strains have been classified as either sialidase sensitive or insensitive, based on whether the strains bind to terminal sialic acids presented on the host cell surface (sialidase sensitive), or to sialic acids in the interior of the cell (sialidase insensitive).

**VP8* of Sialidase Sensitive and Insensitive Strains**

<table>
<thead>
<tr>
<th>Strain</th>
<th>P Type</th>
<th>Sialidase</th>
<th>Site of Attachment</th>
<th>Width of Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simian RRV</td>
<td>P[3]</td>
<td>Sensitive</td>
<td>Terminal Sia</td>
<td>Narrow</td>
</tr>
<tr>
<td>Dormitzer et al., EMBO J (2002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porcine CRW-8</td>
<td>P[7]</td>
<td>Sensitive</td>
<td>Terminal Sia</td>
<td>Narrow</td>
</tr>
<tr>
<td>Human Wa</td>
<td>P[8]</td>
<td>Insensitive</td>
<td>Internal Sia</td>
<td>Wide</td>
</tr>
</tbody>
</table>

Do all sialidase-insensitive HR genotypes recognize sialoglycans?
However, Prasad has shown that rotavirus has other ways to bind to a cell. Examining the precise structure of the V8* site in several different rotavirus strains, Prasad determined that in some genotypes the V8* site perfectly fits A-type histo blood group antigens (HGBA), which are the genetic determinants of blood type.

“Just two or three amino residues changing – subtle changes within the strain’s structural framework – allows this VP8* to switch from sialic acid binding to histo-blood group antigen binding,” Prasad explained.

Additional research revealed that rotavirus’ 35 P genotypes could be further divided into four distinct groups based on the structure of the VP8* site. Further experiments demonstrated that these structural differences could impact infectivity in certain circumstances.

Examination of the P[11] strain, which is specific to newborns, revealed that its VP8* site differs substantially from that of other strains, and that P[11] binds glycans containing HBGA H type II precursor.

In conclusion, Prasad noted, “Interactions with sialoglycans for initial attachment is not an obligatory requirement, as previously thought. Rotaviruses exhibit significant genotype-dependent variations and glycan specificity, which may have implications for host specificity, tissue tropism, susceptibility, pathogenesis, and interspecies transmission.”

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**Correlates of Protection**

Three presenters discussed new analysis and data regarding correlates of protection against rotavirus. All noted that although the rotavirus burden is well known, immunity to the virus is not well understood. While many studies have been performed on the role of various antibodies in protecting against rotavirus infection and disease, a correlate of protection (COP) has yet to be identified.

Dr. Manish Patel explained correlates of protection using a definition from Dr. Stanley Plotkin: a COP is a statistical relation between an immune marker and protection.

An “absolute correlate of protection” means there is a cutoff above which every single person is protected, below which everyone is susceptible. However, most correlates of protection are relative, demonstrating more of a continuum of protection, Patel said. A COP can be either mechanistic or non-mechanistic. And while ideally the mechanism of protection would be known, Patel noted that for many vaccines the correlates of protection are not fully understood. “So I don’t think rotavirus is too unusual in that regard, and that, I think, was somewhat refreshing,” Patel said.
Nonetheless, the search is on for an accurate COP. “For 30 years people have looked for correlates of protection, so some of this may be similarly comical to Monty Python’s search for King Arthur’s search for the Holy Grail,” Patel said. Yet, progress is being made.

To set the context for understanding this progress, several speakers reviewed the basic biology of adaptive immunity to rotavirus, which includes mucosal immunity and systemic immune response. In the mucosal system, rotavirus that enters the gut epithelium goes into gut lymphatic tissue where it stimulates B cells, which leads to the release of IgAs (antibodies) that are secreted into the gut as secretory IgA. This secretory IgA is responsible for intracellular neutralization of rotavirus.

Systemic immunity may be mounted when rotavirus enters the bloodstream, stimulating B cells in the bone marrow and spleen, and leading to the release of monomeric IgA, IgG, and neutralizing antibodies in the blood.

While serum IgA is completely different from secretory IgA, there is some crossover of the secretory IgA in to the blood. This is the “total IgA” measured in serum, which has been used in rotavirus vaccine trials as a COP.

Is IgA a good COP?
Both Patel and Dr. Htay Htay Han from GSK presented data analyzing the usefulness of IgA as a COP.

“Direct demonstration of the vaccine efficacy required a lot of expensive clinical trials with an extended follow-up period in order to provide the sufficient power to meet the pre-defined endpoints,” Han said, noting that evidence of IgA as a correlate of vaccine efficacy would be a valuable tool.

Han’s two-pronged analysis was performed by the in-house statistical team at GSK looking at correlates of protection. One study applied regression analysis to individual level clinical trial data of RIX4414 (Rotarix) in South Africa (involving 3,166 infants) and Malawi (involving 1,773 infants).

The analysis of African data correlated IgA titer in vaccinated and unvaccinated infants with the number of subjects who experienced any rotavirus gastroenteritis and severe rotavirus gastroenteritis.

The study found that, “The vaccinated subjects with anti-rotavirus antibody concentration value below 20 U/mL showed some level of protection as compared to the placebo recipient. In the unvaccinated population, a titer above 50 appeared to confer protection similar to the seropositive vaccinated subjects,” Han said.

Overall, it found that an IgA titer of more than 20 U/mL correlated with protection against rotavirus disease, and that anti-rotavirus IgA in vaccinated infants was associated with a lower percentage of subjects with any or severe rotavirus disease. However, increased titer value in seropositive subjects does not substantially increase the level of protection.

