PROCEEDINGS FROM THE
8th INTERNATIONAL ROTAVIRUS SYMPOSIUM

Sabin Vaccine Institute
International Vaccine Advocacy
2000 Pennsylvania Avenue, NW
Suite 7100
Washington, DC 20006
Phone: 202-842-5025
Fax: 202-842-7689
www.sabin.org

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Foreword

The 8th International Rotavirus Symposium was a collaborative effort of the Sabin Vaccine Institute, PATH, the US Centers for Disease Control and Prevention, World Health Organization and the Norwegian Institute of Public Health. The event attracted representatives from over 67 countries who engaged the full range of scientific, social, and economic challenges that must be overcome in order to prevent this major killer of children.

Rotavirus is the most common cause of diarrheal hospitalizations and diarrheal deaths among children worldwide. Development of safe and effective rotavirus vaccines has been a global health priority for many years. Two vaccines are on the market and others are in the research pipeline.

Rotavirus vaccination is now common in the US, and in several European and Latin American countries. At the time of the conference, decision-makers in Eastern Europe, Central Asia, and the Middle East were initiating a process to consider adding a rotavirus vaccine to their routine schedule of childhood immunizations. Clinical trials were underway to demonstrate vaccine efficacy in low-income countries of Africa and Asia, many of which are eligible to purchase vaccines with the support of the GAVI Alliance.

The incredible progress toward global adoption of a rotavirus vaccination is in large part a tribute to the focus and commitment of the scientific and policy experts from around the world who have worked in close cooperation for many years to ensure rotavirus immunization has progressed steadily from concept to reality.

The organizing committee would like to thank all involved for their diligent efforts and, particularly, to our hosts in Istanbul. The practical insights coupled with the energy and enthusiasm generated at this symposium provide a strong basis for optimism that in the near future, rotavirus immunization will be ubiquitous and rotavirus disease will no longer rank as one of the world’s major health problems.

Symposium Organizing Committee

Roger I. Glass, Fogarty International Center
John Wecker, Rotavirus Vaccine Program, PATH
Ciro de Quadros, Sabin Vaccine Institute
Elmira Flem, Norwegian Institute of Public Health
Cristiana Toscano, World Health Organization
Umesh Parashar, US Centers for Disease Control and Prevention
Duncan Steele, Vaccines and Immunization, PATH
Executive Summary

The 8th International Rotavirus Symposium took place at a crucial time in the history of rotavirus vaccines, which are intended to provide protection from a disease that, according to surveillance data presented by the World Health Organization, kills 527,000 children each year. With two approved rotavirus vaccines in use, and therefore two years of data on their safety and efficacy now available, participants had more information at their command than in any previous year.

Roger Glass, Director of the Fogarty International Center at the US National Institutes of Health, opened the meeting with a keynote address that celebrated the size and geographic span of the meeting noting that the 2008 symposium attracted four times as many participants as the first meeting in 1995. He then went on to discuss how he and colleagues convinced the United States, a country with very few rotavirus deaths, that a vaccine could save a billion dollars a year in direct and indirect health care costs.

Glass also singled out a crucial insight in surveillance data, which shows that rotavirus epidemiology differs dramatically between high-income and low-income countries. In low-income countries, a larger proportion of rotavirus disease victims are under one year old, diarrheal diseases routinely involve a mix of infections, and the fatality rate is high. Studies are underway in these regions to gauge the potential efficacy and impact of rotavirus immunizations, as past experience has shown that there can be important geographical variations in vaccine response. However, the high rate of rotavirus disease in poor countries has left many eager for widespread adoption of rotavirus immunization in the developing world.

“In the developing world, we’ve seen a very high case fatality rate, which has motivated the entire global program,” Glass said.

Glass went on to review a key development in rotavirus vaccine history: the rise and abrupt fall of RotaShield®, the first approved vaccine for rotavirus. Within months of its introduction, some children vaccinated with RotaShield developed intussusception, a rare and dangerous bowel obstruction. The adverse event prompted RotaShield’s manufacturer, Wyeth, to withdraw the vaccine from the market.

Glass and several other speakers noted that the cases of intussusception were in children vaccinated after 90 days of age. They said that since that time, all rotavirus vaccines in trials or routine use are supposed to be given before 90 days, when babies appear to have a natural protection against intussusception.

Experts point out that the two rotavirus vaccines currently in use—GlaxoSmithKline Biologicals’ (GSK Bio) Rotarix® and Merck’s RotaTeq®—are always administered before 90 days of age to avoid intussusception. Company representatives said clinical trials conducted thus far have found the vaccines to be safe and effective.

Norman Begg of GSK said Rotarix was developed from the most common human rotavirus strain. The rationale for the approach, he said, was that natural infections with rotavirus confer excellent immunity to further infections. Begg said that studies show that Rotarix—when given before 90 days of age—does not increase the risk of intussusception compared to placebo. He stated that the vaccine produces broad protection against many rotavirus strains, that the protection lasts at least two years, and that the two-dose regimen can be safely administered with other childhood immunizations.

Max Ciarlet of Merck said the company took a different approach with its rotavirus vaccine. It developed RotaTeq from five human-bovine reassortant rotavirus strains. RotaTeq is administered in three doses because it exhibits low replication capabilities in the human gastrointestinal tract, and three doses are required to build high and consistent immune responses, he said. According to data he presented, RotaTeq’s safety profile showed that RotaTeq is well tolerated and is not associated with an increase in the frequency of serious or nonserious adverse events.

Cristiana Toscano presented the World Health Organization’s (WHO’s) policies on rotavirus vaccines, most notably that efficacy must be shown in at least one low-income country in Sub-Saharan Africa or South Asia before WHO will recommend the use of the vaccines in these regions.

Duncan Steele, PATH’s senior advisor on diarrheal disease, noted that trials were underway to generate efficacy data and results should be available between late 2008 and 2010. He pointed out that, given the high rate of rotavirus disease in poor countries, even less than perfectly effective vaccines would save many lives and prove cost-effective.
Shabir Mahdi of South Africa’s University of the Witwatersrand presented interim results of an efficacy trial conducted in South Africa. He said they show that “the vaccine itself clearly offers a high degree of protection in South African children against severe rotaviral illness during the first year of their life.”

Umesh Parashar of the US Rotavirus Vaccination Program at the US Centers for Disease Control and Prevention presented early results from two years of RotaTeq use in the US. Widespread monitoring of rotavirus immunizations indicates that the rotavirus vaccine appears to be safe (when the first dose is given before 90 days of age). Data on effectiveness show a slight drop in rotavirus diarrhea in the year after RotaTeq was introduced, but a dramatic drop during the second year. Presentations on early experiences in Nicaragua and the European Union followed. The discussions revealed that, despite similar rotavirus burdens, attitudes in Europe vary widely as to when, where and how to introduce a rotavirus vaccine.

Presentations on policy concerns included a discussion of how to communicate rotavirus issues to the public, policy makers and physicians. Mathuram Santosham of the Johns Hopkins Bloomberg School of Public Health believes that researchers, not just advocates, must take a lead in communicating the benefits of rotavirus immunization.

“It’s important that we don’t assume that just because a study has been done in a particular region in Asia or Africa that everyone knows about it,” he said.

Santosham appealed to researchers and decision makers not to block rotavirus vaccines, which could save 2 million deaths by 2020, because of a few inevitable cases of intussusception.

Other discussions focused on future challenges including the need for post-marketing surveillance, stable funding for vaccine procurement, and infrastructure improvements in such areas as cold-storage facilities.

Vaccine costs and financing were also a key issue of concern. Deborah Atherly, senior health economist and policy officer at PATH, detailed a financial model that predicts prices will fall from a current $7.00 per dose to around $1.25 per dose by 2020, and that if widely adopted, the vaccine could prevent the deaths of 225,000 children per year.

Roger Glass concluded that in just two years the situation could change significantly, particularly if new rotavirus vaccines now under development come on the market and boost competition, which would lower prices.

“So we may well have a completely different economic outlook and forecast for the vaccine finance,” he said.
Introduction

The 8th International Rotavirus Symposium brought together scientists, clinicians, public health professionals, immunization leaders, vaccine industry representatives, and members of the donor community.

Dr. Ciro de Quadros, Executive Vice President of the Sabin Vaccine Institute, welcomed participants, noting that the large and geographically diverse group demonstrates that the global health community is committed to the fight against rotavirus disease. This, the 8th International Rotavirus Symposium, he said, would be a model in the history of rotavirus vaccines, and would help advance the cause of children's health worldwide.

“We have one-third of the world present here,” he said “We have 67 countries. We have over 400 participants. And I think this really shows the eagerness of the world community to come to grips with rotavirus disease.”

Dr. de Quadros highlighted the importance of rotavirus vaccine development and deployment with this sobering fact: worldwide, 65 children die of rotavirus diarrhea every hour.

John Wecker, PATH’s Global Program Leader for Immunization Solutions, welcomed participants on behalf of the organizing committee and commented on the quality of research to be presented.

“In our work with the countries, we have come to realize the commitment that you all have to reducing morbidity and mortality associated with diarrheal disease, and improving a child's survival,” he said.

“We have one-third of the world present here. We have 67 countries. We have over 400 participants. And I think this really shows the eagerness of the world community to come to grips with rotavirus disease.”

Ciro de Quadros, Sabin Vaccine Institute, US
KEYNOTE ADDRESS
Roger Glass, Fogarty International Center, US National Institutes of Health

The Emergence of Rotavirus as a Global Health Concern

Roger Glass, who serves as director of the Fogarty International Center at the US National Institutes of Health, delivered a sweeping and detailed overview of how the world has arrived to the point that it now has rotavirus on the ropes.

Glass said he has been gratified to see interest in rotavirus vaccines surge over the last ten years. He compared the huge turn-out in Istanbul in 2008 to an international rotavirus meeting in 1995 at the US Centers for Disease Control and Prevention (CDC), which he said attracted representatives from only half a dozen countries.

Glass first became interested in rotavirus while studying cholera in Bangladesh in 1980. He knew, he said, that cholera was an important diarrheal disease. But it turned out that rotavirus was a much more common and frequent cause of severe diarrhea. Returning to the US, he moved to NIH to work on rotavirus and rotavirus vaccines.

“But I must say,” Glass said, “that in the back of my mind a key issue was that the control of diarrheal disease in a place like Bangladesh, in a low-income country, had to be our primary goal, because diarrhea in these settings was a killer.”

