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Foreword

The 9th International Rotavirus Symposium, held in Johannesburg, South Africa in August 2010, capped a period of dramatic progress in the fight against rotavirus, the most common cause of severe childhood diarrheal disease. Since the 8th Symposium, held in 2008 in Istanbul, several major milestones had been reached:

- Two effective vaccines were licensed in more than 100 countries, and 24 countries incorporated them into mass immunization programs, leading to major reductions of rotavirus disease in several countries.
- The World Health Organization (WHO) recommended universal use of rotavirus vaccines.
- The GAVI Alliance committed to funding introduction of rotavirus vaccination at a cost of as little as 15 to 30 cents per series for GAVI-eligible low-income countries.
- New vaccine candidates under development offer the hope of cheaper and perhaps more effective vaccination within several years.

At the Johannesburg symposium, researchers and health officials presented new data on rotavirus disease and rotavirus vaccines, with special attention paid to reports from Africa and Asia. The participants discussed the significance of the latest surveillance data and the challenge of adding rotavirus vaccines to national immunization schedules, particularly in the poorest countries of the world where rotavirus takes its greatest toll but where vaccine costs are a barrier to adoption.

“There is a serious and growing need to increase access to affordable rotavirus vaccine in the developing world, where 85 percent of rotavirus deaths occur. This need is most severe in impoverished communities where access to medical care for rotavirus is often out of reach,” said Ciro de Quadros, executive vice president of the Sabin Vaccine Institute. “The symposium conveners, as well as the hundreds of attendees, are committed to ensuring that universal access to rotavirus vaccine becomes a reality.”

We are grateful to the physicians, epidemiologists, researchers, public health workers, industry officials, policymakers, donors, economists and health instructors who made the 9th International Rotavirus Symposium possible, and who continue to have a major impact on the health of the world’s most vulnerable children.

Executive Summary

Rotavirus is one of the most common childhood diseases, striking nearly every child in the world before the age of 5. In the industrialized world it causes hundreds of thousands of hospitalizations each year because of severe diarrhea and dehydration. The disease is much more severe in countries with high malnutrition and low access to medical care.

Rotavirus kills an estimated 500,000 children each year under five years of age and causes millions of hospital visits. It is responsible for about 40 percent of all diarrheal diseases serious enough to require hospitalizations in young children. The worst burden of rotavirus is in Africa, Asia, and Latin America.

The virus was identified by Ruth Bishop in 1973. The first international symposium on rotavirus was held in 1985 and involved 50 participants.

“When we started there was an unknown virus, now it’s recognized and it has gotten global priorities,” said Roger Glass, director of the Fogarty International Center at the U.S. National Institutes of Health.

Some 400 people from 65 countries took part in the 9th International Rotavirus Symposium in Johannesburg in August 2010. The meeting was convened by the Sabin Vaccine Institute, the University of Witwatersrand, the global health organization PATH, and the U.S. Centers for Disease Control and Prevention (CDC).
Participants discussed the disease’s epidemiology and the performance of vaccines in preventing serious rotavirus infections. There was a particular focus on the impact of the disease in Africa and Asia, regions where rotavirus is an especially deadly killer but where vaccine introduction has been slow. For example, almost half of all rotavirus deaths occur in sub-Saharan Africa, yet at the time of the symposium, South Africa was the only African nation to have introduced rotavirus vaccination.

Participants analyzed vaccine studies involving 12,000 children that have been conducted in Ghana, Kenya, Malawi, Mali, Bangladesh and Vietnam, which offer evidence of the power of rotavirus vaccines to reduce deaths and hospitalizations in Africa and South Asia.

**Getting Past the Paradox to Consider Major Impact on Deaths, Severe Disease**

During the discussions, a potentially distracting paradox arose that seems to be central to current considerations of rotavirus vaccination. The vaccines appear to be less efficacious at preventing severe rotavirus disease in the poorest countries; the poorer the vaccinated population, in fact, the lower its efficacy to the vaccine.

Yet despite this fact, the benefits of the vaccine appear highest in the poorest countries. When the vaccine was tested in Malawi and South Africa, for example, the vaccine was clearly more efficacious in middle-income South Africa. Yet the number of severe and fatal cases of rotavirus infection prevented by the vaccine was higher in Malawi.

This paradox was explained by Mary Agocs of the World Health Organization: “Although vaccine efficacy may be lowest in (the poorest fourth) of countries,” she said, “more children are severely impacted in these countries, so the vaccine would have a larger impact in terms of numbers of children.”

In other words, rotavirus is such a big problem in these areas that the efficacy of existing rotavirus vaccines is sufficient to have a dramatic impact on deaths and severe disease. In fact, one of the take-home messages at the conference was that rotavirus vaccine advocates should focus on reductions in deaths and severe disease as the best measures of the value of rotavirus immunization.

**The Two Vaccines Currently Available: Rotarix and RotaTeq**

At the time of the conference, 24 countries had begun mass immunization campaigns using one of the two globally licensed rotavirus vaccines, Rotarix and RotaTeq, both of which are administered orally.

From a technical perspective, the vaccines are characterized by the number of rotavirus strains they contain and by variants of two protein complexes that are described as G or P types.

Rotarix, made by GlaxoSmithKline Biologicals, is a monovalent G1P[8] vaccine that originally was isolated from an infant at the Children’s Hospital of Cincinnati. RotaTeq, made by Merck & Co., Inc., is a pentavalent vaccine derived from bovine and human rotaviruses and contains human rotavirus serotypes G1, G2, G3, G4, and P1A[8]. Rotarix is given in two doses, RotaTeq in three, and both can be administered in regular routine immunization schedules.

The Rotarix and RotaTeq vaccines were licensed beginning in 2004 and 2006 respectively. In 2007, WHO recommended the vaccines for regions of the world where efficacy data suggested a high public health impact. In December 2009, WHO recommended that all children be vaccinated against rotavirus.

**Impact of Rotavirus Vaccination**

In the United States, the introduction of rotavirus vaccines has dramatically reduced serious rotavirus infections. In 2008, after the introduction of RotaTeq, health care resource utilization for rotavirus disease was reduced by almost 90%. Thus, preventing some 50,000 hospital stays there each year.

In Latin America, the vaccine has had a major impact on deaths due to rotavirus—reducing diarrhea-related infant mortality by 30-40%.
Preliminary data from South Africa—which in 2008 became the only African country to begin nationwide rotavirus vaccination—indicates cases of severe rotavirus disease have fallen dramatically as well.

In many countries, the vaccine is having an even larger impact than expected, perhaps because rotavirus was under-diagnosed in the past, or because of herd immunity. There’s a lot about the activity of the vaccine and the virus that is not yet understood, said Glass.

“We really don’t know whether the glass is half empty or half full, and how then should we proceed and what can we do,” he said.

One of the unknowns, he said, is the degree of herd immunity one can expect from use of the vaccines in resource-poor countries.

“It may be that by reducing the amount of rotavirus in the environment, we will have a reduced force of infection, and will have less severe disease,” Glass said. “It might be that the vaccine will push disease to an older age so that those small children, the ones at the greatest risk of death, will not die from rotavirus.”

There were also many issues of concern raised at the meeting, ranging from disappointment at the efficacy rates of the vaccines in some countries, to lingering questions about safety. Both vaccines have proven extremely safe, but some data have suggested possible, though rare, links to bowel obstruction or intussusception, the adverse event that caused Wyeth’s RotaShield vaccine to be withdrawn.