The second study was a meta-analysis of eight Rotarix efficacy studies in Europe, Asia and South America (but not Africa). It used linear regression analysis to analyze these population-level data that included 26,000 infants in the vaccine group and 19,000 in the placebo group. This study also found a relationship between the immunological response and the efficacy of the vaccine.

“Two different analyses support the hypothesis that the anti-rotavirus IgA seropositivity with a cutoff of equal or more than 20 U/mL may serve as a useful relative correlate of the efficacy in the clinical trial with the anti-rotavirus vaccine,” Han said.
She also noted that while IgA is a potentially invaluable epidemiological tool at the population level, it couldn’t be used to predict individual protection. “Therefore further studies are needed to support the use of the anti-RV IgA antibody titer as a correlate of efficacy,” he concluded.

Patel took a different approach, with different results, to assess the utility of IgA as a good marker of protection. His team conducted a systematic review of all the immunogenicity and efficacy data for Rotarix and RotaTeq.

The search of PubMed, clinicaltrials.gov, the US Food and Drug Administration website, and the European Medicines Agency together yielded 39 data points from 32 countries. The studies evaluated both IgA titers and seroconversion rates, although Merck and GSK use different measures for the later, complicating that analysis.

The study stratified the data into low-, medium- and high-mortality countries for children under five (based on WHO standards). It found that IgA titers are clearly correlated with under-5 mortality for both Rotarix and RotaTeq.

“You don’t see this in epidemiology too often—to find a nice correlation where higher titers nearly 400 U/mL occur in the lower-mortality countries and low titers of nearly 30 to 50 U/ml occur in the high-mortality countries,” Patel said.

IgA titers correlated with vaccine efficacy for both vaccines; it found high vaccine efficacy in the regions with the highest titers (above 200 U/mL). In Patel’s study, titers of more than 90 U/mL correlated with higher protection and less waning than did titers under 90. Two-year efficacy in countries with titers above 90 U/ml was 85 percent, compared to a two-year efficacy of 44 percent in countries with titers less than 90 U/ml.

### Summary IgA Titers and Efficacy*

<table>
<thead>
<tr>
<th>IgA Titers (U/mL)</th>
<th>Mean IgA Titers (95% CI)</th>
<th>2-Year Efficacy (95% CI)</th>
<th>Relative Decline In Efficacy Year 2 / Year 1 (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>192 (140-228)</td>
<td>85 (77-98)</td>
<td>7% (4-10)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>41 (25-70)</td>
<td>44 (30-55)</td>
<td>66% (15-100)</td>
</tr>
</tbody>
</table>

*Mean values are presented as medians with interquartile range (IQR). Relative decline in efficacy is presented as the percentage decline in efficacy from year 1 to year 2 with the range given in parentheses.*
Patel noted that the importance of the 90 U/ml resides in the fact that researchers are looking for interventions to increase efficacy in low-income countries. “There are many trials with breastfeeding, varying the age of vaccination, giving a booster dose. If you do that in a country where titers are 50 and you withhold breastfeeding and mount that titer up to say 150, I would feel quite comfortable and reassured that’s a great intervention. And I think that’s a huge step forward,” he said.

Despite the findings of IgA as a strong correlate of protection, “The mechanism of immunity obviously still remains elusive for this IgA that we’re measuring in the blood,” Patel said.

**Measurement tools**

Research presented by PhD candidate Anu Paul at the Christian Medical College took a different tact. She examined the variable results possible when different assays are used to determine the actual concentration of IgA in blood plasma.

Paul noted that vaccine trials for Rotarix and RotaTeq both used serum IgA to measure immunogenicity and seroconversion. The IgA levels were determined with ELISA, which uses rabbit polyclonal anti-rotavirus antibody to capture the antigen. The antigen then binds the rotavirus specific IgA antibodies in serum.

Noting that the two major rotavirus vaccines are derived from both human and animal-human reassortant strains, Paul described her study, which compared the use of bovine (G6P5) and human (G1P8) strains as antigens to determine rotavirus specific IgA antibody concentrations in adults, toddlers, and infants. The study tested a panel of 30 samples, 10 from each age group.

Based on a Bland Altman plot there was poor agreement between the assays, particularly in samples with higher IgA units. For example, of the 30 serum samples tested, 11 samples showed less than 20 units of RV IgA with G6P5, versus 9 samples with G1P8.

In conclusion, Paul noted: “Similar concentrations of rotavirus antigens derived from human and animals do not serve as exactly identical antigens in the serum Ig assay.” The geometric mean concentration between the two assays indicated that values estimated using the G1P8 human strain, as the antigen would be consistently higher than the values that were obtained using the G6P5 as the antigen.

**Finding missing antibody responses**

In addition to assessing the value of IgA as a COP, Dr. Manuel Franco, with the Instituto de Genetica Humana of the University of Javerina took a totally different approach. He examined the potential of B cells that express intestinal homing receptors, rotavirus-specific IgA with bound secretory component, and T cells that express intestinal homing receptors as potential mediators of immunity against rotavirus.

“This is based on a long-standing idea, a guiding hypothesis, that immunity has to be in the gut to be efficient,” Franco said. He presented preliminary data exploring whether these immune system cells could serve as parameters in blood that reflect intestinal immunity.

“Of the currently used assays, rotavirus IgA measured shortly after vaccination is probably the best but imperfect correlate of protection,” Franco said. He noted that while IgA correlates well with protection in many settings, it is by focusing on the cases where this does not happen that one can really understand the mechanisms that protect against disease.
As an example of this he noted that in many developing country settings IgA seroconversion rates exceed protection rates against severe gastroenteritis, suggesting that rotavirus can induce systemic IgA responses without inducing local intestinal immune responses. In other cases, the levels of protection induced by the vaccine may exceed the levels of serum rotavirus IgA. In these cases we maybe missing some intestinal antibody responses, and we tried to identify these extra antibody responses,” Franco said.