The study of rotavirus began in earnest, he said, with the 1979 WHO program for diarrheal disease control. Glass recalled that Ruth Bishop, the researcher who discovered rotavirus, Tom Flewett, who named rotavirus, and Albert Kapikian, who later developed the first rotavirus vaccine, told WHO: “The world needs a rotavirus vaccine.”

One issue for Glass was whether wealthy countries would be interested in a rotavirus vaccine. He said that while the disease burden of rotavirus is obvious in developing countries—120,000 deaths annually in India, 100,000 in South Asia, 230,000 in Sub-Saharan Africa, and 20,000 in Latin America—Glass said the need for a rotavirus vaccine in the US was not clear.

But he said further analysis revealed that while the number of deaths in the US was relatively low, rotavirus caused many hospitalizations and clinic visits and

FIGURE 1

Estimated Global Distribution of the >500,000 Annual Deaths Caused by Rotavirus

1 Dot = 1,000 Deaths

Parashar, 2005
From Roger Glass, Fogarty International Center, National Institutes of Health, US
caused parents many days of lost work. The bottom line: Rotavirus in the US was generating $400 million in medical costs and about $600 million in indirect costs for a total financial burden of about $1 billion.

**Developing a Strategy for Rotavirus Surveillance**

In 1995, WHO, Glass and colleagues at the US CDC, including Joe Bresee, began to think about how to conduct rotavirus surveillance. The system they arrived at was based on simple data collection methods. It employed the common ELISA assay (Enzyme-Linked ImmunoSorbent Assay) for detection and allowed for rotavirus strain identification. The method is now being used in more than 50 countries.

“Our first study with this protocol with the WHO grant was in Vietnam where we studied rotavirus diarrhea hospitalizations in six hospitals in four cities in Vietnam,” Glass said. “We found that over half of the children had rotavirus as their cause of hospitalization.”

This study led Glass and colleagues to set up the Asian Surveillance Network, which then led to the establishment of rotavirus surveillance networks around the world. Today, Glass said, 50 countries carry on routine rotavirus surveillance and data collection.

Surveillance has provided surprising data about differences in rotavirus epidemiology between industrialized and low-income nations. In wealthier countries, rotavirus infection is seasonal and frequently affects children above one year of age. Mixed infections are rare and fatality is low. In low-income countries, on

**FIGURE 2**

**BURDEN OF ROTAVIRUS IN THE US**

<table>
<thead>
<tr>
<th>RISK</th>
<th>EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:10⁸</td>
<td>20-40 Deaths</td>
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<tr>
<td>1:80</td>
<td>60-70,000 Hospitalizations</td>
</tr>
<tr>
<td>1:7</td>
<td>500,000 Outpatient visits</td>
</tr>
<tr>
<td>1:0.9</td>
<td>3.2 Million episodes</td>
</tr>
</tbody>
</table>

Cost: $400 M medical; >$1 B total

Value of vaccine depends on direct vs. indirect costs

From Roger Glass, Fogarty International Center of the National Institutes of Health
the other hand, rotavirus strikes all year, 80 percent of cases are in infants, mixed infections are common, and fatality is high.

“In the developing world, we’ve seen a very high case fatality rate, which has motivated the entire global program,” he said.

A Brief History of Rotavirus Vaccines

According to Glass, the successful deployment of rotavirus vaccines is the culmination of several decades of research and development that included crucial setbacks.

In 1983 and 1984, Timo Vesikari, in Finland, established the first rotavirus vaccine trial, which Glass credits for setting the stage for all rotavirus vaccine development since. (See in-depth discussion of rotavirus vaccine development below.) Glass said Vesikari’s work demonstrated that rotavirus vaccines based on bovine virus strains can work, that a poor immune response does not necessarily predict poor efficacy, and that protection was greatest against the most severe cases of diarrhea.

About 14 years later, in 1998, Albert Kapikian, in the US, developed the first licensed rotavirus vaccine, RotaShield, which was produced by Wyeth. RotaShield reduced the duration of diarrhea for infected children and prevented infections with all rotavirus serotypes. But a crucial side effect caused Wyeth to withdraw the vaccine in little more than a year. In small numbers of children, the vaccine was linked to cases of intussusception, a dangerous and potentially fatal obstruction of the bowel.

Worry about intussusception has affected all rotavirus vaccine development and trials since. Glass said evidence indicates that the intussusception risk posed by rotavirus vaccination is time and age limited. When it occurs, it happens within two weeks of the first dose. Also, almost all cases involve children over 90 days old at the time of the first dose. Overall, data indicate that the risk of intussusception following rotavirus immunization increases ten fold after 90 days of age.

“Intussusception spares children naturally in the first three months of life, so that with all the new live oral vaccines, we try to get their first doses in before 90 days of age,” Glass said.

Today, there are two rotavirus vaccines—RotaTeq, from Merck, and Rotarix from GSK—licensed and widely available in more than 100 countries. Rotavirus vaccination is now routine in the US, Australia, Austria,
Belgium, Luxembourg, Brazil, Panama, Nicaragua, Guyana, El Salvador, Venezuela, Bolivia, and parts of Mexico.

RotaTeq is licensed in 70 countries, including many in Sub-Saharan Africa.

In the US, RotaTeq has been incorporated into the routine immunization program. The vaccine is given at two, four, and six months of age, with special emphasis on administering the first dose before 90 days of age, to avoid the naturally occurring intussusception peak that occurs between 5 and 9 months of age.

Recently, Rotarix was also licensed in the US. Globally, Rotarix is licensed in more than 100 countries, including Europe and Latin America where the vaccine has been introduced, but also including countries like Bangladesh and 21 countries in Sub-Saharan Africa.

The licensure in these countries is unusual, Glass said, because no efficacy data exists for populations living in low-income areas of the world.

**Vaccine Cost and Vaccine Efficacy**

Simply put, the two major considerations for a country adopting a rotavirus vaccine focus on affordability and effectiveness.

On the financial side of the equation, Glass said ministers of health focus more on the immediate cost of an immunization, not cost-effectiveness over the long term (which compares the cost outlays for purchasing and administering a vaccine to the treatment and other costs imposed by the burden of the targeted disease).

Rotavirus vaccines range in cost from $7.50 per dose to more than $100 per dose. But, as in the example of the United States, while the cost can seem prohibitive, if compared to the overall financial burden of rotavirus disease the vaccines are likely cost-effective. The issue of cost vs. cost-effectiveness is more of a problem in middle and higher-income countries, Glass said, because in low-income countries, GAVI Alliance is committed to subsidizing vaccine costs.

Glass said that in addition to financial concerns, a key challenge is determining whether “these vaccines work well” in the developing world.

In 1997, when RotaShield was under consideration, Wyeth requested a global recommendation from WHO for global use of the vaccine. The WHO consensus group responded that researchers must demonstrate efficacy of live, oral vaccines in at least one low-income country in Asia or Sub-Saharan Africa. At the time of this symposium, clinical trials of both rotavirus vaccines had been initiated in these regions. But Glass said “preliminary data suggests that they may not work as well” in developing countries, and that “there may be opportunities to improve efficacy.”

For example, past studies have shown that the immune response to Rotarix among children in Bangladesh and South Africa is only a little more than half what one sees in children in Finland. The discrepancy is not peculiar to rotavirus vaccines but is seen with live oral vaccines in general.

“Live oral vaccines have really posed a problem in the developing world,” Glass said.

T. Jacob John, with the Indian Academy of Pediatrics, and an attendee at the 2008 symposium was noted as the first to observe this phenomena during studies of oral polio vaccine. He found that the polio vaccine does not work as well in children in India compared to children elsewhere the world. Similar differences have been observed with oral cholera vaccine and typhoid vaccine.

Glass said there are many biological factors that may be contributing to the problem. For example, breast milk and stomach acid can neutralize the vaccine virus and lower its effective titer. In addition, maternal antibodies may reduce the amount of virus delivered or inhibit the immune response. Finnish studies showed that children who responded poorly to vaccines had higher levels of maternal antibody than did good responders.

“This observation has been repeated in other countries, and is quite consistent,” Glass said. For example, compared to Finland, levels of maternal antibodies are four to five times higher in South Africa, three times higher in Bangladesh and two times higher in Mexico.

Also, a study conducted in Bangladesh showed that breast milk can significantly lower the amount of virus received by a baby during immunization. In Bangladesh and South Africa, it is not uncommon for babies to have breast milk in their mouth at the time of immunization, something that doesn’t happen in the United States where women do not breast feed in public as often.

**Mapping a Way Forward**

One way to deal with this dilemma, Glass said, is to determine the level of efficacy required to provide sufficient protection against rotavirus. Does a vaccine need to be 90 percent effective, or would 80 percent or even 40 percent be worth using?

Another approach would be to provide vaccines
better suited for the biological profile of children in the developing world. Both India and Australia are developing new vaccines based on neonatal rotavirus strains. These are strains that reproduce in the presence of maternal antibody. Vaccines that use inactivated rotavirus also could provide an alternative.

A major question, said Glass, is who will provide affordable rotavirus vaccines to the world? Today, he said, GSK and Merck are supplying the vaccine. But vaccine manufacturers in China, Brazil, India, Indonesia, and Germany are also potential suppliers for developing countries.

Still, Glass said while challenges remain, overall progress on the path to widespread use of rotavirus vaccines is impressive.

"Rotavirus vaccines have become a priority for GAVI, for WHO, and for the Gates Foundation," he said. "We have two vaccines licensed, and we have others in development. Eight countries have national programs for rotavirus vaccination. So the train has really left the station."

"We have two vaccines licensed, and we have others in development. Eight countries have national programs for rotavirus vaccination. So the train has really left the station."

Roger Glass, Fogarty International Center of the National Institutes of Health, US

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1973</td>
<td>Ruth Bishop and co-workers publish the discovery of human rotavirus and its association with severe diarrhea in infants and young children in Melbourne, Australia</td>
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<td>1978</td>
<td>Oral Rehydration Therapy (ORT) was found to be useful in treating and preventing most of the deaths due to Rotavirus.</td>
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<tr>
<td>1982</td>
<td>Vesikari tests bovine rotavirus vaccine in children; safe and immunogenic.</td>
</tr>
<tr>
<td>1983</td>
<td>Vesikari tests bovine rotavirus vaccine in infants; safe and protective against rotavirus diarrhea.</td>
</tr>
<tr>
<td>1995</td>
<td>First trials in infants.</td>
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<tr>
<td>1996</td>
<td>Phase II trials begin, testing effectiveness in infants at four centers across the US.</td>
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<tr>
<td>1997</td>
<td>Rotavirus ELISA developed.</td>
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<tr>
<td>1997</td>
<td>AVANT sublicenses vaccine to GlaxoSmithKline (GSK).</td>
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<td>1998</td>
<td>August</td>
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<td>2008</td>
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**Discovery of Rotavirus to a Vaccine in 25 years**

**Bovine Beginnings**

Timo Vesikari of the Vaccine Research Center of University of Tampere, Finland offered a detailed history of rotavirus vaccine development.