Most speakers agreed that rotavirus vaccines would be valuable to poor countries, but there was some uncertainty about which countries would be able to pay for it.

Some of the key research findings discussed at the symposium included the following:

- Rotavirus is the leading cause of diarrheal hospitalizations in children, accounting for about 40% on average. In Africa and Asia, rotavirus vaccines have shown a potential to prevent more than 20% of all diarrhea-related hospitalizations in children.

- In Mexico, rotavirus vaccination has prevented more than 600 deaths a year, with 41% fewer diarrhea-related deaths in infants. Similar results appeared after use of the vaccine in Brazil.
Currently, manufacturers in India, China, Vietnam, and Brazil have developed experimental vaccines and are at relatively advanced stages in the clinical process. But the fate of any such product depends both on its eventual safety and efficacy record, and on clear demand for the product.

GAVI is offering the GSK and Merck vaccines at 15 to 30 cents per series for five years to the poorest countries. But while their initial contributions are fairly modest, these developing countries must demonstrate that they are interested in becoming markets for rotavirus vaccine. Expanded markets could lead GSK and Merck to expand vaccine production and will also incentivize developing-world manufacturers.

Some speakers at the symposium stressed the need for newer vaccines, including injectable killed-virus or subunit vaccines that may not require the large clinical trials of the type done to evaluate RotaTeq and Rotarix (which are both live, oral vaccines).

“I think we realize that we should not put all the eggs in one basket,” said the CDC’s Baoming Jiang, who is working on an injectable vaccine.

But others stressed that it was crucial to introduce existing vaccines as quickly as possible, despite their potential imperfections. “We can’t wait until we get 100% efficacy,” said Kathleen Neuzil of PATH. “We really need to introduce these vaccines now, with the impact that they can have, while simultaneously working for better vaccines.”

“We can’t wait until we get 100% efficacy. We really need to introduce these vaccines now, with the impact that they can have, while simultaneously working for better vaccines.”

— Kathleen Neuzil, PATH
Introduction

The 9th International Rotavirus Symposium was held 2-3 August 2010 in Johannesburg, South Africa. It brought together 400 participants from 65 countries to discuss the burden of rotavirus and progress in preventing the disease through vaccination.

“Rotavirus is the most severe cause of diarrhea in children,” said Roger I. Glass, director of the Fogarty International Center at the U.S. National Institutes of Health. “Rotavirus does the greatest damage in the developing world, where it kills thousands of children. In the developed countries, the issue is hospitalizations, illness, and the costs of treatment.”

The symposium addressed rotavirus disease from a number of perspectives, including:

- Global rotavirus epidemiology;
- Global and regional serotype predominance;
- Safety and efficacy of live-virus oral vaccines;
- Variable vaccine efficacy and impact on mortality in different regions and socioeconomic conditions;
- Economic costs and benefits of vaccination now and in the future;
- Update on vaccines in development; and
- Advocacy for vaccination and other treatment and prevention options for diarrheal disease.

Shabir Madhi, of South Africa’s University of Witwatersrand and a convener of the conference, noted that Johannesburg had hosted the first World Cup in Africa only a few weeks before the symposium. South Africa also had recently become the first country to incorporate vaccination against rotavirus. Like the World Cup matches, he said, the Johannesburg rotavirus symposium would have its moments of contention.

“We’re very much at the crossroads in terms of rotavirus and its introduction in low-income countries,” said Madhi. “There’s a lot of hype about rotavirus vaccines, but there are a number of challenges which still remain.”

Dr. Glass, who helped introduce the conference, noted that the issue of intussusception—telescoping of the bowel causing obstruction—has had a profound influence on rotavirus vaccine development. Wyeth’s RotaShield vaccine, introduced in 1998, was quickly withdrawn from the market because of indications that it caused the disorder.

“This rare adverse event has really colored the field ever since,” Glass noted. “It has made us think about doing extremely large and expensive trials for efficacy, worrying about intussusception with every new vaccine and wondering if any new adverse event could doom the next generation of vaccines.”

In the 11 years since RotaShield was shelved, an estimated 5 million children have died of rotavirus disease in low-resource countries.

But while the benefits of RotaShield had yet to be proven when it was withdrawn, the benefits of the current vaccines, Rotarix and RotaTeq, have been amply demonstrated. And there is little indication that intussusception is a serious risk of either vaccine.

“We’ve clearly come a long way. We’re on the right path, we’re moving fast, but we still have some way to go to really affect the change in the developing world,” said Glass.

Glass and other speakers agreed that achieving the potential of rotavirus vaccination to reduce disease and death would require concerted efforts to convince donors and policymakers of their value. Also needed, they said, are stronger alliances among the various groups fighting diarrheal diseases and professional and civil society organizations focused on infant health.

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— Roger Glass, Fogarty International Center, U.S. National Institutes of Health
Disease surveillance is essential to, among other things, generating evidence of the effect of immunizations on the overall burden of disease. Jason Mwenda, the WHO/AFRO Regional Coordinator of Surveillance, described some of the guidelines for collecting data.

He noted that rotavirus surveillance began in the region in 2006. WHO is providing assistance, but health ministries in each country conduct the surveillance. There are currently about 15 countries and 24 sentinel sites in Africa. WHO would like to expand this network but will not do so unless it can assure the sentinel sites will generate high-quality data, Mwenda said.

WHO advises countries to choose their largest pediatric hospital as the major sentinel site for surveillance activities. Larger countries—for example Ethiopia, Angola, and Nigeria—have as many as three sites. The sites currently conducting surveillance are using a standardized WHO protocol that assures there is consistency in the data collected across the region and the world.

Pediatric hospitals chosen as sentinel sites should be treating at least 250 children under five years old for acute diarrhea each year, Mwenda said. (Children under the age of five who are admitted for acute gastroenteritis or diarrhea are enrolled into the surveillance system.) They also should have a virology lab capable of making a rotavirus diagnosis.

WHO recommends surveillance of rotavirus infections in a country both before and after a vaccine is introduced. The preliminary surveillance helps demonstrate disease burden and provides information for decision-makers on whether to introduce the vaccine, as well as identifying the circulating rotavirus serotypes and establishing a baseline to measure the vaccine’s impact. After introduction, continued surveillance helps assess the impact of the vaccination program, including disease reduction, while highlighting potential safety issues and changes in the predominant viral strains.

Surveillance conducted thus far has shown that about 40% of all acute diarrhea hospitalizations in the region have been due to rotavirus. Serotypes in Africa seem to be a good deal more variable than in other parts of the world. For example, while the G1P8 type accounted for about 52% of rotavirus diagnosed globally during the period up to 2005, this type accounted for about 24% of the diagnoses genotyped in the African region. In Cameroon, where surveillance began recently, Mwenda said early data indicates that G1P8 comprises only 10% of samples.

Global Surveillance of Rotavirus

Globally, 55 countries are reporting to the WHO’s surveillance network, which uses a laboratory structure similar to the one used for polio and measles. A global reference lab is based at the U.S. Centers for Disease Control and Prevention in Atlanta, while there are also reference labs for each WHO region, said Mary Agocs of the WHO.

Between 2008 and 2009 alone, there has been a 20% increase in the number of countries reporting to the rotavirus network and a 20% increase in the number of children enrolled.