He noted that the immune system is compartmentalized in its response against rotavirus, with a B cell compartment in the intestine, and a B cell compartment in the systemic circulation. B cells in the intestine express homing receptors (alpha-4, beta-7, and CCR-9) that permit them to circulate among intestinal lymph nodes where the B cells can secrete dimeric IgA (two linked molecules of IgA) into the intestine.

On the other hand, systemic memory B cells produce antibodies in the bone marrow, which then circulate in blood. However, systemic antibodies can get to the intestine, and some of the intestinal antibodies can go back into the blood.

Franco reviewed a number of studies that led to the identification of intestinal IgA in the plasma of different groups of children with diarrhea. The experiments eventually led Franco to postulate that children with natural infection get rotavirus secretory Ig that can be either IgA or IgM in plasma.
Genotype constellations shine

Dr. Jelle Matthijnssens, of the University of Leuven, reviewed the genetics of rotavirus, on the level of genotype constellations.

At the most basic level, rotaviruses have 11 segments of double stranded RNA, each of which produce one or two gene products: six structural proteins and five or six nonstructural proteins.

VP4 and VP7 form the outer capsid proteins, which elicit neutralizing antibody responses. They were originally used to define serotypes, information that has since been complimented with genotypes based on sequence data. There are now 27 G-genotypes (determined by VP7) and 35 P-genotypes (determined by VP4).

The most common human strains are G1, G3, G4, and G8 in combination with P[8], and G2 in combination with P[4]. And in more recent years, G9 and G12 have become important human rotavirus strains, and are usually found in combination with P[6] or P[8].

Reassortments among rotavirus strains are common, and can produce novel human and animal rotavirus strains. Of the 133 different described G and P combinations, a little more than 70 have been detected in humans.

Matthijnssens reviewed a classification system he developed based on sequence data for each of the 11 gene segments (not just G and P). The system facilitates the comparison of complete rotavirus genomes of different strains. It uses the acronym: Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx to describe the VP7-VP4-VP6-VP1-VP2-VP3-NSP1-NSP2-NSP3-NSP4-NSP5 encoding gene segments of a rotavirus.
Whole genome analysis of human rotavirus strains revealed the presence of three main human genotype constellations, named: Wa-like (I1-R1-C1-M1-A1-N1-T1-E1-H1), DS-1-like (I2-R2-C2-M2-A2-N2-T2-E2-H2), and AU-1-like (I3-R3-C3-M3-A3-N3-T3-E3-H3).

Viewed through this whole-genome lens, there are only two major genotype constellations that are epidemiologically significant for humans, and they are represented by Wa and DS-1. There have been sporadic detection of reassortants of Wa-like and DS-1-like rotaviruses of very limited epidemiologically importance. In addition, a few animal-derived rotavirus genotype constellations are of minimal human epidemiological significance.

“Although we see a very large genetic diversity existing among human rotavirus strain with respect to G- and P-genotypes, the genetic diversity is much smaller if we compare these strains on the complete genome level,” Matthijnssens explained.

From a vaccine perspective, “The observed limited genetic diversity of these epidemiologically important human rotavirus strains is actually quite good news,” he pointed out, since both Rotarix and RotaTeq have been shown to confer good protection against both Wa-like and DS-1-like human rotavirus strains.

**Can gene constellations explain lower vaccine efficacy in Asia and Africa?**

However, the majority of the strains that have been sequenced are from Belgium, the USA and Australia, with relatively few strains from Africa and Asia. Given the more limited vaccine efficacy in Africa and Asia, this raises the question of whether the circulation of rotaviruses with unique genotype constellations in these settings is responsible for lower vaccine efficacy.

To answer that question, Matthijnssens sequenced 126 rotavirus strains from RotaTeq clinical trials in Africa and Asia and determined their genotype constellation. Findings thus far indicate that those genotype constellations are similar to the ones analyzed in the rest of the world, mainly possessing a Wa- and DS-1-like genotype constellation.

“The lower vaccine efficacy observed in Africa and Asia is most likely not due to circulation for rotavirus strains with distinct genotype constellations,” he concluded, while noting that more detailed analysis of the African and Asian strains is ongoing.

**Jelle Matthijnssens, University of Leuven, Belgium**

**Explaining RotaTeq’s high efficacy against African G8 Strains**

Ms. Elisabeth Heylen, of the University of Leuven, examined the possible genetics explaining RotaTeq’s high efficacy against G8 rotavirus strains circulating in Africa. At 87.5 percent [95 percent CI: 6.5-99.7], RotaTeq vaccine efficacy against G8 rotaviruses is much higher than its efficacy against genotypes (G1-G3, P[8]) contained in the vaccine (34 percent, [95 percent CI: 11.2-51.2]).

The RotaTeq vaccine consists of 5 reassortant rotavirus strains with a bovine genetic backbone, each possessing a single human rotavirus VP7 or VP4 gene segment, representing different genotypes (G1-G4 and P[8]). The G8 genotype is typically found in cattle but has also been detected at significant rates in people in Africa, the middle East and only sporadically elsewhere.

Clinical trials for RotaTeq found a high prevalence of G8 rotavirus strains: 4.7 percent of strains in Mali, 6.5 percent in Ghana, and 23.6 percent in Kenya were identified as G8.
Heylen studied the relationship between the complete genomes of eight wild-type G8 rotavirus strains collected during the clinical trials of RotaTeq in Sub-Saharan Africa and the RotaTeq vaccine strains. Full genome sequencing and the construction of phylogenetic trees revealed a number of insights.