He noted that vaccine development began in 1971, when Canadian veterinary biologist C.A. Mebus published a description of bovine rotavirus vaccine, named RIT 4237. The highly attenuated vaccine was safe for cattle.

In a 1982 study involving 25 children, Vesikari and colleagues found the vaccine to be safe and to produce an appropriate immune response in humans as well. A trial in 8 to 11-month-old infants followed the next year. Vesikari and colleagues gave a single dose of vaccine in January, just before the rotavirus season, and followed the babies throughout the season.

The bovine vaccine offered protection against rotavirus diarrhea in these infants. Furthermore, Vesikari learned that the protection was greater for more severe diarrhea: 88% protection against severe diarrhea and 50% against any rotavirus diarrhea.

“We also saw that that even some of the children who did not respond serologically to the vaccine seemed to benefit from it, so the antibody response did correlate with protection,” Vesikari said.

In a 1983-1984 study, Vesikari collaborated with Tom Flewett, one of the pioneers of rotavirus research. By studying the rotavirus strains in Finland, Vesikari showed that the bovine vaccine offered protection against several strains. The study also showed that the bovine vaccine was adversely affected by stomach acid. The simple measure of giving milk to the baby before the vaccination improved the immune response, by acting as a buffer against stomach acid.

“Whether the children received the bottle milk or breast milk before vaccination did not seem to make a difference,” Vesikari said. “We’re very, very happy about that.”

Following up on the discovery of rotavirus, in 1983 Ruth Bishop followed infants in Australia with and without a neonatal rotavirus infection. No difference appeared between the groups in the number of rotavirus infections during the first three years of life. But an early rotavirus infection did protect the babies against rotavirus disease.

“So what we did,” Vesikari said, “was to do the same with vaccine, and we gave the vaccine to neonates.”

As with the Australian study of natural rotavirus infections, the bovine vaccine offered little or no protection against rotavirus infection over the three years of the study. However, it provided 71% protection against severe rotavirus diarrhea and 100% protection against very severe disease.

“So we thought that the neonatal immunization was perhaps a chance, but it has not really been further developed after this,” Vesikari said.

**KEY FACTS, BOVINE ROTAVIRUS VACCINE, FINLAND 1982-1987**

- efficacious against severe rotavirus gastroenteritis.
- optimal efficacy at 6–12 months of age and neonatal.
- vaccination protective against severe disease.
- one dose as good as 2 doses.
- no obvious side effects (intussusception not seen).
- buffering against stomach acidity needed.
- breast-feeding did not interfere.
- Oral Polio Vaccine interfered (studies in Italy and Yugoslavia).

“The reason why the bovine rotavirus vaccine of the 1980s did not succeed was mainly that nobody was interested. In Europe few people knew about rotavirus much less were interested in a vaccine, they had other priorities. The WHO’s position here was basically that a perfect vaccine was required. A good vaccine was not enough.”

Timo Vesikari, Vaccine Research Center of University of Tampere, Finland
While the researchers saw no intussusception when administering bovine vaccine to older children, Vesikari said, “I think we were just lucky.” Also, the vaccine effectiveness varied from country to country. “So the situation at the time this vaccine was withdrawn was that it was efficacious in a country like Finland,” Vesikari said. “It did have low efficacy in Africa, and Latin America was somewhere in between. But the reason, really, why it did not succeed was mainly that nobody was interested. In Europe few people knew about rotavirus much less were interested in a vaccine. They had other priorities.”

“The WHO’s position here was basically that a perfect vaccine was required,” he added. “A good vaccine was not enough.”

The Rhesus Rotavirus Vaccine

Some researchers felt that the bovine vaccine was too weak for use in low-income countries. The NIH’s Albert Kapikian and colleagues responded by developing a vaccine from a rhesus monkey rotavirus, which provoked a stronger immune response.

From rhesus rotavirus vaccine researchers developed RotaShield, which combined rhesus and human viral genome segments. But when some vaccine recipients developed intussusception, RotaShield was withdrawn from the market about a year after introduction.

“It was an efficacious vaccine,” Vesikari said, “and it still has remained so, but then we have the safety issue. I don’t know how—how much we appreciate—that most of the intussusception cases were in infants who participated in the catch-up program, who got the first dose of the vaccine when they were over the age of three months.”

Since the withdrawal of RotaShield, intussusception has been a key safety issue for all rotavirus vaccines.

Matching Safety with Efficacy

In 2001, The Rotavirus Efficacy and Safety Trial (REST) began. (The study was published in 2006). REST showed that Merck’s RotaTeq was safe. There were no more cases of intussusception in vaccinated infants than in unvaccinated ones. In the trial, the first dose of RotaTeq was given at 6-12 weeks. “So when this vaccine is given properly this way, it is really safe for intussusception. That’s the lesson from this trial,” Vesikari said.

A similar study of GSK’s Rotarix showed fewer cases of intussusception among vaccinated infants than unvaccinated infants. Meanwhile, Wyeth pulled a UK bovine-human vaccine candidate because of a single case of intussusception in a five-month-old infant.

“The bottom line to me is that all of these vaccines can be associated with individual cases, in the older infants at least, with intussusception,” he said.

The key, he said, is to avoid the mistakes of the RotaShield experience by initiating vaccination before a child is 90 days old.
Rotarix and the Key Challenges of Rotavirus Immunization

For Norman Begg, vice president of clinical development of pediatric vaccines at GSK—manufacturer of the Rotarix vaccine—the withdrawal of the Rotashield vaccine made it clear there were five key challenges for any new rotavirus vaccine.

1. A vaccine must not cause an increased risk of intussusception compared to placebo.

2. It should provide broad protection against new and emerging rotavirus strains and must cover the existing geographic variation in rotavirus strains.

3. It should protect children against rotavirus infection from infancy up to at least two years of age.

4. It should not interfere with other vaccines so that it is easy to include in national immunization schedules.

5. It must be effective in developing countries as well as developed countries.

“The first decision for GSK and for other manufacturers is which strain to use, and at GSK we took the decision to go forward with the development of a human strain,” Begg said. The rationale for using a human strain rested on studies from 1991, 1996 and 2000, he said, showing that natural rotavirus infections confer immunity against all strains of rotavirus. One infection is 87 percent effective against moderate to severe diarrhea and two previous infections confer 100 percent protection.

GSK developed a monovalent vaccine based on G1P[8], the most common circulating rotavirus strain. The vaccine is freeze-dried and diluted before oral administration. It requires only two doses, Begg said, the first as early as six weeks, but not later than 90 days. The second dose can be given from four weeks after the first dose up to 26 weeks of age.

FIGURE 5

Rational for Vaccination with Human RV Strain

Natural RV infection attenuates severity of subsequent infections, regardless of serotype1-3

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From Norman Begg, GlaxoSmithKline Biologicals

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Two pivotal studies, by Guillermo Ruiz-Palacios in Latin America and Timo Vesikari in Europe assessed the safety and efficacy of Rotarix.

**CHALLENGE 1: No intussusception**
The Latin American study included 63,000 subjects. Intussusception was assessed during two risk periods: the first month after a dose and the first three months after a dose. In the first risk period, six vaccinated children suffered from intussusception, but there were seven cases in the placebo group.

“So there was no evidence of an increased risk based on that evaluation period,” Begg said. “And if you look further out, up to 100 days, it starts to look a little bit imbalanced in favor of the vaccine. There were 16 cases in the placebo group compared to 9 in the vaccine group. I think what you certainly can conclude is that there is no increased risk of intussusception compared to placebo.”

Similar data show that Merck’s RotaTeq is equally safe, when the first dose is given at under 90 days.

**CHALLENGE 2: Broad protection**
The same two studies both showed broad protection against the five major rotavirus strains, most importantly, the G9 strain, which is emerging in several countries.

“The overall efficacy rates were higher in Europe compared to Latin America, and I think this reflects the fact that the European study was done in highly developed countries while in Latin America, they were middle to low income countries,” Begg said.

**CHALLENGE 3: Protection over time**
The studies showed that Rotarix protected children well against severe rotavirus diarrhea throughout the first two years of life. “There is no significant decline in efficacy against severe and hospitalized rotavirus diarrhea over the two year period,” Begg said.

Furthermore, the vaccine proved about 40 percent effective against severe gastroenteritis from all causes.

“This shows you that considering the fairly broad range of organisms that cause diarrhea, you can nonethe-

**CHALLENGE 4: Co-administration with other vaccines**
“We have done studies with all the commonly used vaccines globally,” Begg said. “And in all those studies, high responses of rotavirus Rotarix were maintained, and no impairment of immune responses was observed to any of the co-administered vaccine antigens.”

In a separate Latin American study, 6 to 12-week-old infants were given Rotarix or a placebo along with oral poliovirus vaccine (OPV). Rotarix maintained both its immunogenicity and effectiveness in this study as well. (This study was presented at the 13th International Congress of Infectious Diseases June 19-22, 2008, Kuala Lumpur, Malaysia.)

Begg contends that because of the flexibility of dose timing with Rotarix, it can be included in any of the common schedules, the Expanded Program of Immunization (EPI), with the classical European and US schedules and with the Scandinavian schedule. “So the vaccine could be implemented in pretty much any immunization schedule without scheduling additional visits,” he said.

**CHALLENGE 5: Efficacy in low-income countries**
The study in Latin America referred to above showed Rotarix to be effective in 11 countries, Begg said. Ongoing studies, including the Rotarix/OPV study in Latin America, and a study in South Asia also show high efficacy, in the 80-100 percent range, he said.

“With the completion of that study in South Africa,” Begg asserts that GSK will “have demonstrated efficacy of the vaccine in all regions of the world.”

“There is no significant decline in efficacy (of Rotarix) against severe and hospitalized rotavirus diarrhea over the two year period.”

Norman Begg, GlaxoSmithKline Biologicals, Belgium
**RotaTeq: A Pentavalent Approach to Rotavirus Immunization**

Max Ciarlet, director of the Clinical Rotavirus Vaccine Program at Merck, explained that Merck developed its oral rotavirus vaccine, RotaTeq, as a pentavalent vaccine containing five human-bovine reassortant rotavirus strains to induce direct protection against the most common human rotavirus serotypes.