In 2009 about 50,000 children were enrolled in the WHO surveillance system. The percentage of rotavirus-positive stool samples varied from a high of 46% in the Western Pacific to 25% in the Americas, which is the only region in the system where rotavirus vaccines are being administered on a national level in many countries.

WHO’s surveillance system enables it to examine the seasonality—or lack of seasonality—of rotavirus infections in the different regions. It is beginning to collect data regarding the distribution of various genotypes of rotavirus. So far, G1P8 is the most common strain worldwide.
Rotavirus Surveillance in Uganda

Andrew Bakainaga of the WHO office in Uganda described surveillance efforts there, which were based initially at the country’s largest pediatric hospital, the Mulago Hospital in Kampala. They were later expanded to a hospital at Mbarara.

In 2003 and 2004, diarrhea accounted for 8% of pediatric admissions at Mulago Hospital, and a study of 156 stool samples from these patients showed that rotavirus was present in 54.5% of the cases. Nearly all rotavirus admissions were in children under two, with the highest frequency in infants 7-12 months old.

Beginning in 2006, the Ministry of Health began a program to estimate the incidence of hospitalizations associated with rotavirus, to determine the age and seasonal distribution of hospitalizations, and to identify the prevalent strains of the virus. Mulago had built up its laboratory capacity during earlier studies of pneumococcus, while Mbarara came on line a bit later. Mulago is a national referral hospital that receives sick children from all over the country.

Researchers in Uganda define a suspected case of rotavirus diarrhea as any child under five years of age who is admitted for treatment of an acute diarrhea. A confirmed case is defined by demonstration of the presence of rotavirus through enzyme immunoassay.

Bakainaga said surveillance conducted from July 2006 to March 2010 revealed that rotavirus infections in Uganda tended to be cyclical but not seasonal. The majority of cases were recorded in children 3 to 17 months old, with the greatest number in the 12 to 17 month old age group. In terms of serotype prevalence, G1P8 was the most common, accounting for 24% of typed samples. Overall, rotavirus accounted for 41% of acute diarrhea cases in the under-5 group at Mulago Hospital, a figure that clearly indicates Uganda would benefit from a rotavirus vaccine.

Bakainaga noted that the Ugandan government has taken the lead in establishing surveillance and therefore “owns” it as well as any decisions that arise from the process.

“The surveillance team members are employees of both public and private hospitals and, therefore, they are fully funded, fully engaged, and fully enrolled by the
government itself,” Bakainaga said. “The advantages of this are that it ensures sustainability, it forges ownership, and it affects integration of surveillance into the mainstream health activities,” which includes surveillance for other diseases.

Bakainaga said the fact that the government is running the surveillance program validates its use as a tool for guiding decisions regarding new vaccine introduction. Rotavirus infection data gathered through the program, he said, has been instrumental to government efforts seeking GAVI support for rotavirus immunizations in Uganda.

“We want to make it very clear that Uganda would definitely benefit from the rotavirus vaccine,” Bakainaga said.

“We want to make it very clear that Uganda would definitely benefit from the rotavirus vaccine.”

-- Andrew Bakainaga, WHO, Uganda

Rotavirus Surveillance in Togo

Enyonam Tsolenyanu of Tokoin Teaching Hospital, which includes a pediatric ward with 100 beds, presented data on a rotavirus surveillance project conducted in Togo.

Togo is a country of approximately 5.8 million people, including 1.6 million children under age 5. Rotavirus surveillance in Togo began with a preliminary three-month study initiated in November 2006, when a diarrhea outbreak occurred in the capital Lome, site of the Tokoin hospital.

Formal surveillance began in February 2008 at Tokoin. Positive ELISA samples were sent to regional centers in South Africa or Ghana for genotyping. All cases of diarrhea that had started within seven days of hospitalization and stool samples containing blood were excluded from the study. Samples were taken from the children within 48 hours of being hospitalized. From February 2008 to January 2010, 8,895 children were hospitalized in the ward, with 477 of them (5%) admitted for gastroenteritis. From this group, 356 cases were selected for the study. The prevalence of rotavirus in this sample was 42%.

During the two years of surveillance, rotavirus gastroenteritis was highest in December, January and February, which accounted 69% of the cases. About 85% of the children admitted for gastroenteritis were under 2, and 93% of this group presented with rotavirus. Prevalence was highest among children in the 4- to 11-month-old age group. Rotavirus gastroenteritis was rare among children above 2 admitted to the hospital. The virus struck boys and girls roughly equally—of confirmed cases of rotavirus infection, 52% were girls and 48% boys.

Children with rotavirus infections suffered more episodes of diarrhea compared with rotavirus-negative patients, and had symptoms such as vomiting and dehydration more frequently.

“Overall, the clinical chart was more severe in confirmed cases of rotavirus gastroenteritis, but statistically the variation observed was not significant,” she said.

The Togolese researchers were able to genotype only 69 samples. Of these cases, for VP7 genotype, the G1 type was highest with 32 cases, and then G2 with 26 cases. The dominant VP4 genotype was P6, 28 cases, followed by genotype P6/8, 18 cases.
This surveillance showed that Togolese children suffer from rotavirus to a great extent, given that 42% of gastroenteritis stool samples tested were positive for the virus.

While the data collected thus far will help decision-makers introduce the rotavirus vaccine into Togo’s Expanded Program on Immunization (EPI), researchers intend to broaden the number of sites collecting samples to learn more about the disease’s prevalence and the genotypes involved.

**Rotavirus Surveillance in Ethiopia**

Almaz Abebe from the Ethiopia Health Nutrition and Research Institute described a project of hospital-based rotavirus surveillance among young children in Addis Ababa, the capital city of 4 million people.

Hospital studies done in Addis and in Jimma had shown that rotavirus accounted for 18% to 27% of acute gastroenteritis in hospitalized infants and young children. With this knowledge, Ethiopia joined the African rotavirus surveillance and epidemiology network in 2007.

The Ethiopian sites include the pediatrics department at Addis Ababa University’s medical school pediatrics department, which has satellite sites at the Black Lion Hospital and Yekatit 12 Hospital. The Ethiopia Health Nutrition and Research Institute, a government agency, conducts the surveillance and does testing, genotyping, and data management. The WHO provides financial support and data quality control.

From August 2007 through April 2010, 875 stool samples were collected from children who came to the hospitals with gastroenteritis and required hospitalization and rehydration for at least six hours. The samples were tested for rotavirus antigen by using enzyme immunoassay (EIA). G and P genotyping was done by RT-PCR with sequencing.

EIA detected rotavirus in 165 children, about 19% of the enrolled patients. Among the rotavirus-positive children, 89% were under 2 and 29% were under six months. Although 61% of the children were male, this was not statistically significant.

The disease circulated year round, with peaks usually in December or November. The researchers managed to genotype 93 of the samples, of which about a third were G1P8, with G2P4, G3P6 and G10P6 accounting for an additional 41%. Infection with more than one type was identified in 7% of the cases.
In conclusion, fewer of the acute diarrheal cases than expected were positive for rotavirus, a finding that may be due to shortcomings in the program. For one thing, all the samples were from children living in Addis only. Also, researchers had difficulties getting quality samples and capturing all diarrhea cases, in part because the country is in the midst of a healthcare system reform that is creating more decentralization.