The G8P[1] strain from Ghana had a backbone of complete animal origin, suggesting that it was probably an interspecies transmission from an animal rotavirus to a human. For the G8P[6] strains from Ghana, the majority of the segments were of animal origin except for NSP1 and NSP3, which were more closely related to typical human DS-1-like strains.

The G8 strains from Mali possessed 5 gene segments more closely related to animal rotaviruses, whereas 5 other gene segments were of typical human rotavirus origin. An unusual G8P[6] strain from Kenya had a majority of typical human DS-1-like gene segments, except for G8 (VP7) and E2 (NSP4).

“*The fact that RotaTeq possesses a bovine rotavirus genetic backbone may explain its high vaccine efficacy against African G8 rotavirus strains with their partial or complete bovine-like genetic backbone.*”

Elisabeth Heylen, University of Leuven, Belgium

Mixing it up in Brazil: Reassortment Among Rotarix Strain and Brazilian rotavirus strains

Dr. José Paulo Gagliardi Leite, with the Oswaldo Cruz Institute at Brazil’s Ministry of Health reported on the emergence of new genotypes in Brazil following the introduction of Rotarix in 2006, and ultimately leading to the identification of virulent virus based on Rotarix reassortants.

He reviewed the rotavirus disease situation in Brazil, which is home to 192 million people -- approximately 40 percent of the Latin American population. Regional differences across the country are reflected in both socio-economic and environmental diversity.

Between May and October 2005, an epidemic of acute gastroenteritis occurred in Rio Branco city, Acre State, Northern Brazil, associated with rotavirus genotype G9P[8]. A total of 12,145 persons aged ≤ 5 years with acute diarrhea were reported to Rio Branco’s Surveillance System and eight deaths occurred in children between two and 16 months of age. The year after the outbreak, the Brazilian government decided to introduce the Rotarix vaccine, based on an attenuated G1P[8] strain. Significant declines in diarrhea hospital admissions and deaths from diarrhea followed vaccine introduction, particularly in Northern and Northeastern Brazil.

Epidemiologists also tracked rotavirus strains over the following years. Prior to Rotarix introduction, G5 was epidemic. This was replaced by G9s, and G2P[4] also emerged after 2005. In 2009, surveillance detected a number of cases of disease caused by rotavirus genotype G1P[8], in vaccinated and unvaccinated children, particularly in Northeastern Brazil. By that time, Rotarix coverage had reached 86 percent. Meanwhile, there was also a gastroenteritis outbreak in south Brazil, associated with rotavirus genotype G3, which was emerging in Paraguay, Argentina, the United States and Australia as well.
Whole genome sequencing of G1P[8] circulating strains found that the identity values between the Brazilian G1P[8] strains and Rotarix vaccine ranged from 88.4 percent to 100 percent for nucleotides and 83.4 percent to 100 percent for amino acid sequences.

“The first intra-genotypic reassortment observed was associated with one child 32 months old, vaccinated with one dose of Rotarix,” Leite reported. While closely resembling Rotarix, it also contained an NSP3 gene belonging to genotype 3. Further intra-genotypic reassortants were found. One was a shedding of the Rotarix vaccine (collected 7 days after immunization). The disease strain in one unvaccinated 42-month-old child contained VP1 from Rotarix, and a two-month old unvaccinated child was infected with a strain that possessed 7/11 segments identical to Rotarix.

Genetic analysis later documented a similar phenomenon with RotaTeq, including sibling transmission of RotaTeq-derived rotavirus. In Nicaragua, epidemiologists found a vaccine-derived NSP2 segment in rotaviruses from vaccinated children with gastroenteritis.

Leite also pointed to evidence of reassortment in that one strain of G1P[8] differed from previously circulating G1P[8] Brazilian strains in that their VP7, NSP2 and NSP3 genes were 100 percent similar to Rotarix.

“In conclusion, it can be inferred that reassortment events are possible between the human RVA derived vaccine Rotarix and wild type strains,” Leite said.

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“Rotavirus surveillance that includes full genome sequencing will help to understand the impact of the vaccine gene introduction into circulating human rotavirus strains and to determine the real frequency of inter-genogroup reassortment events.”

José Paulo Gagliardi Leite, Oswaldo Cruz Institute, Brazil

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Circulating Rotavirus Strains in Africa

Dr. Mapaseka L. Seheri, with the WHO Regional Reference Laboratory, University of Limpopo, reviewed the strains of rotavirus circulating in Africa, where the disease claims the lives of 232,000 children a year.

The data was based on work done by the African Rotavirus Surveillance Network (AFR RSN). Since 1998, twelve AFR RSN training workshops were successfully organized by the WHO AFRO and the Rotavirus Regional Reference Laboratory (RRL) in South Africa. The network has assembled a collection of laboratory samples that includes 25,000 human stool samples and more than 5,000 animal samples.

She reported the summary of the rotavirus genotypes generated during the three AFR RSN training workshops from 2009 to 2011. Representatives were from 17 African countries and they supplied 2,729 data stool samples that tested positive for rotavirus. The P- and G-types were determined by RTPCR, and a portion of the samples were sequenced in order to confirm the genotype.
Genetic analysis revealed the distribution of circulating genotypes from 2009 to 2011, confirming that the worldwide common strains are not present in the same rates in Africa as compared to the industrialized countries.