He noted that because of the lower replication capability of RotaTeq, it requires three doses to build high and consistent immune responses, with the first dose at 6-12 weeks and two subsequent doses at 1-2 month intervals. This schedule integrates easily into pre-established immunization schedules.

Studies indicate that, like Rotarix, RotaTeq does not interfere with or lose potency from other common childhood vaccines. Three phase III studies have provided data on safety and efficacy of RotaTeq. Protocol 006, also known as the Rotavirus Efficacy and Safety Trial (REST), was the pivotal large-scale study. It took place in 11 countries on three continents from 2001-2005. REST was published in 2006. More than 71,000 children were enrolled in all three studies.

"One thing that was really striking, whether we look at the results from the phase II trials or the phase III trials, we see that RotaTeq provides consistent high protection against severe rotavirus gastroenteritis and gastroenteritis of any severity," Ciarlet said. Efficacy ranged from 98 percent to 100 percent for severe rotavirus gastroenteritis, and almost 75 percent for any rotavirus gastroenteritis, he said.

Since REST was so large, the trial also assessed hospitalizations, emergency room visits and doctor's office visits. Ciarlet said the evidence indicates that RotaTeq reduces hospitalizations and ER visits by 95 percent and office visits by 86 percent.

RotaTeq is also effective against a broad range of rotavirus strains, including those that belong to serotype G9, he said.

"The efficacy, when we go to serotype-specific data, is very consistent and is very high," Ciarlet said.

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**FIGURE 6**

- **Phase III Studies: Protocol 006 (Rotavirus Efficacy and Safety Trial [REST]), Protocol 007, and Protocol 009**
  - Multi-centre, 11 countries on 3 continents, from 2001 to 2005
  - Randomised, double-blind study: RotaTeq® versus placebo controlled
  - Age at enrolment: 6 to 12 weeks of age, 3 oral doses provided every 4–10 weeks

![World Map showing countries involved in the study](image)

- **71,799 Subjects Vaccinated**
  - 36,203 in RotaTeq® Group
  - 35,596 in Placebo Group

- **REST Subjects Lost to Follow-Up:** 81 (0.2%) V: 97 (0.3%) P

From Max Ciarlet, Merck Vaccines, US
Furthermore, he noted that the vaccine reduced health care resource utilization for gastroenteritis of any kind by 59 percent.

At both 42 days and one year from the first dose, numbers of intussusception cases were similar in the vaccine group and the placebo group. A similar profile emerged for serious events, including deaths. “The most common cause of death was SIDS,” Ciarlet said, “and the number of subjects that were discontinued due to a serious adverse event was equal between the two groups.”

Ciarlet also stated that neither breastfeeding nor prematurity (gestation equal to or less than 36 weeks) appeared to have any effect on vaccine efficacy or safety.

Ciarlet said the trials were not designed to evaluate vaccine efficacy for fewer than the recommended three doses, and the numbers of children who got only dose one or two doses were too small for statistical significance. But he said that among children who got all three doses, RotaTeq appeared to confer protection between doses: 100 percent between dose one and dose two and 91 percent between dose two and dose three.

In Finland, Timo Vesikari followed up approximately 21,000 trial participants for efficacy, as measured in rate reduction of hospitalizations and ER visits emergency visits due to rotavirus gastroenteritis, up to the age of three and a half. These results, which showed high and consistent efficacy of the vaccine for up to 3 years postvaccination, were to be presented at the 13th International Congress of Infectious Diseases. In addition, large-scale safety surveillance studies continue. The US Vaccine Adverse Event Reporting System collects information on possible side effects. In addition, Merck has its own ongoing Phase IV safety study of intussusception, which will enrolled more than 44,000 subjects. And there are trials being conducted in Bangladesh, Ghana, Kenya, Mali, and Vietnam that are expected to generate data on safety, immunogenicity, and efficacy of RotaTeq in the regions of Sub-Saharan Africa and South East Asia. In addition, a surveillance and effectiveness study is ongoing in Nicaragua.

“We have almost 13 million doses distributed, and monitoring is ongoing,” Ciarlet said. Finally, a phase I safety and immunogenicity study of HIV-positive infants in Tanzania and Zambia is about to start in early 2009.

“We will soon show that the vaccine is efficacious up to three years post vaccination, and Merck is working with partners to make RotaTeq available to those countries that actually need it the most,” Ciarlet said.

There was a question about whether RotaTeq and Rotarix can be used interchangeably, with, for example, a first dose utilizing Rotarix and the second RotaTeq. However, experts at the symposium said there is no data on interchangeability of the vaccines, so this practice cannot be recommended at this time.

World Health Organization Policies on Rotavirus Vaccines

The World Health Organization (WHO) Strategic Advisory Group of Experts or SAGE has recommended a phased introduction of rotavirus vaccine in areas where Phase III trials have been completed, said the WHO’s Cristiana Toscano. She said SAGE also stresses the importance of post-marketing surveillance and communication strategies.

WHO recommends the inclusion of rotavirus vaccination into national immunization programs, but, again, only in regions where efficacy trials have been completed and, also, where infrastructure and financing are in place. Vaccine efficacy has been
demonstrated in the US, Europe and Latin America, but new studies are expected to be completed shortly. “In 2007, WHO was not prepared to recommend global inclusion of rotavirus vaccines into national immunization programs,” Toscano said. “Rather we’re suggesting a phased introduction.”

Based on a review of data on RotaShield, she said WHO has recommended that the first dose of rotavirus vaccine should not be given after 12 weeks of age. Toscano said WHO advises against using rotavirus vaccines in catch-up programs because of the danger that the first dose may mistakenly be given to children older than 12 weeks of age. The entire rotavirus immunization series should be completed by 24 weeks for Rotarix and 32 weeks for RotaTeq. This recommendation arises from the lack of safety data for older children.

Duncan Steele, PATH’s Senior Advisor on diarrheal disease, noted that, due to the lack of evidence from clinical trials, SAGE has not recommended the use of rotavirus vaccines in the regions of the world with the highest mortality from rotaviruses, which are low-income countries. Thus, the GAVI Alliance, an international coalition of public and private partners (formerly known as the Global Alliance for Vaccines and Immunization) that subsidizes vaccine purchases for the world’s poorest countries, has yet to provide support for rotavirus vaccines.

“Where the majority of the disease and mortalities are associated, those countries are not yet in a position to apply for these vaccines,” Steele said. But if studies now underway in the developing world show that the rotavirus vaccines would have even “moderate efficacy,” Steele said they are likely have an dramatic impact on lives saved and to be “cost saving.”

He said that phase III efficacy trials are currently being conducted under a collaboration between the Rotavirus Vaccine Program at PATH (which is a partnership including WHO, and the US CDC), and with both Merck and GSK Bio rotavirus vaccines.

There was a question about the ethics of conducting rotavirus vaccine trials in low-income countries. Steele noted that studies must be done in the populations that need the vaccines and that extrapolating results from trials conducted elsewhere would not be sufficient. He noted that vaccine manufacturers, WHO and PATH follow high ethical standards and all studies are reviewed by local ethics boards and conducted according to Good Clinical Practice.

**Vaccine Concerns: Interactions and Disease Transmission**

There was some discussion about whether rotavirus vaccination would have any effect on the oral polio vaccine (OPV). Max Ciarlet responded that while no efficacy studies have been undertaken, OPV antigen titers were normal when the vaccine was administered along with RotaTeq. Merck recommends that RotaTeq

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**FIGURE 7. When will we know whether rotavirus vaccines will benefit children in Africa and Asia?**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Region</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK Vaccine, Rotarix® (Human, Monovalent)</td>
<td>Asia</td>
<td></td>
<td>Bangladesh effectiveness study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Africa</td>
<td>South Africa</td>
<td>Malawi &amp; South Africa</td>
<td>Malawi &amp; South Africa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interim Analysis</td>
<td>Final Analysis</td>
<td>Extended Follow-up Analysis</td>
</tr>
<tr>
<td>Merck Vaccine, RotaTeq® (Bovine, Reassortant, Multivalent)</td>
<td>Asia</td>
<td>Bangladesh &amp; Vietnam</td>
<td>Final Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Africa</td>
<td>Ghana, Kenya, &amp; Mali</td>
<td>Final Analysis</td>
<td></td>
</tr>
</tbody>
</table>

From Duncan Steele, PATH
“In 2007, WHO was not prepared to recommend global inclusion of rotavirus vaccines into national immunization programs. Rather we’re suggesting a phased introduction.”

Cristiana Toscano, World Health Organization

SIDEBAR
Interim Analysis of Vaccine Efficacy in South African Infants

S habir Madhi of South Africa’s University of the Witwatersrand offered an interim analysis of a Rotarix trial in South African infants.

The communities in which the study was performed are burdened with a high prevalence of HIV, 50% of children born are born to mothers with HIV. About 5 to 6% of infants are infected with HIV. And the unemployment rate stands at 40%. In addition, Madhi said, “Only about a third of children actually receive appropriate oral rehydration therapy when having an episode of gastroenteritis.”

The study set out to determine Rotarix efficacy against severe rotavirus gastroenteritis in infants up to one year of age. Rotarix was given according to the routine EPI schedule, which included oral poliovirus vaccine. The study used standard definitions of gastroenteritis and severity of the episodes was assessed by the internationally recognized Vesikari score. The presence of rotavirus was detected by a commercial ELISA assay. The pre-determined interim analysis was performed by an independent data center.

Madhi said the results show that the vaccine efficacy against rotavirus gastroenteritis of any severity was 66.5 percent. Against severe rotavirus gastroenteritis, the vaccine proved 82.7 percent effective according to the interim results.

“The vaccine itself clearly offers a high degree of protection in South African children against severe rotaviral illness during the first year of their life,” Madhi said. “The results I believe are extremely important in terms of informing decision making both in South Africa as well as in other countries in southern Africa.”

In Sub-Saharan Africa, rotavirus accounts for 25 percent of all diarrheal deaths and 25 percent of all hospitalizations for diarrhea, with a clear peak in dry cooler months of autumn and winter.

be administered first if the vaccines are not given together because OPV may replicate for up to 6 weeks.

Norman Begg added “The data show that there is no interference and it's in the label of the vaccine that you can actually co-administer at the same visit.”

Duncan Steele noted that “The WHO position paper clearly says that the vaccines need to be given with OPV. We're not talking about additional EPI visits for a new rotavirus vaccine”

T. Jacob John, with the Indian Academy of Pediatrics, wondered whether children who receive the rotavirus vaccine can transmit the rotavirus through virus “shedding.”