Since finishing the study, Abebe said, she and her colleagues had expanded surveillance beyond the big hospitals to smaller health centers. They were providing lectures and training for pediatricians, nurses, laboratories, and data managers as they try to gain better understanding of the country’s rotavirus problem.

Discussion of Rotavirus Surveillance

Brendan Flannery, a vaccine consultant from the Pan American Health Organization (PAHO), shared advice about laying the groundwork for rotavirus vaccination. He pointed out that in the Americas, several of the largest countries have had a difficult time implementing a national rotavirus surveillance program.

“As demonstrated from the presentations from Togo and Uganda, I think it is better to start small and have well-functioning sites that are committed than to try to have nationally representative data in a large country,” Flannery said. He noted that national programs ultimately require a great deal of coordination, given the need to send samples to national laboratories and work with states that have varying levels of surveillance capabilities.

“Don’t let the perfect be the enemy of the good,” he said.

In the Americas, PAHO has supported training and funding for the initial start-up of a surveillance program, but health ministries themselves fund all surveillance.

As was stated in the presentation on Uganda, Flannery said, it is key to locate sites that are already conducting surveillance of other diseases and are staffed by clinicians interested in conducting research and publishing articles. Such sites can generate the funding for surveillance or obtain the small amounts required from health ministries. Sometimes health ministries choose inexperienced hospitals as surveillance hubs, in the interest of getting representative data. But they risk getting no data rather than representative data.

Researchers should look for partnerships with health ministries, so that the ministries can take ownership of data even if they didn’t fund the research, Flannery said.

Agocs said that from a global perspective, WHO’s emphasis in the next few years will be engaging health ministries in the ownership of the surveillance systems, and improving the quality of surveillance data. WHO experts are trying to determine how to assess surveillance sites, including the types of indicators that are illustrative of data quality.

Anthony Nelson, professor of pediatrics at the Chinese University of Hong Kong, raised the question of whether hospital sites in the rotavirus network should also be conducting surveillance of bacterial causes of gastroenteritis. Mary Agocs agreed that WHO’s partners, pediatricians in particular, would likely have an accurate diagnosis for cases that do not involve rotavirus.

Mwenda summed up the discussion by saying that data quality was key to informed policy decisions. Everyone involved should be focused on this goal. Standardized guidelines and tools are an important step in this direction, as is engagement by ministries of health and academic centers of excellence. Periodic data auditing is also essential.

Nelson said he believes “we still have a long way to go to make sure that the data that we have is of highest quality.”

“As demonstrated from the presentations from Togo and Uganda, I think it is better to start small and have well-functioning sites that are committed than to try to have nationally representative data in a large country.”

— Brendan Flannery, PAHO
SESSION II: Update on Rotavirus Vaccines

Rotarix – GSK’s Monovalent Rotavirus Vaccine

Dr. Bernd Benninghoff, director of worldwide medical affairs at GSK Biologics, began his talk by discussing rotavirus immunity issues. Based on studies around the world, he said, a natural infection with rotavirus attenuates the severity of a subsequent infection, regardless of strain, and two infections provide 100% protection against all but mild to asymptomatic infections.

When it comes to rotavirus vaccine—Rotarix, specifically—efficacy in trials has varied depending on the region.

While efficacy against severe rotavirus disease was nearly 100% in Rotarix trials in Southeast Asia and 96% in Europe, it was about 85% in Central American trials and 61% in African trials. The vaccine has not been as efficacious in low-income countries, including four African vaccine trial locales—Ghana, Kenya, Malawi and Mali.

But the number of severe rotavirus infections is much greater in these countries. Thus, despite the lower efficacy of the vaccine, it prevents a greater number of severe gastroenteritis episodes. For example, the data from trials showed the vaccine prevented 6.7 severe rotavirus episodes per 100 vaccinated children in Malawi, and 4.2 episodes per 100 in South Africa, a middle-income country where the vaccine’s efficacy rate against disease was much higher than in Malawi.

**Severe RVGE Episodes Per 100 Infants Prevented in South Africa & Malawi**

![Figure 2.1](image_url)

N = 4939 infants. Randomised, placebo-controlled trial. First year follow-up. Rotarix™ was coadministered with OPV and other EPI vaccines, HIV-positive infants were not excluded and breastfeeding was not restricted.

Despite the lower efficacy, the number of severe RVGE cases prevented was greater in Malawi than in South Africa (6.7 vs 4.2/100 infants)

During these trials, 40.5 percent of the placebo group in Malawi seroconverted during the trial period, meaning they showed evidence of rotavirus antibodies. Over the same period of the South African trial, just 16.7 percent of the controls seroconverted. This difference may indicate that a larger percentage of Malawian children were not “rotavirus-naïve” when they entered the trial. In fact, Benninghoff said that exposure to natural rotavirus infection is appearing much earlier in life in Malawian infants compared to higher income countries.

He said early scheduling of universal mass vaccination might help reduce the number of infections in African countries with a high burden of rotavirus.

**Rotarix Safety Profile**

As far as vaccine safety, Benninghoff noted that no intussusception signal had arisen in any of the clinical trials of Rotarix. The company has 64 million doses of the vaccine in its database, and the 123 cases of intussusceptions post-Rotarix reported so far is much lower than the expected rate of background incidence. Active surveillance data from Australia showed an elevated risk of intussusceptions in the 21 days following the first dose, but the data are not statistically significant.

GSK is conducting post-authorization safety studies in Mexico and in the United States. Interim data from Mexico are in line with trends from other countries, Benninghoff said, and cases of intussusception have been reported in temporal association within seven days following the first dose, identifying the possibility of a small increased risk of intussusception after rotavirus vaccine administration. Whether or not Rotarix affects the overall incidence of intussusception has not been established.

Contraindications against vaccinating HIV-positive and immuno-compromised babies have been removed, and premature babies may be vaccinated on the same dosing schedule as pre-terms born after 27 weeks of gestational age.

As for the porcine circovirus, traces have been found in GSK’s vaccine, testing shows that the material was present in the vaccines before clinical trials began, yet there was no evidence that the circovirus affected children. The European Medicines Agency has confirmed the positive risk/benefit balance on Rotarix, and both WHO and the FDA have said there is no evidence that the presence of the porcine virus poses a safety risk. GSK is currently investigating processes to manufacture the vaccine free of the circovirus.

Finally, Benninghoff discussed data from Brazil on the real-life efficacy of the vaccine. After the vaccine was introduced in 2007, the percentage of rotavirus-positive infections in children admitted to a São Paulo hospital dropped from 30.9 percent to 10.4 percent. The G2P4 serotype was the most common circulating strain in that region. In Mexico, cases of acute gastroenteritis in children below 11 months declined 66% in 2009 after the vaccine’s introduction. By the second year of the vaccine’s introduction in Belgium, the number of rotavirus-positive stool tests fell by 75%.

Overall, Benninghoff sees strong evidence for the benefits of mass rotavirus immunizations.

“The implementation of routine rotavirus vaccination globally is expected to have a positive impact on the public health especially here in Africa where the disease burden is high,” he said.
RotaTeq – Merck’s Pentavalent Vaccine

Max Ciarlet, from Merck, gave a presentation on his company’s pentavalent rotavirus vaccine.