Seheri reported that, among the common strains, G1P[8] was the predominant strain detected, followed by G9P[8], G2P[4], G4P[8], and G3P[8]. However, these strains represented 41 percent of the rotavirus infection. There has been increased circulation of P[6] strain in most African countries and different human and animal reassortants strains including G8P[14], G6P[6], G4P[6], G9P[14] and G10P[6] were also detected.

"These results clearly support the need for continuous assessment and monitoring of the genotypes that are circulating in Africa."

Mapaseka L. Seheri, University of Limpopo, South Africa

Vaccine genes contributing to break-through disease

RotaTeq was launched as part of the National Immunization Program in Nicaragua in 2006. By 2009, coverage rates of at least 90 percent were associated with significant reductions in mortality and morbidity due to rotavirus infections. However, the vaccine efficacy rate of 58 percent against severe diarrhea was less than ideal, raising the question of whether the problem was one of poor protection against common circulating strains, or one in which the circulating strains were unique.

To answer the question, Dr. John Patton, at the US National Institutes of Health, analyzed rotavirus strains in vaccinated children who presented with diarrhea in a northern Nicaragua hospital from April to August 2010. Stool samples from 107 children were collected, and 18 tested positive for rotavirus.

"Of 18 children, 12 of them had received two or three doses of RotaTeq, and two of the children had not been vaccinated, and four we didn’t know their vaccine status," Patton reported.

Researchers sequenced the entire rotavirus genome from each of the 12 children who had been vaccinated. Eleven strains were G1P8 and one was a G3P8. And while all the G1P8 strains had typical VP7 and VP4 genes, two had unusual genes for NSP2, a gene engaged in viral replication.

Further analysis revealed that this NSP2 gene was identical to the RotaTeq NSP2 sequence. One other oddity emerged, distinctive VP6 genes in the two strains.
Patton surmised that both of the atypical strains were reassortants formed between the RotaTeq vaccine and one or two different circulating G1P8 viruses, and that they represent distinct reassortment events.

“It’s clear that reassortants can be formed between vaccine virus strains and circulating human rotaviruses,” Patton concluded. He also noted that, because the reassortants lack the highly conserved genotype 1 genome constellation, they may be less biologically fit, and therefore may fade from the circulating virus pool.

On the other hand, “With the constant use of RotaTeq, the possibility constantly exists that you can recreate the reassortants all over again each year, particularly in the winter season.”

John Patton, National Institutes of Health, United States

**Allele-based Genome Constellations of Nicaraguan RVs**

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<th>NIC18J G1P[8]</th>
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- **Two RVs (NIC9J and NIC25J) contain RotaTeq NSP2 genome segments.**
- **The VP6 genome segments of these two viruses differ.**

“With the constant use of RotaTeq, the possibility constantly exists that you can recreate the reassortants all over again each year, particularly in the winter season.”
Introducing the session, Dr. Kathy Neuzil of PATH and the University of Washington recapped highlights from the preceding sessions. She noted that surveillance and modeling confirms that rotavirus causes a substantial portion of severe dehydrating diarrhea in diverse settings and diverse populations, and that rotavirus vaccine significantly reduces severe gastroenteritis, death, and other important outcomes under real-world conditions of use.

“We also heard the consistent message that the number of severe rotavirus cases prevented by the vaccine is consistently greater in low-resource as compared to high-resource populations, despite modest relative effects,” Neuzil said.

During the course of the meeting, the first results from a GAVI-eligible country were reported: in Bangladesh with the Rotarix® vaccine. And review of new data on intussusception finds only one to two per 100,000 that can be attributed to the rotavirus vaccine. “We have robust safety surveillance that can detect these rare events and we should feel very reassured from that data.”

Neuzil noted that more of the world’s countries, including more low-resource ones, are starting to introduce rotavirus vaccines. Still, she said, a number of nations have not done so, and many of those are in Asia. To date, only the Philippines has introduced the vaccine, and only in the poorest part of the country.

Introducing rotavirus vaccines into more Asian countries will require scientists to become better advocates for rotavirus vaccine, Neuzil said. She pointed out that the Symposium speakers and attendees are the experts who understand the relevant issues better than anyone else, so they can potentially help decision makers to make good decisions.

“The most compelling messengers are passionate and invested—and see the big picture,” she said. “But we need to learn how to translate the data that we have heard at the Symposium and channel our passion into action.”

Rotavirus Advocacy 101

Andy Seale of PATH defined advocacy as “the act of strategically supporting a cause, ideal, or policy—and convincing the right people that it is important and that they need to take action.” Moving an agenda forward is both an art and a science, he said, drawing on social science, political theories, human psychology, public health principles, and studies of organization and international development.

Most important:
- Know what you are striving for, and be able to articulate it quickly and succinctly.
- Understand the problem, and explore the context in which you are operating.
- Recognize that every interaction that you have—even if it initially appears as a threat—is a potential opportunity to help move your agenda forward.
- An individual champion can be crucial, but you can become a more effective advocate by working with others.
Scientists are trained to savor complexity; many may struggle to express their ideas in short sentences, without caveats. But the effort to communicate simply and concisely is worthwhile. Clear, unambiguous messages can help convince nonscientists—including decision makers—of the moral imperative of your agenda. Try to link the science to human impact: This often involves focusing on an individual case, a human face, not on statistics.

Dr. Mathuram Santosham, of Johns Hopkins Bloomberg School of Public Health, agreed about the importance of telling personal stories, including testimony from the parents of children who have died from rotavirus. While noting that celebrities, including presidents’ wives, can be powerful spokespeople, Santosham cautioned that they must be given accurate information that they understand well.