Norman Begg responded that, “As you would expect with a live orally administered vaccine, the vaccine replicates in the gut and there is shedding following vaccination.”

The concern is that if virus shed from a vaccine recipient undergoes a mutation that confers virulence, it may transmit rotavirus disease. “We are actually doing a study at GSK to look at transmission of the known shed virus, so we will have the answer to that question,” Begg said.

Max Ciarlet added that researchers at Merck “have only detected shedding after the first dose. It is usually only one or two days and it only happens in 9 and 12 percent of the subjects.”

Duncan Steele added that the differences between the two vaccines when it comes to shedding virus may reveal differences in the vaccines’ functions, with Rotarix conferring most of its immunity in the first dose, and RotaTeq conferring increasing immunity with each of the three doses.
Regional Perspectives: The WHO European Region

The WHO European region encompasses 53 member countries that include nations in Western and Eastern Europe, former Soviet states and the Russian Federation. It is a very diverse region with a wide range of economic conditions—the GNP in the richest country is 30 times that of its poorest country—to match its geographic expanse. Currently, there are 8 countries eligible for GAVI assistance.

According to the WHO’s Eric Laurent, Rotarix is licensed in 33 countries in the European region and Rotateq in 32. But he said thus far only three countries—Austria, Belgium and Luxemburg—include rotavirus vaccination in their immunization schedule, though Slovakia may soon add it.

Laurent said what is needed now is “further research into the cost-effectiveness of universal rotavirus vaccinations, particularly in low-mortality, high-income settings.” He said there is also a need for more surveillance, particularly in countries where estimates indicate a rotavirus mortality rate of greater than 10 per 10,000.

“We realize that many, many countries do not have strong enough surveillance to make decisions about these new vaccines,” Laurent said.

He said in general, universal rotavirus vaccination should be considered in countries where “more than 20% of the gastrointestinal mortality is due to rotavirus, or where more than 30% of the hospitalizations are due to rotavirus.”

Laurent said countries in the region are “pretty sensitive” about the need to monitor for intussusception as part of vaccine introduction. And, as is the case for introducing any new vaccine, he noted that countries will have to consider the impact of a rotavirus immunization program on cold chain storage capacity.

Regional Perspectives: Latin America and the Caribbean

Lucia De Oliveira, Regional Advisor for New Vaccines at the Pan American Health Organization (PAHO),

FIGURE 8

Countries from Latin American, Caribbean and Mexico Introducing Rotavirus Vaccine into their Routine Schedule

- Mexico: May 2007
- Panama: Mar 2006
  birth cohort of 70,000
- Venezuela: Apr 2006
  birth cohort of 574,000
- ELS: Oct 2006
  birth cohort of 166,000
- Nicaragua: Oct 2006
  birth cohort of 150,000
- Ecuador, Oct 2007
  birth cohort of 294,300
- Peru, Apr 2008
  priority areas
- Brazil: Mar 2006
  birth cohort of 3,330,000

From Lucia De Oliveira, Pan American Health Organization
discussed the progress made and lessons learned in what has been a fairly aggressive introduction of rotavirus vaccination in Latin America and the Caribbean (LAC).

She said the potential benefits from immunization in the region is clear, noting that “rotavirus causes an estimated 1,500 deaths, 7,500 hospitalizations, 2 million clinic visits, and 10 million cases of rotavirus diarrhea annually.”

In 2006, Panama became the first LAC country to adopt rotavirus vaccination and there are now eight countries in the region that have added the vaccine to their EPI schedule. Seven are using Rotarix, she said, and one is using RotaTeq.

“To date, no evidence of an increased risk of intussusception or any other serious adverse events has been suggested,” De Oliveira said.

She added that PAHO is seeking additional information on risks of intussusception through a collaborative study with Brazil and Mexico (conducted with support from US CDC, the US Food and Drug Administration (FDA) and PATH). The results may be ready at the end of 2009.

She said challenges to rotavirus immunization in the region have involved both supply and cost concerns. She said some countries ran out of vaccine “soon after introduction.” In addition, the vaccine costs countries $7.50 per dose if it is obtained through the PAHO Revolving Fund for Vaccine Procurement, which helps Latin American countries reduce immunizations expenses by negotiating bulk purchases from manufacturers. But De Oliveira said at that price, the rotavirus vaccine accounts for about 97% of the cost of a country’s basic immunization schedule.

“Even though all Latin American countries using the vaccine have a budget line for vaccine purchase, insufficient funds continue to pose constraints for some countries,” De Oliveira said.

Regional Perspectives: Impact and Cost-Effectiveness in Central Asia

Elmira Flem of the Norwegian Institute of Public Health presented a case study that looked at the economic impact of rotavirus and the cost-effectiveness of rotavirus vaccination in the Central Asian countries of Uzbekistan and Kyrgyzstan.

Economic evaluations of rotavirus vaccination programs have been done in most industrialized countries, Flem said, whereas very few studies have been done in settings with low resources.

In general, immunizations in Uzbekistan and Kyrgyzstan are free and both republics have an effective immunization system with routine coverage of vaccines that are part of the Expanded Program on Immunizations of above 90 percent. In 2003, Uzbekistan and Kyrgyzstan became the first GAVI countries in the WHO European region to initiate hospital-based surveillance of rotavirus.

Flem said she and her colleagues were interested in estimating the costs of rotavirus disease to the health care system and nation and the cost-effectiveness of routine rotavirus vaccination as a way to help policymakers to decide if new rotavirus vaccines should be used in national immunization programs.

For each country, they identified a sample of children under five-years old who had been hospitalized with acute diarrhea and collected information on healthcare and family costs associated with the illness.

“To estimate the rotavirus burden,” Flem said, “we used the country-specific data from the hospital surveillance to decide which fraction of diarrhea hospitalizations was in fact caused by rotavirus, and that is 30 percent in Uzbekistan and 26 percent in Kyrgyzstan.”

The average total cost per child was estimated to be around $94 in Uzbekistan, and $87 in Kyrgyzstan.
Julie Bines with the University of Melbourne looked specifically at the need for post-vaccination monitoring of intussusception. Why do we need to monitor for intussusception after vaccine introduction when risks have been assessed in clinical trials? Bines said the reason is that clinical trials adhere to strict protocols, while in the broader world, administration schedules can differ, different drugs or vaccines might be administered alongside the rotavirus immunization, and there could be a wide variety of pre-existing illnesses present in vaccine recipients.

The overall incidence of intussusception varies from country to country, she said, which could be due to variety of factors, including differences in genetics, cultures, exposures to infections, environmental conditions, therapeutic practices, diagnostic methods, and access to health care.

“Whether this will influence the safety of vaccines when they’re implemented in countries with varying incidence of intussusception, we don’t yet know,” Bines said. One problem, she said, is that the precise causes of intussusception are not well understood.

Also, while intussusception is rare in babies under three months—which is why there is a recommendations to administer rotavirus vaccine during that time period—it’s severity may be higher at that age.

“So maybe intussusception, although uncommon, has a greater impact in the very young children, and we need to be aware of that,” Bines said.
Based on current levels of immunization coverage in the countries and an estimated vaccine efficacy of 85 percent, the rotavirus vaccination was projected to prevent 5,296 hospitalization and 463 rotavirus deaths per year in Uzbekistan with a projected saving of nearly US $500,000. The figures for Kyrgyzstan came to more than 3,000 hospitalizations and 128 death averted per year, and a savings of more than US $265,106.

Considering GAVI financial help is available to both countries, Flem said the rotavirus vaccine program would meet World Bank standards for highly cost-effective interventions in both countries.

"Vaccination could be cost-effective in economic terms, and it could reduce the disease outcomes, but the ability of the country to introduce the vaccine will be highly dependent on the affordability of the vaccine," Flem said.

Vaccine Monitoring Post-Introduction

Several speakers emphasized the importance of monitoring the impact of a rotavirus vaccination program after introduction.

Manish Patel, a medical officer at the US CDC discussed how the agency worked with WHO and individual researchers to assemble a standard approach to post-introduction monitoring. The monitoring had three objectives: to monitor disease trends, to assess vaccine effectiveness and to monitor rotavirus strains.

For any vaccine Patel said, researchers ask two questions: "Is the vaccine program modifying disease like it's intended to do, and can you quantify the impact of the program?"

"The season after rotavirus introduction, you may notice an impact in the two to six-month age group," he said. "In the second season you might notice impact among less than 1-year old, perhaps less than 2-year olds. And in the third season, you should definitely see an impact in the less than 2-year old age group if the vaccine is performing as well as it's intended to perform. In regions where the disease is obviously seasonal, you should see a blunting of the winter peaks."

Data to evaluate vaccine program performance comes from several sources. Standard WHO active surveillance involves sentinel hospitals where investigators monitor all children less than five who come into the hospital setting, testing for rotavirus disease. Other sources include clinics, passive lab surveillance and mortality data.

Patel cited data from Nicaragua (which uses RotaTeq) showing some of the predicted blunting of rotavirus peaks after vaccine introduction. Data from El Salvador (Rotarix) indicated a drop in incidence of rotavirus disease in the first season after vaccine introduction, but a more marked reduction in the second season.

Assessing the impact of vaccination on rotavirus strains is a hot topic, Patel said. While some data do show a change in the mixture of rotavirus strains after vaccine introduction, it's not clear if the vaccination program is the cause.
The Importance of Global Surveillance

Marc-Alain Widdowson with the Division of Viral Diseases at the US CDC discussed the importance of having a global network focused on conducting surveillance of rotavirus disease.

“The important thing about having a network of sites is you standardize data collection, you can compare and contrast and combine data and you have a much stronger voice in terms of advocacy,” he said.

Widdowson said there are now >50 countries who are either conducting “rotavirus surveillance or have done rotavirus surveillance in the past.” They are working within five different networks, one in the Americas (coordinated through PAHO), one in Africa (the WHO AFRO network), one in the Eastern Mediterranean (the WHO EMRO network), one in Southeast Asia and Western Pacific regions (WHO SEARO/WPRO network) and one in the Europe (the WHO EURO network).

Global surveillance uses the WHO generic protocol for hospital-based data collection. The same protocol is used in, for example, the Asian Network, with 19 countries, and the African network with 10 countries. Data are published in traditional journals as well as on the CDC web site.

“We’ve got a couple other supplements in the works now trying to get much of this surveillance data out in the open,” Widdowson said.

He noted that the data derived from this network routinely provides valuable insights into the nature of the disease in different regions. For example, he said that the surveillance has revealed that children in poorer countries get rotavirus infections earlier than children in wealthier countries. Widdowson said the surveillance also has detected a change in strain diversity in Korea where there was a “quite rapid rise in G3 genotypes over one year.”