The Merck vaccine was made by reassorting human and bovine rotaviruses. It contains five live rotavirus strains, expressing the 5 most common human rotavirus serotypes (G1, G2, G3, G4 and P1A[8]) that circulate worldwide. Merck’s Phase III trials of the vaccine, including the pivotal Rotavirus Efficacy and Safety Trial (REST), was conducted in 11 countries and on three continents. From 2001 to 2005, the studies enrolled approximately 72,000 subjects. The vaccine’s efficacy against severe rotavirus gastroenteritis was 98-100%, and it prevented 73 to 75% of all rotavirus illness.

It eliminated 96% of hospitalizations, 94% of emergency department visits, and 86% percent of office visits for rotavirus illness.

The vaccine was efficacious against all strains of rotavirus, slightly more so against serotypes G1-G4. Vaccination efficacy against serotypes G1-G4 was 100% between doses 1 and 2 and 91% between doses 2 and 3. For all serotypes, efficacy was 82% between doses 1 and 2 and 84% between doses 2 and 3.

Merck has also completed separate trials of the vaccine in GAVI eligible countries in Asia and Africa. A major trial was conducted from 2007-2009 in Bangladesh, Ghana, Kenya, Mali, and Vietnam to test safety and measure immune response. Approximately 5,400 children vaccinated in Africa and 2,000 in Asia were followed through at least one year and most through the second year of life. Efficacy in Africa was 64% in the first year of life and 39% through 2 years of follow up, while the efficacy of the vaccine is Asia’s poorest countries was 51% in the first year of life and 48% through 2 years of follow up. Merck’s rotavirus vaccine is the only one that has been tested in Asian GAVI eligible countries.

**Rotavirus Test Results, Pre- and Post-Introduction of Rotarix™, in Children <5 Years Evaluated at a São Paulo Hospital, 2004–2008**

![Graph showing rotavirus test results](image)

**FIGURE 2.2**

**Reduction of 66.3% (p < 0.001) in the positivity rate for rotavirus**

Safadi M et al. Pediatr infect Dis J 2010;29
The Efficacy Paradox

As is the case with the GSK vaccine, the overall efficacy of RotaTeq in poorer countries was lower. However, due to the high burden of disease it prevented many more cases of severe rotavirus gastroenteritis.

“The 50% efficacy in Africa or in Asia is worth twice the amount of what a 100% (efficacy) will mean for the US” in terms of cases prevented, Ciarlet said. Evaluating the rotavirus infections during the African trial using the Vesikari score—a measure of disease severity—the vaccine’s overall efficacy was about 60% in the first year of life.

The vaccine has an excellent safety profile, Ciarlet said. Extensive post-marketing surveillance in the United States has not shown any link to intussusception or other serious adverse events.

As for the porcine circovirus issue, very small numbers of viral fragments have been identified in the Merck vaccine, but no intact viral DNA, and tests of circovirus infectivity have all been negative. The most likely source for the introduction of circovirus into the vaccine is trypsin, a pig-derived protease used in the vaccine manufacturing process.

RotaTeq has had a dramatic impact on rotavirus morbidity including emergency room and doctors’ visits in the United States. Six U.S. hospital-based studies reported reductions in rotavirus-related cases of 85-95% in 2008 compared to previous years. Rotavirus reporting in insurance claims has fallen by 72% compared to the pre-vaccine era.
Discussion of GSK and Merck Vaccines

There was a wide-ranging discussion about rotavirus trials of the GSK and Merck vaccines in low-income countries. It was led by Dr. Kathleen Neuzil of PATH, along with Drs. George Armah, Nigel Cunliffe and K. Zaman, the principal investigators from selected sites for vaccine efficacy trials in Ghana, Malawi and Bangladesh, respectively.

Kathleen Neuzil noted that the impetus for the trials was the fact that these lowest-resource countries carry the greatest burden of rotavirus disease. The trials represented a comprehensive response to the need for evidence from poor countries and involved three large randomized controlled studies including over 12,000 children in seven different countries. The sites were chosen because of the excellent track record and talent of their investigators, but also because each of the locations had high rates of infant and child mortality, and in some cases high prevalence of HIV.

Results from these trials have been published. The primary efficacy results for the GSK trials, headed by Drs. Madhi and Cunliffe, were published in January 2010 in the New England Journal of Medicine. The Merck trials, led by Drs. Zaman, Armah and others, were published in The Lancet in August 2010.

Trials that Merck and GSK had conducted in the U.S., Europe, and Latin America were intended to show that the vaccine worked biologically and to get it licensed. The purpose of the African and Asian trials, Neuzil said, was to help inform policy. The GAVI Alliance wanted to include both vaccines in trials that included a representative population of children living in Asia and Africa. While the pivotal licensure trials had narrow exclusion criteria, the trials in Africa and Asia were quite different.

“We included children who were exposed to mothers who had HIV. We included children who were malnourished. We included children with various chronic diseases,” Neuzil said. “In terms of outcome measures,
we know that every child gets rotavirus disease before
the age of three generally, so we were really interested in
preventing the most severe disease. We concentrated our
outcome measures on severe illness.”

The overall efficacy of the two vaccines in these trials
was 51 to 64.2 percent. They thus met PATH’s goal
of influencing policy. In June 2009, the World Health
Organization recommended that rotavirus vaccines be
included in national immunization programs throughout
the world.

**Half Empty, Half Full, or Too Big a Glass?**

“We heard the question posed earlier, ‘Is the glass half
empty or is the glass half full?’” Neuzil said. “I would ask
a different question: I would say, ‘How big is the glass?’
The glass is very big.

“There are a half a million children dying every year from
rotavirus, and we know that with even a 60% efficacy we
can prevent a tremendous amount of deaths,” she added.
“In the United States, we assume about 50 children a year
die from rotavirus. If we can prevent 98% of those deaths
it will take us 30,000 years of vaccinating in the United
States before we can prevent as many deaths as we could
prevent in 15 years by introducing this vaccine into low
resource regions.”

The goal of clinical trials should be to learn how to
maximize the impact of rotavirus vaccines, she said.
The trials have shown regional and country differences
in the behavior of the vaccine, with waning efficacy in
the second year of life that wasn’t seen in the U.S. and
Latin America or Europe. Maternal antibody interference,
concomitant vaccination with oral polio and other factors
may be complicating the picture.

“In the United States, we assume about 50 children a year
die from rotavirus. If we can prevent 98% of those deaths it will take
us 30,000 years of vaccinating in the United States before we
can prevent as many deaths as we could prevent in 15 years by
introducing this vaccine into low resource regions.”

— Kathleen Neuzil, PATH

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**FIGURE 2.5**

**Efficacy Against Severe Rotavirus Gastroenteritis
in the First Year of Life**

<table>
<thead>
<tr>
<th>Region</th>
<th>Vaccine</th>
<th>Countries</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Rotarix™</td>
<td>Malawi, South Africa</td>
<td>61.7</td>
<td>44.0, 73.2</td>
</tr>
<tr>
<td>Africa</td>
<td>RotaTeq®</td>
<td>Ghana, Kenya, Mali</td>
<td>64.2</td>
<td>40.2, 79.4</td>
</tr>
<tr>
<td>Asia</td>
<td>RotaTeq®</td>
<td>Bangladesh, Vietnam</td>
<td>51.0</td>
<td>12.8, 73.3</td>
</tr>
</tbody>
</table>

Madhi/Cunliffe, Steele et al. January 28, 2010 NEJM
Rural Settings, Different Results

George Armah noted that the studies in Kenya and Ghana were done in rural settings, while in Mali the surveillance was conducted in a city. The first year data from Mali are perplexing, because it records four cases of severe rotavirus disease in the vaccine group, and four in the placebo group during the first year of life, for a point efficacy estimate of 1%, with wide confidence intervals (-0.0 to 81.6).