Constantly thinking about context is critical to effective advocacy work, according to Seale. For instance, he advised, be ready and prepared to advocate not only for rotavirus vaccines but also for vaccines broadly, for child survival, for investments in health systems, and for economic development.

Santosham agreed about the importance of context: “We don’t want to pit one vaccine against another. We want kids to receive all these vaccines—and interventions, including ORS and zinc supplementation.”

Scientists should recognize opportunities to move their agenda forward at different levels, seeking out not only organizational interactions and formalized policy consultation opportunities, but also personal interactions. For instance, they might happen to share a ride on an elevator or in a taxi with a politician, and should treat the encounter as an opportunity to promote an agenda.

If such an opportunity should arise, briefly to plan what you want to say, and say it. Then reflect on the interaction and assess how you might have phrased your agenda more clearly. Take advantage of any opportunities to follow up with the person. That can lead to working together as a team.

In planning for such opportunities, there are basic steps to be followed for effective advocacy. They mirror those of any planning cycle, applying similarly to a one-on-one meeting and a long-term advocacy campaign:

- Identify the problem.
- Analyze the situation.
- Articulate your goal.
- Plan what you want to do.
- Take action.
- Evaluate.
- Start again.

What about anti-vaccine groups? Santosham cautioned that not everyone who is concerned about vaccine safety is necessarily part of such a group. The groups’ messages may have influenced them, he said, but “these people may be converted if they are given the right information.” In contrast, he advised not engaging with anti-vaccine groups: “No matter how good your vaccine is, they will attack,” he said. “There is no point in trying to convert these people.” Instead, he recommended continuously putting out positive messages, including op-eds, for instance about the impact that the rotavirus vaccine has had in other countries.
Seale suggested that scientists work with people who are advocacy professionals, contracting with them if an organization can afford it. And he offered prepared messages, tools, and ideas for activities to use in order to become a more effective advocate, including these two resources:

- The Rota Council’s Advocacy Toolkit: [http://rotacouncil.org/toolkit/](http://rotacouncil.org/toolkit/)

The ROTA Council

Dr. Mathuram Santosham, of the Johns Hopkins Bloomberg School of Public Health, described the ROTA Council as a group of scientific leaders from all parts of the world. They advocate for the rotavirus vaccine by providing credible evidence for decision-making that is free from bias by industry or other bodies.

“We want to make sure that people have the right information, both about the efficacy and also about any adverse effects of rotavirus vaccine, including intussusception,” he said. The ROTA Council provides the scientific and technical evidence that policymakers need to accelerate the introduction of rotavirus vaccines. The Council’s mission is to “save lives and improve health by promoting the use of rotavirus vaccines as part of a comprehensive approach to addressing diarrheal disease.” More information is at [http://rotacouncil.org/](http://rotacouncil.org/).

Success in Ghana

Dr. George Armah, of the University of Ghana, shared the success story of Ghana’s recent dual introduction of rotavirus and pneumococcal vaccine. It involved a sustained effort to convince both the Ministry of Health and the news media. Ghana was lucky, Armah said, because it already had an ongoing surveillance program and good data that could be fed into the system. He and others had conducted clinical trials in Ghana, and conducted work on the economic costs of diarrhea. He translated that work into easily understandable language: “It was a good buy if you invested in it. There were good returns.”

The surveillance data had been given continually to the WHO, which has been involved in immunization in Ghana for a decade. “We had good contacts with the WHO office in Ghana,” Armah said.

The first challenge was to convince the national Ministry of Health, which is responsible for using data to change policy and persuade the politicians to agree to introduce vaccines. Thanks to his existing relationship with the staff of the local WHO office, they appointed Armah to their advisory committee on the Ghanaian immunization program. The committee, which met yearly, also included the surveillance group, as well as Ghana’s chief epidemiologist, its chief logistics officers, some budgetary officers, and representatives of UNICEF (a major donor), the Lions Club and Rotary International.

Being on the committee gave Armah an opportunity to share disease data, including rotavirus updates from other parts of the world, information on the available vaccines, and the potential impact of intervention. He adapted some handouts and communication messages from GAVI into “very simple messages that we always kept on bringing up.”
After around a year and a half, “we were able to get them onboard; they understood the message, and then also bought into the program,” Armah said. “Gradually rotavirus became part of the discussions that the committee had.” Then he was asked to present to the committee justification for vaccine introduction.

At the same time, Armah worked on spreading the word through the news media. He took cues from the successful publicity campaign about malaria in Ghana, with messages that were clear and well sustained. Working with two journalists who already understood malaria, he trained them about the burden and causes of diarrhea, including rotavirus, and the potential of the interventions including the rotavirus vaccine. Once these journalists’ stories started to appear, the messages were spreading to the public.

Armah volunteered to help to implement the vaccine. “But the WHO played a key role—and many other players helped to generate all the data,” he said. “So it’s teamwork.”

Understanding Asia’s Surprisingly Slow Pace

Dr. Tony Nelson, of the Chinese University of Hong Kong, discussed why Asia has been slow to introduce rotavirus vaccines. It seems surprising: Data have been collected in Asia, showing the disease burden, economic evaluations, and vaccine safety and efficacy, including a phase III study in Hong Kong. “It looked like it was going to be so simple,” he said. “I thought it would be a no-brainer, and we would introduce these vaccines quickly.”

One reason why Asia has lagged Latin America may be that most vaccine studies were conducted in Latin America and Europe. So when the WHO made its initial recommendation, it did not include Asia. “That’s a message to industry,” Nelson said. “You should try to conduct future vaccine studies in every WHO region.”