He said the regular flow of illuminating information is key to “keeping people motivated and interested” and fighting what he called “surveillance fatigue.”

Widdowson also noted how the data can point to the limits of hospital-based surveillance to actually capturing the true burden of disease in a country or region. For example, in rural Kenya between 2005 and 2006, 22% of children admitted to the hospital had rotavirus. However, because they receive rehydration therapy, only 2% of hospital deaths are in children who are “rotavirus positive.”

“Most of the deaths from rotavirus are not occurring in the hospital and this is a real challenge for hospital-based surveillance,” he said.

Estimating Deaths from Rotavirus

According to Tony Burton of the WHO, WHO has issued an estimate which asserts that in 2004, 527,000 children under five died of rotavirus disease. Deaths were found to be highest in Africa, India, and South Asia. The estimate relied on a model starting with all deaths of children under five, and then factoring in first:

- the percent of deaths caused by diarrhea and then,
- the percent of diarrhea deaths believed to be due to rotavirus.

Several issues may influence the accuracy of the estimate. According to Burton, there are those who...
could argue that the estimate is too low because laboratories may be missing about 30% of all infections while there were elements of the study design—such as the decision to collect data during a period when there was a high rate of diarrhea caused by something other than rotavirus—that could mask the actual percentage of rotavirus-induced mortality.

Meanwhile, he showed that one might also argue the opposite, that the estimate was too high, because it was conducted in the winter, when rotavirus levels are elevated, and that the study population was not a representative sample of a whole country.

The next challenge, according to Burton’s presentation, is to develop a model for assessing the impact of vaccination.

Surveillance in the WHO EURO and EMRO Networks

David Mercer, with the WHO Regional Office for Europe, said WHO plans to support rotavirus surveillance, integrating the WHO generic protocol into existing surveillance, with top priority given to GAVI-eligible countries. The most important data to be collected, he said, includes disease burden, strain prevalence, and public and health-care worker awareness of rotavirus disease. Finally, the laboratory component of surveillance must be strengthened, with the applications of both internal and external quality controls.

Nadia Teleb with the WHO Rotavirus Surveillance Network in the Eastern Mediterranean Region (WHO/EMRO), presented data showing that diarrhea diseases, including rotavirus, cause almost two-thirds of hospitalizations due to acute gastroenteritis in the Eastern Mediterranean Region.

All children under five-years-old in the region who are hospitalized at a sentinel hospital for treatment of suspected rotavirus gastroenteritis are enrolled in the surveillance system, she said. An enzyme immunoassay (EIA) of stool is used to prove the presence of rotavirus and genotyping of subset of the positive specimens are systematically performed.

In addition to availing local data on disease burden and genotype prevalence, the main strength of this

**FIGURE 10**

Rotavirus Mortality Rate per 100,000 Population Less than 5 Years of Age: 2004

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2008. All rights reserved.
surveillance network, Teleb said, is building the network as part of national programmes which ensures national ownership of data and, hence, using the data by the Ministries of Health, for decision making on rotavirus vaccine introduction.

But as has been noted elsewhere, Teleb said that the influence of hospital surveillance on government policy in some countries is complicated by the fact that deaths from rotavirus in hospitals “is almost nil,” even in “very high burden countries.”

“We need stronger advocacy in order to convince some decision makers that these mortality results from hospitals do not mean that there is no mortality from rotavirus diseases,” Teleb said.

“We need stronger advocacy in order to convince some decision makers that these mortality results from hospitals do not mean that there is no mortality from rotavirus diseases,” Teleb said.

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SIDEBAR

On the Lookout for Rotavirus Mutations

Jim Gray, who works with EuroRotaNet Strain Surveillance at the UK Centre for Infections, is interested not just in documenting circulating rotavirus strains before and after vaccination but also in detecting newly emerging strains.

These strains may result from an accumulation of mutations, he said, and can occur in such a way as to prevent the binding of the antibody stimulated by the vaccine. This is not just a theoretical concern, he said, but has been documented, for example in a strain in Taiwan in the 1990s that underwent such a mutation and then circulated around the world.

“The rate of mutation with the rotavirus gene is relatively high because the RNA replication is error-prone,” Gray said.

Another potential genetic event to monitor, he said, is antigenic shift, which can occur when a single human cell is infected by more than one rotavirus strain.

“These reassortments of human strains, although they’re interesting, are unlikely to have any major public health importance because they’re carrying antigens that are already circulating in the human population,” Gray said. But dual infections can also occur with animal and human strains.

“Animal strains replicate very poorly in the human host and they transmit very rarely between humans,” Gray said, but added that the potential exists for a mixed infection to create a new, virulent strain, with the replicative advantage of the human strain and the novel antigens of the animal strain.

Yet strain diversity does not by itself bode ill for rotavirus vaccines, he said. In practice, the vaccines spur an immune response against many strains, including potential reassortants.

Meanwhile, Gray is looking beyond childhood infections to study rotavirus infections in adults as a way to develop a more detailed understanding of the disease.

“Because we don’t restrict our database to 5-year-old or under, we’re seeing the interesting phenomenon here of adults having a symptomatic rotavirus infection, probably parents being infected by their children and grandparents by their grandchildren,” he said. “So we’re beginning to see the whole picture of the epidemiology of rotavirus and the multiple times that we get infected and disease throughout life.”
SESSION IV

Early Experience with Routine Use of Rotavirus Vaccines

United States: “A Steady, Progressive Climb”

Umesh Parashar with the US CDC discussed his country’s experience with rotavirus vaccination. As of 2008, RotaTeq had been available for about two years. Rotarix was licensed in 2008 and was under consideration for wider use in childhood immunization programs.

At the time of the conference, US health officials were still collecting comprehensive data on rotavirus vaccine adoption, but preliminary information was available through CDC’s Immunization Information Systems (IIS), which monitors vaccine administration at six Sentinel sites nationally. According to IIS, through 2007, about 60 percent children 3 months old at the sentinel sites were getting the vaccines, Parashar said.

“It’s been a steady progressive climb, but we are still not where we would like to be,” Parashar said.

Thus far, Parashar said that according to information gathered by CDC’s Vaccine Adverse Events Reporting System (VAERS), along with a study by Merck, there have been 226 cases of intussusception since the vaccine was introduced. Of those, 65 have occurred after the first dose, 100 after the second, and 61 after the third.

Parashar said that when one compares the reports of intussusception involving RotaTeq to the earlier vaccine, RotaShield, key differences emerged. First, “almost all of the cases” with RotaShield occurred “immediately after vaccination,” he said, while reports associated with RotaTeq were “much more spread out and you have quite a few reports occurring further out from vaccination.”

“This really gives us confidence that you’re not talking about a risk anywhere like what was seen with RotaShield vaccine,” Parashar said.

In addition, an analysis conducted with data from the Vaccine Safety Datalink (VSD), which studied 165,000 vaccinations administered in a managed care setting, documented five reports of intussusception, which was

FIGURE 11

First dose rotavirus vaccination coverage among children aged 3 months in IIS Sentinel Sites, by quarter and site

From Umesh Parashar Centers for Disease Control and Prevention
There are remarkable changes, which we see from each of these systems showing substantial declines (post-immunization) in rotavirus this year.

Umesh Parashar, Centers for Disease Control and Prevention, US

slightly less than what was expected. An analysis of 130,000 first doses found no reports of intussusception were in the first week of vaccination, Parashar said.

In terms of the effect on the burden of disease, Parashar said that in 2008, surveillance systems showed a marked reduction in severe diarrhea from all causes, and almost no rotavirus diarrhea.

“So there are remarkable changes, which we see from each of these systems showing substantial declines in rotavirus this year.” Parashar said. “I think we feel confident saying that the changes are unlike what we have seen in all the data we have from before and the trends are beyond natural variation.”

A study of the attitudes toward rotavirus vaccines among physicians across the country showed pediatricians to be very aware of rotavirus disease and to support vaccination. Family physicians, however, were significantly less likely to promote rotavirus vaccination.

“Family medicine physicians deal with patients across all ages, so they have to digest many recommendations for many, many interventions and generally their uptake of vaccines are slower than pediatricians,” Parashar said.

Nicaragua: Responding to an Epidemic with a Vaccine

Nicaragua, with 140,000 births per year and a per capita annual income of less than $1,000, is divided between the well-developed Pacific side and the underdeveloped Atlantic side.

After cholera was eliminated in 2000, Nicaragua began to track rotavirus disease, which shows the seasonality seen elsewhere in the world. In Nicaragua, rotavirus peaks from January to April, during dry season.

According to Juan Jose Amador with PATH, RotaTeq was introduced in Nicaragua in October 2006 in the wake of a rotavirus epidemic that hit the country the previous year. As in the US only a slight drop in rotavirus deaths occurred in 2007. But the proportion of rotavirus-positive tests was significantly lower in May to November of 2007 than in the previous three months.

From 2007 to early 2008, about 86 percent of children under one year of age were getting the first dose of the vaccine. At the same time, deaths in that age group from acute diarrheal diseases appear to be going down, dropping from 97.5 per 10,000 in 2000 to 2005 to 77.9 in 2007, a 20% reduction.

Amador said the vaccine has been well accepted by the medical and scientific community in Nicaragua and has exhibited a good “safety profile and minimal secondary effects.”

European Union: Considering Disease Burden and Vaccine Costs

According to Pierre Van Damme with the Center for the Evaluation of Vaccination at Belgium’s University of Antwerp, as of March 2007, five EU countries had made a decision regarding rotavirus vaccination.

He said Belgium and Luxemburg will integrate rotavirus vaccine into the national immunization schedule at low net cost to families, with a more than 80% reimbursement by National Health Insurance. Austria will integrate the vaccine, but has not decided on cost. Germany and France will not integrate the vaccine. Issues driving country considerations include overall rotavirus burden and an economic assessment of the rotavirus vaccination program.

Scientific societies in Germany, France, Spain, Italy and Belgium have moved forward with recommendations to introduce rotavirus vaccines.

“Despite similar burden of disease, countries differ in their attitude towards rotavirus vaccine introduction,” Van Damme said. “We know there is a lack of awareness of potential disease severity and overall burden of disease in many countries.” Furthermore, he said countries are realizing that the overall burden of rotavirus disease must be considered, not just mortality.

Van Damme said the official recommendation for the use of the current vaccine remains: “two doses for one vaccine, three doses for the other vaccine.”
Engaging the Public

According to Lulu Bravo, an infectious disease expert at the University of the Philippines, "for many countries of both the developed and developing world, a vaccine will be the most cost-effective way to stop rotavirus."