Armah explained that the studies were designed in such a way that there were monthly follow-up visits to homes, and parents were asked to send their children to the corresponding clinic any time the children felt unwell.

In Ghana and Kenya, the PATH teams had staff embedded within the community, which made it easy for the mothers to contact them, and assured a capture of 90 percent or more of all children who were sick. The Mali trial site did not have the same penetration of healthcare personnel, and not that many people reported to health centers during the trial. Also, hospitalization for diarrhea generally was very, very low during the period of the trial.

Investigators went back through the data and looked at the intent to treat group—anybody who had received at least one dose of vaccine. This first year analysis captured three more cases of rotavirus infection in the placebo group, bringing the vaccine’s efficacy to 42.9% (CI <0.0 to 87.7). The experience in Mali shows that it is easier to conduct African trials for the vaccine in rural settings, Armah said.

When all the data from the African and Asian settings was put together, the vaccine provided 23% efficacy against all causes of severe gastroenteritis during the first year of life, assuming vaccine efficacy of 59% against severe rotavirus illness. These results suggest that about 39% of severe GI disease in these regions was caused by rotavirus during the first year of life. Efficacy against severe gastrointestinal illness through the second year of life was about 11.2%.

In Kenya, investigators employed monthly home visits—about 15,000 were made in all—to collect data on illness, hospitalizations, and medications. The data from this study showed that the vaccine was about 7% effective in preventing all-cause gastroenteritis and 25% effective in preventing severe dehydration episodes in the first year.

### FIGURE 2.6

**Vaccine Efficacy (VE) of PRV Against All Diarrhoea Episodes and Dehydration as Determined by Household Visits Through the Entire Follow-up Period**

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Monthly follow-up visits</td>
<td>7,655</td>
<td>7,648</td>
<td></td>
</tr>
<tr>
<td>All AGE episodes</td>
<td>1653 (22%)</td>
<td>1775 (23%)</td>
<td>7.0% (1.3–12)</td>
</tr>
<tr>
<td>AGE with severe dehydration</td>
<td>92 (1.2%)</td>
<td>123 (1.6%)</td>
<td>25.3% (57–98)</td>
</tr>
<tr>
<td>AGE with moderate dehydration</td>
<td>259 (3.4%)</td>
<td>271 (3.5%)</td>
<td>4.5% (-13–19)</td>
</tr>
</tbody>
</table>

1st year of life: VE against severe dehydration: 29% (3-48%)
2nd year of life: VE against severe dehydration: 15% (-43%-50%)
Rotavirus contributed to about 39% of cases of severe infantile gastroenteritis in the Siaya district of Kenya, data that could be employed to make an argument for widespread vaccination, Armah said.

Strain Diversity: Is it a Problem?

The trials in Africa and Asia provided the stiffest challenges of the vaccine so far, and one of the challenges is strain diversity, which was wider than seen previously, said Nigel Cunliffe of Liverpool University.


Similarly, the studies of Rotarix conducted in South Africa and Malawi turned up a wide distribution of strain types. The three main strains in Malawi were G8P[4], G9P[8], and G12P[6], which together accounted for 75% of the strains characterized. The globally common G1P[8] strain comprised a rather meager 13% of samples in Malawi.

The variation in strain types does not necessarily explain the reduced vaccine efficacy seen in these trials, Cunliffe said. Rotarix maintained efficacy of about 75% against all G and P types during the trial in South Africa. In Malawi, efficacy was closer to 50%, but again the match between serotype and vaccine was not relevant in a statistically significant way.

![FIGURE 2.7](image)

Vaccine Efficacy Against Severe Rotavirus GE Due to Different Serotypes: Malawi

N = 1030 (Rotarix)
N = 483 (Placebo)

Rotavirus strains can vary not only in different settings but also over time in the same setting, Cunliffe noted. He said in Malawi over the last ten years he has observed serotypes often shifting without conditions being present that would lead one to suspect vaccination, by targeting specific serotypes, had prompted other, non-vaccine serotypes to become more common.

“I think we will need to be cautious in attributing changes in relative percentages of strains isolated to vaccine introduction,” he said.
Bangladeshi Data on Vaccine Efficacy

Dr. Zaman, principal investigator on the Bangladesh study with RotaTeq, said the vaccine’s efficacy against severe rotavirus gastroenteritis was 48.3% to 70%, depending on the criteria employed to define efficacy. It was 27% effective against severe gastrointestinal disease of any type during the two years of the trial study.

During the first year of life, the vaccine’s efficacy against severe rotavirus disease was 45.7% in Bangladesh. In Vietnam, it was 72.3% and the pooled efficacy was 51%. Yet because the severity of rotavirus disease is greater in Bangladesh, the vaccine prevented 2.5 severe cases per 100 vaccinated children, compared to 1.2 cases per 100 prevented in the Vietnam trial.

Roger Glass asked whether any of the vaccine efficacy trials had pointed to good correlates of protection for rotavirus disease.

Zaman said that geometric mean titers of the antibody immunoglobulin A (IgA) were lower in Bangladeshis than in Vietnamese children and the efficacy of the vaccine was lower. Shedding vaccine virus might also be a potent correlate of protection, he said. Neuzil said that vaccine trials had failed to identify correlates of protection so far, though researchers continue to work on the issue. There also was a question of whether a minimum protective level will be increasingly important as new vaccine candidates are tested. In the future, it will be harder to conduct placebo-control trials, so whatever analysis can be provided on a reasonable protective level would be important.
Neuzil noted that serum anti-rotavirus IgA was tenfold lower in Africa and Bangladesh compared to levels recorded in studies in the United States and Latin America. This difference suggests that even with low immunogenicity, protection can occur, Neuzil said. It also shows that “something is affecting the immunogenicity of these vaccines.”

There was speculation that part of the explanation could be simultaneous administration of oral polio, which lowers the immune response to the rotavirus vaccines. Also, many of the children in the trials were given the vaccines at six weeks, rather than eight weeks as was the case in more developed countries.

In addition, vaccine efficacy appears to drop in the second year of life. Anita Zaidi of the Aga Khan University in Pakistan hypothesized that the lower efficacy could be an indication that the rotavirus pathogen is less important in the second year. In Pakistan, she said, so many infections occur that by the second year, rotavirus can be identified with equal frequency in cases and controls. “Unless you look at the whole panorama of different pathogens in the second year, you don’t know if your vaccine recipient has had diarrhea due to rotavirus or due to something else,” Zaidi said.

“Unless you look at the whole panorama of different pathogens in the second year, you don’t know if your vaccine recipient has had diarrhea due to rotavirus or due to something else.”

— Anita Zaidi, Aga Khan University
SESSION III: Impact of Rotavirus Vaccines on Diarrhea Burden

Umesh Parashar of the U.S. Centers for Disease Control and Prevention (CDC) described the impact of rotavirus vaccines on diarrhea burden in the U.S. healthcare system. Both rotavirus vaccines are now licensed in the U.S. RotaTeq was licensed and recommended for infants by the CDC in February 2006, and in June 2008, Rotarix vaccine was also recommended. Most of the data has been generated from use of the RotaTeq vaccine, which up until recently dominated the U.S. market.