Also, Nelson said, Asia lacks an equivalent of the Pan American Health Organization (PAHO). PAHO allows decision makers in Latin America to see a price list, so they know what they will pay for vaccines: PAHO’s Revolving Fund supplies countries with vaccines, and ensures quality and affordable prices, helping countries to introduce new vaccines. Asia has also lacked an individual champion to play the role of Armah in Ghana or that of Dr. Ciro A. de Quadros, who was once with PAHO and is now with the Sabin Vaccine Institute. De Quadros was able to generate such enthusiasm for new vaccines that when they became available, many Latin American countries adopted them quickly.

Hong Kong was part of the Asian Network. And like Armah, Nelson worked hard to get assigned to the appropriate committees. Nelson was on the rotavirus working group of Hong Kong’s vaccine advisory committee, serving alongside ministry officials. In 2008, he and his colleagues presented data showing that one in 24 children in Hong Kong has been hospitalized with diarrhea by the age of five. They also showed cost-effectiveness, suggesting that a Hong Kong rotavirus vaccine program, given a vaccine priced at under US$90 a dose (less than the list price), would save money. They also presented safety and efficacy data from Hong Kong, Singapore, and Taiwan.

The ministers at the meeting concluded that more data were needed: an economic evaluation using the list price, not the tender price. But in Hong Kong, an analysis based on the private market list price, would not show the vaccine as cost-effective. “The issue of price is a major problem,” Nelson said.
Learning from Hib
Dr. Mathuram Santosham, of Johns Hopkins Bloomberg School of Public Health, shared his experience with the GAVI-funded Hib Initiative, a joint effort of the WHO, CDC, London School of Hygiene and Tropical Medicine, and Johns Hopkins Bloomberg School of Public Health. By now, every GAVI-eligible country either is using the Hib vaccine or has made the decision to do so, but the Initiative was “a struggle” at first, he said.

Among the obstacles was the difficulty of demonstrating whether Haemophilus influenzae type B (Hib) or Pneumococcus was the actual cause of pneumonia in a child. By contrast, nearly anywhere in the world, it is relatively simple to demonstrate that rotavirus causes 40 percent of childhood hospitalizations for diarrhea.

Another obstacle was the challenge of developing consensus among partners about which messages to use. “If the leaders and scientists give different messages,” he said, “they confuse the decision makers, who don’t want to deal with it.” The best messages are clear, he said, like “every day, 400 kids die, the equivalent of a jumbo jet crashing”—instead of “the incidence of Hib disease is 50 per 100,000.” “For a decision maker,” he said, “‘50 per 100,000’ means nothing.”

A third obstacle was that children continue to die every day of various causes, before and after a vaccine is introduced. By chance alone, several children will die right after a vaccine is given. In Kerala, India, the Initiative held several meetings with the Ministry of Health, and gave them question-and-answer sheets to help them address questions from the news media.

In introducing a rotavirus vaccine, Santosham advised acknowledging that there could be intussusception cases, while communicating to decision makers that the advantages of the vaccine—including the lives saved—far outweigh those few cases. And he advised preparing ahead of time, ensuring all the key players have the right information, and engaging all stakeholders in the country or state.

In a lively question-and-answer session that followed the formal presentations, Dr. Khalequz Zaman, of the International Centre for Diarrhoeal Disease Research (ICDDR,B), described the successful history of immunization in his country. “In my effectiveness study, I actually faced difficulties,” he said. Mothers in the villages that were not receiving the rotavirus vaccine were clamoring for their children to receive it. Bangladesh now has a political commitment to the rotavirus vaccine. Already the higher- and middle-classes have purchased about 5,000 doses for US $17 per dose. “I think with support from GAVI and other donors, it will be committed in Bangladesh, and it will be used more,” Zaman said. Another attendee said that Bangladesh has plans to introduce the rotavirus vaccine in 2014.

Dr. Naveen Thacker, of Deep Children Hospital and Research Centre, in India, offered two more suggestions for advocacy: First, he said, highlight equity issues. For instance, advocates could point out that a rotavirus vaccine is available for higher-income children but not for lower-income children in countries like India and other middle-income Asian nations. Second, he suggested arranging meetings in Asia to show success stories from places like Latin America, where rotavirus is saving lives.
One attendee brought up another factor in the successful adoption of vaccines, including the rotavirus vaccine, in Latin America: When one country introduces a new vaccine, it shares its experience with other countries and sends members of WHO’s Expanded Programme on Immunization (EPI) from that country to other countries.

“It’s Latin America that showed us the decrease in deaths in the real world due to rotavirus vaccine,” Neuzil said. “And that’s probably one of the best pieces of advocacy that we have.”

Other attendees said it is important to explain to parents that rotavirus is only one of many causes of diarrhea, so that even with the vaccine, children still may have diarrhea. Also, ORS and zinc supplementation continue to be necessary. Some participants suggested delivering ORS and zinc as part of administering the rotavirus vaccine.

Others suggested collecting more evidence in Asia, recommending improvements in sentinel surveillance. Others countered that Asia already has some of the world’s best data on disease burden. But decision makers sometimes demand local data, even when data from nearby countries are available.

Ministries of Health feel overwhelmed by so many vaccines these days, while their budgets are being strained. Of course, if public health money were spent on rotavirus vaccine, it would end up saving money in the public hospital system. But, because prevention and treatment are addressed under separate budgets, it is difficult to argue for the cost-effectiveness of introducing the vaccine.

Cost Effectiveness and a Pilot in Thailand

Dr. Arthorn Riewpaiboon of Mahidol University in Thailand reviewed the cost-effectiveness study on rotavirus vaccine in Thailand, where the vaccine is not yet part of the national Expanded Program of Immunization. The study itself represented a collaboration among academic and government experts.