Advocacy and elevating public awareness are seen as key elements to encouraging widespread adoption of rotavirus vaccines, particularly in countries with limited resources. Bravo described how health authorities in her country engaged in a multifaceted effort to educate the public about the dangers posed by rotavirus and the benefits of prevention.

Rotavirus has been a known problem in the Philippines for 25 years, affecting children under five, and especially from six to eleven months. In 2007 rotavirus caused 38% of hospitalizations for diarrhea in the Philippines.

In 2000, the Philippine Foundation for Vaccination was launched, the first organization of its kind in Asia, aiming to reduce childhood morbidity and mortality.

In 2005, Bravo said a group of gastroenterologists, infectious disease physicians, pediatricians and epidemiologists formed ROTAPhil to improve communication about rotavirus disease in the Philippines. ROTAPhil organized a program consisting of pamphlets, media ads, press kits, “meet-the-expert” booths at conventions and other communication strategies.

“Most of all I think we had to partner with media,” Bravo said.

ROTAPhil also partnered with physicians’ societies to educate physicians about the burden of rotavirus infections. Family physicians were another target of rotavirus education.

“We have heard lots of reasons in the last two days to support rotavirus vaccination, but the best reason of all is to say that every child has the right to good health,” Bravo said.

Confronting the Costs of Rotavirus Vaccines

Deborah Atherly, a health economist with the PATH Rotavirus program, focused on cost concerns and financing strategies for deploying rotavirus immunizations where they are needed most.

PATH has completed and submitted for publication an analysis on the cost-effectiveness and impact of introducing rotavirus vaccines in all GAVI-eligible countries.

Mathuram Santosham of the Johns Hopkins Bloomberg School of Public Health said researchers need to understand that many of the people in a position to make a decision about rotavirus vaccination know very little about the disease.

“I want to point out that for a decision maker, rotavirus means very little,” Santosham said. “If you can go to a decision maker and say I can reduce your diarrhea mortality, that means something.”

Researchers also must focus on the things most important to Ministers of Health: how much the vaccine is going to cost and how many lives will it save.

Clear WHO recommendations are also important, Santosham said.

“If we go out and give ambiguous messages to countries we will never get these vaccines into countries,” he said.

In addition, Santosham said it is important to acknowledge how immunizations are delivered in real world settings. For example, he said it is likely that in some countries, rotavirus vaccines would be administered outside the ideal time-frame for minimizing risk of intussusception.

Overall, he said the process for encouraging adoption of rotavirus vaccines must “include all stakeholders (and) be aware that research without appropriate inclusion of stakeholders may delay introduction.”

“We have heard lots of reasons in the last two days to support rotavirus vaccination, but the best reason of all is to say that every child has the right to good health.”

Lulu Bravo, University of the Philippines, Philippines
countries, which collectively represent nearly 85% of the rotavirus mortality burden. Atherly views the analysis as providing a platform for discussion of market issues: supply, demand and affordability.

She said it will be the first vaccine analysis to combine a cost-effectiveness assessment with demand forecasting and price assumptions to estimate both cost-effectiveness and impact over time.

The PATH model shows rotavirus vaccine prices dropping (they are currently about US $7 per dose) as new manufacturers enter the market around 2012. By 2020, the model predicts, rotavirus vaccine will reach a stable $1.25 per dose. And as costs drop, the study predicts the number of children vaccinated per year will rise, reaching some 60 million children in 72 countries by 2025.

"Under a range of assumptions, we can consider the vaccine cost-effective, especially in the low income setting, and it has a potential to avert over 225,000 deaths per year by 2020 or 2 million deaths over time," Atherly said. "As suppliers increase [around 2012], you actually start to create more of a robust market, or supply side market for vaccines”

Atherly said the analysis reveals that as prices go down, the vaccine becomes more cost-effective. Economists analyze the cost-effectiveness of vaccines or other health interventions by looking at what they call “disability adjusted life years or DALYS.” Essentially, a DALY measures a year of life lost to either death or disability caused by a particular disease of condition. Atherly said for rotavirus vaccination, the cost per DALY saved could fall from nearly $450 in 2008 to below $50 around 2020.

“As the countries with high mortality rates come on board, those cost-effectiveness ratios obviously improve quite dramatically,” she said.

While the study took the perspective of GAVI as the key donor, Atherly said, “I think we can also look at this from a more generic donor perspective, that is, GAVI may not be here forever, and we need to look at other possibilities for funding and funding resources for rotavirus beyond say 2015.”
Future issues and challenges for rotavirus vaccination include evolving needs for disease surveillance and the likelihood that new vaccines will be arriving on the market.

PATH’s Duncan Steele said that as routine surveillance demands are shifted to countries and ministries of health, there will be a need for enhanced surveillance in sentinel sites, with particular emphasis on the analysis of strain diversity.

“The research studies that we are doing at the moment, which are going to generate really important information for Africa and Asia, are, in some ways, only the tip of the iceberg of what is coming,” Steele said.

Also, the WHO Strategic Advisory Group of Experts has recommended conducting post-marketing surveillance of vaccine impact and safety. These studies are especially important, Steele said, in developing countries.

“We are not going to see clean data like [the preliminary results from the US] in developing countries, because they don’t have the same reporting systems and surveillance systems,” he said.

Meanwhile, as demand rises there are expectations that new rotavirus vaccine candidates will be coming from manufacturers in Brazil, China, India, Australia and Indonesia.

Steele noted that “[GSK and Merck] are not capable of supplying the numbers of doses, the millions of doses that will be needed once countries in the poorer resource areas start to introduce rotavirus vaccine.”

Recommendations emerging from a WHO meeting that focused on vaccine candidates now in the product pipeline cited the need for internationally standardized quality assurance programs for the safety, the production and the conduct of efficacy trials of live attenuated vaccines, and also called for the continued development of non-living, inactivated rotavirus vaccines. Several approaches to non-living rotavirus vaccines are now under consideration by research groups in the US and Japan, amongst others.

Also, Steele said PATH’s Advancing Rotavirus Vaccine Development initiative is working with manufacturers in India and China throughout the full vaccine development cycle, to ensure that these international acceptable standards are achieved.

The challenges rotavirus vaccines present to the health care and immunization infrastructure systems are also a key concern, he said. For example, the vaccines now available will challenge each country’s system of refrigerated storage—known as “cold chain.” Steele said the Rotarix vaccine and associated supplies require

FIGURE 12. Other Candidate Live Oral Rotavirus Vaccines

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>NAME</th>
<th>COMPANY</th>
<th>STRAIN(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Bovine-human reassortant rotavirus</td>
<td>UK</td>
<td>Butantan, Brazil</td>
<td>Bovine (G6) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wuhan &amp; Chengdu, China</td>
<td>G1,G2,G3,G4,P[8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SSI, Shanta, Biologicals E, Bharat, India</td>
<td>+ designer reassortants</td>
</tr>
<tr>
<td>Australian neonatal rotavirus</td>
<td>RV3</td>
<td>M CRI / Biofarma , Australia / Indonesia</td>
<td>G3, P[6]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bharat Biotech Ltd, India</td>
<td></td>
</tr>
<tr>
<td>Rhesus-human tetravalent rotavirus</td>
<td>RRV-TV</td>
<td>BIOVIRx / USA (IM F) US IDT / Germany</td>
<td>Rhesus (G3) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VP7 (G1,G2,G4)</td>
</tr>
<tr>
<td>Lamb rotavirus — lamb human reassortant vaccine</td>
<td>LLR LLR+</td>
<td>Lanzhou Biologicals / Xinkexian Biological Technology, China</td>
<td>G10,P[12] + G1,G2,G3,G4</td>
</tr>
</tbody>
</table>
more storage space than do the traditional childhood vaccines including DPT, polio or measles vaccines. In particular, he pointed out that the current formulation of Rotarix immunizations, with the buffer and connector - take up to ten times as much space in a refrigerator as the vaccine itself.

“There has to be an effort in formulation and in repackaging these vaccines if we want to roll them out into huge countries in Africa or Asia,” Steele said.

Immunization Access and the Role of the GAVI Alliance

Ranjana Kumar of the GAVI Alliance offered an overview and update of an international organization that is expected to play a central role in helping the world’s poorest countries implement widespread rotavirus immunization.

GAVI is a global public-private partnership established in 2000 with the mission of saving children’s lives, and protecting people’s health by increasing access to immunization in poor countries.

Currently GAVI works with 72 of the world’s poorest countries, those with less than $1000 per capita income as of the year 2003. Founding members included The World Bank, WHO, and UNICEF. The Bill & Melinda Gates Foundation jump-started GAVI with a large grant.

“GAVI has committed about $2.6 billion dollars for new vaccines and the rest, which is Health System and Immunization Service Support, comes to about $800 million,” Kumar said.

Kumar explained that GAVI funding pays most of the cost of vaccines, but eligible countries remain responsible for part of the cost. For example, haemophilus influenzae type B or Hib vaccine may cost approximately US $3.00 per dose. The country pays only US $0.30, and GAVI pays the remainder. A second vaccine costs the country even less.

“Policy makers need to be convinced that it’s really cost-effective, it’s affordable, and it will indeed save lives,” Kumar said.

GAVI also seeks funding from a variety of sources. The International Finance Facility for Immunization (IFFIm) raises $4 billion in capital markets to provide funding for GAVI-supported

SIDEBAR
Vaccine as a Catalyst for Conquering Diarrheal Diseases

John Wecker, director of the PATH Rotavirus Vaccine Program, endeavored to take the audience “beyond the world of rotavirus disease and beyond rotavirus vaccines into the broader world of diarrheal disease.”

Moreover, Wecker said “we have to remember that mortality due to rotavirus disease only accounts for about 31 percent of all diarrheal disease deaths.”

“We have the other 69 percent that we have to deal with, if we’re serious about reducing under five mortality,” he said.

Wecker pointed out that more proven interventions are available to prevent and treat diarrhea than any other major child killer. He said oral rehydration has reduced mortality—saving the lives of more than 40 million children—and has further potential if it can be delivered to the children who need it most.

Zinc can control both acute and persistent diarrhea, he said, and is approved by WHO and the World Health Assembly. Also, Wecker observed that exclusively breastfeeding babies for the first five months reduces the risk of diarrhea death by seven times.

“Credible research results can help push donors and policy makers to take action, he said, but research results must reach policymakers to have an effect.”