In the United States, recommended vaccines are gradually introduced at the state level. There is no reliable national data for uptake of the rotavirus vaccines, Parashar said, but by June 2009 roughly 70% of children five months of age had received the vaccine in nine states where intake is closely monitored. Vaccination for rotavirus was still lagging relative to administration of diphtheria, tetanus, and pertussis (DTaP) or pneumococcus vaccines, more in some states than in others. There was still room for another 15% to 20% additional uptake of rotavirus vaccine in U.S. children.

In terms of the vaccine’s effectiveness, a case-control study from a large Texas children’s hospital during the 2008 rotavirus season enrolled children 15 days to 23 months of age who presented for treatment of acute gastroenteritis. The vaccination rate in cases defined as children with gastroenteritis who tested positive for rotavirus was compared with two groups of controls—children who also had gastroenteritis but tested negative for rotavirus, and children with acute respiratory infections. Depending on the control group, efficacy ranged from 85% to 89% after three doses. After a single dose, efficacy was 65% in both comparisons.

U.S. Surveillance: the Disappearing Seasonal Epidemic

The CDC operates a national surveillance network with about 67 laboratories that have contributed weekly reports on rotavirus sampling since 2000. In the pre-vaccine era, rotavirus followed a regular seasonal curve, with increasing positive diagnoses through the winter months. With the vaccine’s introduction, the seasonal peaks had almost disappeared by the 2009-2010 season.
“The consistency of this decline over three years and the timing relative to vaccination and the stable pre-vaccine trends all support that this is largely due to vaccination—a big reduction in rotavirus detections,” Parashar said. There has also been a shift in the peak of the rotavirus season, from early February toward a month or two later in the year. This may be due to slower transmission, which would require more time for all susceptible children to be exposed to the disease.

Parashar also presented data from an active rotavirus surveillance system, a three-county hospital program that records all children who present with acute gastroenteritis. In pre-vaccine years, half of all cases presenting in hospitals in these counties were positive for rotavirus. In 2008 and 2009, the percent of positives were 6% and 15%, respectively, and early data from 2010 show a level similar to 2008.

**Herd Immunity Effects**

Introduction of rotavirus vaccines seems to have resulted in unexpected benefits through herd immunity. The decline of rotavirus hospitalization from 2006 to 2008 in the three-county system was 66% in infants, and 95% in children 1-2 years of age. About half of the children in these two groups had been vaccinated. Surprisingly, there was also an 85% decline in cases in children 2 to 3 years old, although only 1% of children in that cohort had been vaccinated. This strongly suggests that in addition to protecting vaccinated children, non-vaccinated cohorts and older children were protected by herd immunity.

**FIGURE 3.2**

**Age-Specific Rotavirus Hospitalization Rate Reduction and Vaccine Coverage, NVSN**

<table>
<thead>
<tr>
<th>Age</th>
<th>Decline in rotavirus hospitalization rate (2008 vs. 2006)</th>
<th>Rotavirus vaccine coverage in 2008 (&gt; = 1 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>66%</td>
<td>56%</td>
</tr>
<tr>
<td>1 - &lt; 2 years</td>
<td>95%</td>
<td>44%</td>
</tr>
<tr>
<td>2 - &lt; 3 years</td>
<td>85%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

This age cohort was ineligible to receive rotavirus vaccine

Payne D et al PAS, 2009 and unpublished data
Another means to study the impact of the vaccine is a database of national hospital discharge records, which cover roughly 50% of the U.S. population. These data show that in 2008, there was a sharp drop-off in rotavirus gastroenteritis diagnoses. If extrapolated to the entire U.S. population, the data suggest a reduction of about 50,000 hospitalizations, four or five percent of childhood hospitalizations for all causes.

“It’s a remarkable drop and it’s really more than what we expected,” Parashar said.

A participant from GSK noted that the rotavirus vaccine’s introduction seemed to have had an impact on gastroenteritis hospitalizations beyond those caused by rotavirus. He asked if there was an explanation.

Parashar responded that U.S. hospitalization rates for gastrointestinal disorders in young children have decreased more than would be expected by the decline in rotavirus disease. What this may mean, he said, is that officials have underestimated the burden of rotavirus in the past. Hospitals don’t always test for the virus, since treatment is the same for rotavirus and other diarrheal-caused cases of dehydration, and thus a case of rotavirus diarrhea may not be coded as such. It’s also possible that rotavirus vaccines have a protective effect against some other agents—some studies with the previous rhesus vaccine showed protection against enteric adenoviruses and sapoviruses, he said.

Comparing Rotavirus Vaccines in Australia

Australia is unique in that different states have adopted different rotavirus vaccines, which provides some basis for comparison of Rotarix and RotaTeq. The federal government initiated and paid for vaccinations, but it allowed states and territories to pick which vaccine to introduce. Thus Victoria, New South Wales, Western Australia and Queensland—60% of the country in total—selected RotaTeq, while New South Wales, Northern Territory, and Tasmania decided to use Rotarix.

Carl Kirkwood, from Murdoch Children’s Hospital in Melbourne, reported on the success of rotavirus vaccine in Australia. Before the vaccination era, the virus resulted in an annual disease burden of 120,000 doctors’ visits, 25,000 ER visits, 10,000 hospitalizations and a handful of deaths each year. Both rotavirus vaccines became commercially available in Australia in 2006, but they were not included in a fully funded initiative until July 2007. As of December 2009, 87% of individuals who were eligible for vaccination had received at least one dose, and 84% had a full course—two or three doses depending on which vaccine was used.

Kirkwood presented data comparing post-vaccination rotavirus hospitalizations in Australia’s two most heavily populated states—New South Wales, which introduced Rotarix, and Victoria, which chose RotaTeq. The two sites chosen for the study were similar socioeconomic and cultural settings.

At the Royal Children’s Hospital in Victoria, there was a 60% reduction in short-stay ward admissions and hospital admissions following introduction of RotaTeq in 2007. Rotavirus hospitalizations declined significantly in all the under-two age subgroups.

In New South Wales there was a similar decline. The annual peak in rotavirus infections, which typically occurred around August or September, essentially disappeared. Gastrointestinal emergency department visits for all age groups under 5 have significantly declined.

The data, in short, provide compelling evidence that the introduction of both Rotarix and RotaTeq vaccines into a routine vaccine program resulted in significant decreases in rotavirus-associated gastroenteritis.

Variable Impact on Genotypes?

The Australian researchers also wanted to know what impact the two vaccines have had on circulating rotavirus strains in Australia. This surveillance seeks to detect whether the use of specific disease genotypes in the vaccine has allowed other, non-vaccine genotypes to become more common. The concern is that if non-vaccine strains are impervious to the protection induced by immunization, their growing prevalence can potentially lead to what vaccine experts call replacement disease, which in a worst case scenario would, over time, dilute the initial success of vaccination.

Of potential interest in this respect was the declining prevalence of the G1 genotype, dominant in 2007, following the introduction of the vaccines, which both contain this strain. Of potentially greater interest was the emergence of the G2P4 serotype.
In 2007 it represented just under 10% of cases in Australia, but by 2009, half of the children hospitalized for rotavirus tested positive for this type. The patterns of serotype change differ in the Rotarix and RotaTeq areas. In the post-vaccination era, G2P4 was more prevalent in the Rotarix states, with G3P8 more common in Rotarix states. When scientists compared the prevalence of these strains in the pre- and post-vaccine eras in the two states, the pattern was less clear. While there has been an increase of G2P4 in the Rotarix states, there has actually been a decrease in both G2P4s and G3P8s in the RotaTeq areas. This variability raised the question of whether the genotype changes were due to natural fluctuation of rotavirus populations, or if the vaccines were less effective at protecting against certain strains.