Thailand has a population of 67 million, and a GNI per capita of US$ 4,210 in 2010. The country has nearly 100 percent health care coverage, with a Universal Healthcare Coverage Scheme managed by the National Health Security Office (NHSO) covering 75 percent of the population.

The NHSO also takes care of financing for vaccines and all main aspects of vaccine delivery. For a new vaccine to be incorporated into the EPI, it must first be recommended by the Advisory Committee on Immunization Practice (ACIP). Recommendations only come after thorough review of data on disease burden, public health impact, vaccine safety and efficacy and cost implications.

Riewpaiboon led a modeling study on the latter. The study addressed several questions: Based on the current situation, is rotavirus vaccination cost-effective? If not, at what price is it cost-effective? And, what is the budget needed for vaccine supply?

The study considered both societal and provider perspectives, and medical and non-medical costs. It investigated both the 2-dose and 3-dose vaccines, using a birth cohort in 2009, monitored until the age of 60 months. Evidence-based assumptions were made for the model inputs of vaccine efficacy and coverage, disease incidence, and deaths averted. Outcome measures were deaths averted and disability-adjusted life years (DALYs) averted.

Based on the market price of the vaccine, US$ 42 per dose for the two-dose vaccine, and US$ 31 per dose for the three-dose vaccine, the cost per DALY avoided was more than three times the gross domestic product (GDP). This meant the vaccine at market prices would not be cost effective (Thailand’s definition of cost-effectiveness requires that the cost per DALY averted be no more than one times GDP).
“It’s not surprising that for Thailand it’s not cost effective, because in Thailand the incidence is not so high, and mortality is also very low. So for the current price we can assume that it would not be cost effective,” Riewpaiboon said.

Further analysis showed that the break-even price for the vaccine to be cost effective would be no more than US$ 4.98 or US$ 3.32 per dose, for the two- and three-dose regimens respectively, based on a birth cohort of more than 700,000 children per year.

After delivering this analysis to the ACIP, Riewpaiboon said that he assumed there was some informal price negotiation with the vaccine manufacturers, for the government went on to conduct a two-year pilot program in one of Thailand’s 77 provinces.

Riewpaiboon's team plans to begin its assessment of the pilot data in October 2012, and to have an analysis of cost-effectiveness in 2014 based on real-life data, enabling an evidence-based decision on rotavirus vaccine introduction in Thailand.

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**Perspective from the Philippines**

Dr. Eric Tayag from the Ministry of Health said the Philippines introduced rotavirus vaccine in 2012, with the government purchasing enough doses for just 700,000 of the 2.5 million children who could have been vaccinated. “This will only benefit the poorest households,” said Dr. Eric Tayag. Before it will scale up the program, the government wants to know the impact of its initial investment; Tayag and his colleagues are now working on an impact study.

Tayag described how the rotavirus vaccine program fits into the country’s larger goals for addressing poverty.

Today, the Philippines has 95 million people, and the per capita GDP is US$ 2,120, half that of Thailand. In 2010, health expenditures were 3.6 percent of the GDP. Every day in 2010, 107 died at birth; 170 children died before their first birthday, and 230 died before their fifth birthday. Today, one of the main pillars of the national anti-poverty program is universal healthcare, or *Kalusugan Pangkalahatan*. The other three are education for all, decent housing and conditional cash transfers modeled on Mexico's program.

“Through universal healthcare, *Kalusugan Pangkalahatan* we want Filipinos to be prevented from falling ill when there is improved access to preventive and promotive health goods and
services,” Tayag said. The program aims to improve health outcomes and reach the health-related Millennium Development Goals.

The universal healthcare program began by enrolling the poorest quintile of the population. “We made sure the poorest of the poor are covered for their health insurance,” Tayag said. Today, at least 85 percent of the population has health insurance coverage.

“Saving children has been a priority,” Tayag said. He reported that the country is on track for attaining the MDG goal for reducing deaths in children under 5 by 2015.

“How do we get there?” he asked. The roadmap for reducing under-five child deaths includes a goal of fully immunizing 2.4 million babies before their first birthday.

Rotavirus vaccines are therefore an important part of the road map. But, “We have competing priorities. We do not have enough resources,” Tayag said.

Recognizing this gap, in 2006 a group of academics, including some in government, became advocates for rotavirus vaccines. “We become an advocacy (team) that would pave the way for the introduction of the rotavirus vaccine,” Tayag said.

“Beyond the science, what then is the policy?” Tayag asked. He noted three key ingredients needed for the introduction of rotavirus vaccine to be introduced: political will on the part of the government; and explicit commitment by vaccine manufacturers to support vaccine delivery, and advocacy.

“The vaccine launch in July had the President, President Aquino himself, initiating the vaccination of target populations for the rotavirus vaccine.”

Eric Tayag, Ministry of Health, Philippines
In closing, Dr. Mathuram Santosham, of Johns Hopkins Bloomberg School of Public Health contrasted the situation with rotavirus and diarrheal diseases today to when he had started his career. “We didn't even have oral rehydration therapy,” he said. “Five million children were dying each year of diarrhea. Now we're down to less than 800,000. We have very effective vaccines, and we also have a finance mechanism.”

“We are in a very exciting stage,” he continued. “We need to not only introduce vaccines, we need to get ORS coverage up. ORS coverage is only 30 percent. There is no reason why it should be only 30 percent. We need to get zinc supplementation up, we need to get breast-feeding up, and we need to work on water and sanitation.

“We are within a range of getting to a stage where we can say no child should die of diarrhea, and that’s not too far away. And all of that has been possible because of all of you in this room.”
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