John Wecker, PATH, US

But despite the available approaches and interventions, Wecker said diarrhea still accounts for 17 percent of deaths in children under five years old. And since 1995, he said, the use of oral rehydration has dropped in countries where it’s most needed, especially countries of Sub-Saharan Africa.

Wecker said rotavirus vaccine introduction can provide an opportunity to improve treatments for all diarrheal diseases by prompting far-reaching changes in national health systems. For example, he said that when Nicaragua introduced rotavirus vaccine, it simultaneously worked to retrain health-care workers nationwide, increase access to oral rehydration and, with a donation from UNICEF, introduce zinc therapy for diarrhea.

A study of perceptions, Wecker said, found that diarrhea has dropped off the map of globally important diseases, while AIDS, malaria and TB remain prominent. “Diarrheal disease ranked actually last in terms of its current priority for donors, for funders on the global health agenda.” Wecker said.

“Take your data and get out there and let the policy makers know what you’re doing,” Wecker said.
immunization activities. In addition, GAVI hopes to use its Advance Market Commitment program (AMC) to entice more companies to develop new vaccines by assuring them a future market for their products. But Kumar said ultimately, “it’s really up to the countries to decide which of the vaccines they want according to their own priorities.”

Kumar noted a WHO analysis that has provided a “consensus assessment” for which diseases deserve the highest priority. Malaria and pneumococcal disease are considered the “highest priority,” while rotavirus is in a group of ten diseases, which include seasonal influenza, cervical cancer and Japanese Encephalitis, classified as “high priority.”

Decision Making at the Country-Level

Shahin Huseynov of the WHO initiated a panel discussion of government health officials from the WHO EURO region—all of whom represented former Soviet states—by asking whether rotavirus vaccine was a priority in their country.

Sabirjon Abdukarimov, Deputy Minister of Health for Kyrgyzstan, said “We need to convince our political actors to be committed, and of the economic efficiency, first of all, and the social importance of this issue.” He said rotavirus disease may account for 40-60 percent of all diarrheal disease in Kyrgyzstan.

In Georgia, other vaccines still to be introduced will have first priority, but cost-effectiveness research on rotavirus vaccine will be conducted, said Paata Imnadze, of the National Center for Disease Control. He said one factor that could influence vaccine adoption is the impending privatization of the country’s health care system.

Ludmila Chernyshova from the Ukraine said it is difficult to determine when rotavirus vaccine may be introduced. Anti-vaccine lobbying has been strong in Ukraine, especially after a recent death due to measles vaccine. On the other hand, rotavirus research is ongoing, as is communication about rotavirus to the public. Rotarix is currently being registered in Ukraine.

Armenia’s Gayane Sahakyan said the country has had several outbreaks of gastroenteritis, half of which

FIGURE 13

WHO Disease Prioritization (Nov. 2007)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>0.160</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>0.102</td>
</tr>
<tr>
<td>Influenza (seasonal)</td>
<td>0.076</td>
</tr>
<tr>
<td>Meningococcal ACWY</td>
<td>0.068</td>
</tr>
<tr>
<td>Cervical Cancer (HPV)</td>
<td>0.066</td>
</tr>
<tr>
<td>Cholera</td>
<td>0.066</td>
</tr>
<tr>
<td>Rabies</td>
<td>0.066</td>
</tr>
<tr>
<td>Japanese Encephalitis</td>
<td>0.065</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>0.064</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>0.055</td>
</tr>
<tr>
<td>Typhoid Fever</td>
<td>0.054</td>
</tr>
<tr>
<td>Dengue</td>
<td>0.043</td>
</tr>
<tr>
<td>Meningococcal B</td>
<td>0.031</td>
</tr>
<tr>
<td>Rubella</td>
<td>0.021</td>
</tr>
<tr>
<td>Varicella</td>
<td>0.017</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>0.016</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>0.016</td>
</tr>
<tr>
<td>Mumps</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Consensus Assessment of Relative Importance (n=27)

From Ranjana Kumar, GAVI Alliance
were caused by rotavirus. She said Armenia's Ministry of Health is interested in rotavirus vaccination, but because Armenia has no sentinel epidemiological surveillance, there is no concrete data on the disease. Infrastructure is also a concern. For example, there is inadequate cold storage at treatment facilities.

Dilorom Tursunova of Uzbekistan said there has been research on rotavirus in the country, and sentinel surveillance is in place, as are training programs for family physicians.

"Naturally, after listening to the two days of this symposium, we think that the research we are conducting is of course not enough," Tursunova said. "And we would like to conduct more research, to continue, and to convince our government of the necessity of introducing a rotavirus vaccine."

Nadia Teleb of the World Health Organization asked health officials from countries in WHO's Eastern Mediterranean Region (EMRO) to discuss how they go about evaluating a new vaccine.

Ali Moghaddam of Libya said vaccines are evaluated by a national advisory committee of pediatricians. But because surveillance is not good, making evidence-based decisions remains difficult, he said. In addition, Moghaddam said, Libya is struggling to prioritize: "Is it the rotavirus first or is it pneumococcal or is it chicken pox or is it human papillomavirus?"

Libyan mothers are overwhelmingly in favor of vaccinations, he said, and some even travel outside the country for vaccinations.

In Iran, an expert committee convenes every two years to consider how to budget for both communicable and non-communicable diseases, said Iran's Abdoul Reza Esteghamati. Research in Iran shows about 55% of children hospitalized for gastroenteritis test positive for rotavirus. As a result, Esteghamati said Iran has decided to introduce rotavirus vaccine in the next two years, probably with funding from the Ministry of Health. But rotavirus must take second place to introducing vaccine against Hib, Esteghamati said, as Hib occurs at a surprisingly high rate in Iran.

WHO recommendations can be influential, Esteghamati said, but affordability is also important. One approach Iran is considering is to reduce costs by producing more vaccines domestically.

Ataya Medasate noted that Sudan, with a total population of 7 million, has separated into North Sudan and South Sudan, each of which have different health systems. Decision making on vaccines in North Sudan begins with data collection, moves on to a presentation to a joint forum between the Ministry of Health and the Pediatric Association, and finally to the Federal Ministers of Health and Finance.

"If you have a strong recommendation from WHO, that is enough for the Federal Administrator of Health, but sometimes, we face problems with the Pediatric Association," Medasate said. "They are very insistent to have local data regarding the burden of disease in the country."

Sudan plans to apply for GAVI funding for rotavirus vaccination in 2010.
Concluding Remarks

Roger Glass of the Fogarty International Center observed that the presentations at the conference offered a clear sense of rapid progress. He said they showed that in just the last three years, many countries have begun data collection, surveillance procedures and made a general movement toward introduction of rotavirus vaccines.

"Where will we be now in two years? What will be different in two years from where we are today? That's the question I'd like to pose," he said. “In two years, we will know how well these vaccines work in the poorest, low-income countries of world. We'll have definitive data to know whether these will be the lifesavers that we're all expecting or whether we have to think of other iterations to accomplish our goal.”

“In two years,” he added, “we should have data, literally, on millions of children about the safety of this vaccine, so we might, potentially, be able to put the intussusception issue to rest. In two years, we'll have new issues and new knowledge on pricing. We'll have new vaccines on the horizon. We'll have some competition in countries. We'll have experience with the vaccines, so we may well have a completely different economic outlook and forecast for the vaccine finance.”

Almost all of these insights, he said, will come “from people in this room” who would be departing from the conference “invigorated” by a wealth of new data, contacts and networks.” Glass said for people like him who have devoted a large part of their careers to the study of rotavirus disease, the groundswell of global interest on display in Istanbul is “absolutely inspiring.”
Sabirjan Abdukarimov
Ministry of Health, Kyrgyzstan
Juan Jose Amador
PATH, Nicaragua
Deborah Atherly
PATH, United States
Norman Beggs
GlaxoSmithKline, Belgium
Zulfiquar Bhutta
Aga Khan University, Pakistan
Julie Bines
Royal Children’s Hospital, Australia
Lulu Bravo
University of the Philippines, Philippines
Anthony Burton
World Health Organization, Switzerland

Ludmila Chernyshova
Ukraine
Max Clairiet
Merck, United States
Lucia De Oliveira
Pan American Health Organization, United States
Ciro de Quadros
Sabin Vaccine Institute, United States
Abdoul Reza Esteghamati
Ministry of Health, Iran
Elmina Flam
Norwegian Institute of Public Health, Uzbekistan
Roger Glass
 Fogarty Center, National Institute of Health, United States

Jim Gray
Health Protection Agency, United Kingdom
Shahin Huseynov
World Health Organization, Azerbaijan
Pasta Immadze
National Center for Disease Control, Georgia
Ranjana Kumar
GAVI Alliance, Switzerland
Eric Laurent
World Health Organization
Shabir Madhi
University of Witwatersrand, South Africa
Ataya Medasate
Sudan

Evelyn Caullin
Franco
Noureddine Chaukou
Morocco
Leticia Chapuis
Ivdyt Chikovani
Georgia
Ergin Çiftçi
Turkey
Candan Çıray
Turkey
Romulo Colindres
Brazil
Marina Conyn
Netherlands
Jalison Barros Correia
Brazil
Margaret Cortege
United States
Cisterna Cristina
Spain
Celso Cunha
Portugal
Nigel Cunliffe
United Kingdom
Tim Dallman
United Kingdom
Norbert De Clercq
Belgium
Serge Debus
Belgium
Değerli
Turkey
Mohammed Dekna
Madagascar
Yulia Demina
Russia
Özge Demir Leman
Turkey
Tatlevetina Dimitrova
Ener Çağır Dinleymi
Turkey
Quesma Mednine Diop
Senegal
Chantal Claire Donde
France
Elena Donosa
Dana Dragan
Romania
Shamsidin Dzhabirov
Tajikistan
Osama Edward
Egypt
Hanaa El Karaksy
Egypt
Ali El Mkaddim
Libya

David Mercer
World Health Organization, Denmark
Ali Moghaddam
Libya
Umesh Parashar
Centers for Disease Control & Prevention, United States
Manish Patel
Centers for Disease Control & Prevention, United States
Gayane Sahakyan
Ministry of Health, Armenia
Mathuram Santosh
Johns Hopkins Bloomberg School of Public Health, United States
Duncan Steele
PATH, United States

Nadia Teleb
World Health Organization, Egypt
Cristina Toscano
World Health Organization, Switzerland
Dilorom Tursonova
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Preben Aavitsland
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Sabin Vaccine Institute
International Vaccine Advocacy
2000 Pennsylvania Avenue, NW
Suite 7100
Washington, DC 20006
Phone: 202-842-5025
Fax: 202-842-7689
www.sabin.org

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