To try to answer this question, the researchers compared genotypes in two states that have introduced RotaTeq vaccination—Victoria and Queensland. Data from Victoria showed that G3P8 genotypes were common from 2007 right through the vaccination era, persisting and increasing in dominance over three years. In Queensland, by contrast, G1P8 strains were the dominant strain in the vaccination era. The suggestion, Kirkwood said, is that at this stage at least, G3P8 persistence is not due to RotaTeq introduction, but is simply part of the natural fluctuation.

Similarly, in the first two years of vaccine usage, G2P4 increased in predominance in the Northern Territory, where Rotarix is in use. But the first six months of 2010 witnessed the emergence of G1P8 genotypes as the main disease-causing agent in the Northern Territory. Again, this suggests that G2 emergence and persistence is due to natural fluctuations rather than use of Rotarix.

In conclusion, Kirkwood said, Australia’s rotavirus vaccination program has had a significant impact on rotavirus-induced gastroenteritis in children. Thus far, there is no clear evidence that the vaccines are causing changes in genotype that pose the risk of replacement disease.

The Latin American Experience

Brendan Flannery of the Pan American Health Organization (PAHO) told the story of rotavirus vaccination in Latin America and the Caribbean (LAC). At a meeting in 2006, the LAC health ministers resolved to mobilize additional funding to introduce new vaccines against rotavirus, pneumococcal, and human papillomavirus diseases. By mid-2010, 13 of the 20 countries in the Americas with the highest mortality rate for children under five years old had introduced rotavirus vaccine.

About 93% of the financing for immunization programs in the PAHO region comes from government funds, which are paid into a collective PAHO Revolving Fund that negotiates vaccine purchases from manufacturers. The Revolving Fund price in 2009 was approximately $15 to fully vaccinate a child. Adding rotavirus vaccines essentially doubled that cost.

Despite this increase, of the countries that introduced the vaccine, only Bolivia and Honduras have received financial assistance from GAVI. (In Africa, one GAVI-eligible country—Ghana—decided to finance the vaccine on its own to guarantee sustainability; other African countries have applied for GAVI funding for rotavirus immunization.) But the introduction of rotavirus vaccine is big news in the Americas, because the results are so dramatic.
Rotavirus accounts for about 7% of all deaths in children under 5 years of age in the Americas—second to pneumococcus among vaccine-preventable illnesses. Rotavirus disease causes an estimated 15,000 deaths, 75,000 hospitalizations and 2 million clinic visits in the LAC region.

Beginning with Panama in 2006, Latin American countries were the first in the world to introduce national rotavirus vaccination programs. The vaccine as of May 2010 had been introduced in 14 countries and the Cayman Islands. Thirteen countries are using Rotarix, two RotaTeq.

Some 10 million children in the region were vaccinated in 2010. Argentina and Chile, two large and relatively wealthy countries, have decided not to introduce rotavirus vaccines yet. The countries with the highest rates of rotavirus related deaths, most of which are in Central America, have almost all (except Belize) introduced a rotavirus vaccine.

Rotavirus vaccine is the only vaccine in LAC immunization programs that has a maximum age limit. Most of the countries using Rotarix have limited vaccination to infants under 24 weeks. There are questions about whether some children would benefit from vaccination after that.

In Nicaragua, vaccination rates with RotaTeq quickly jumped to 80% after the vaccine’s introduction in late 2006, but have not increased since then. This plateau could be a result of the policy of withholding the rotavirus vaccine from children who, when they arrive to receive their regular vaccinations, have aged out of the WHO-recommended group for rotavirus vaccination.

In other Latin American countries there is a 5%-20% difference in the percentage of children who are fully vaccinated with DPT or pentavalent vaccine and those who are vaccinated against rotavirus. Mexico, which has attained almost equal levels of coverage, is an exception.
Impact of Rotavirus Vaccines in the Americas

PAHO supports a rotavirus surveillance network of 61 hospitals, which report monthly in 11 countries. Mexico and Brazil, the largest and most populous countries in the region, do not send data to PAHO but have some surveillance of their own.

From country to country in 2006-2007, which was before the vaccine was introduced, 25% to 50% of the stool samples from children hospitalized for diarrhea were rotavirus-positive. Rotavirus spikes in May and August in the Southern Hemisphere countries, and around February in the Northern Hemisphere countries.

Flannery showed data from El Salvador that demonstrated the graphic impact of the vaccine in that Central American country. Soon after Rotarix was introduced late in 2006, hospitalizations due to diarrhea plummeted, as did rotavirus-positive cases, similar to what occurred in the United States and Australia. Rotavirus-related hospital admissions declined by 76%.

Data from hospitals in Brazil show a 50% decline in rotavirus hospitalizations after introduction of the vaccine. Immunization may have contributed to an apparent herd impact on older, unvaccinated children as well. Overall, Brazil alone has had some 50,000 fewer hospitalizations per year in children under 1. Diarrhea deaths in children under 1 year old declined from an average of 1,701 per year in 2003-2005 to 849 deaths in 2008. Studies in Nicaragua showed a 58% decline in severe diarrhea.

In terms of post-marketing surveillance, Brazil and Mexico are participating in an evaluation of RotaTeq safety that is looking for any risk from intussusceptions.
Rotavirus Vaccination and Mortality: Lessons from Mexico

Like many countries, Mexican authorities have used improved sanitation, safer water, breastfeeding counseling, oral rehydration, and vitamin A supplementation to dramatically reduce the number of diarrhea-related deaths in small children, said Vesta Richardson of the National Center for Child and Adolescent Health. But in the winter months, in the rotavirus season, infantile deaths persisted at a high rate. In 2006, Mexico became one of the first countries in the world to introduce Rotarix in its national immunization program.

Pre-licensure trials of Rotarix did not assess its effect on mortality from diarrhea, though they had shown protective efficacy against 85% of severe rotavirus disease and 42% against severe diarrhea of any cause.

Mexico has 110 million inhabitants, and an annual birth cohort of 1.9 million. The vaccine was phased in gradually beginning in February 2006, when it was introduced to about 5% of the cohort—impoverished children in Mexico’s poorest states. By May 2007 the vaccine was recommended for all infants at two and four months of age.

The federal government purchases and distributes all vaccine to the 32 states in Mexico. Through an electronic registration system, all clinics report to the state on a monthly basis the number of vaccines administered, and the data is submitted to the National Center for Child and Adolescent Health. This administrative data showed that the eligible population had been thoroughly vaccinated prior to the beginning of the January-May rotavirus season in 2008.

As of January 2008, 74% of children under a year of age had received one dose of the vaccine, and 51% had received the second dose. Coverage among children over 1 was low. By January 2009, coverage rates for infants had increased to 81% for the first dose and 74% for the second dose.

The impact on deaths was dramatic. From 2003 to 2006, an average of 1,793 children under 5 died of diarrhea-related illness each year, a rate of 18 per 100,000 children. Two-thirds of these deaths were in children under a year old. Deaths were seasonal, peaking during the winter months. In 2008 that peak began to disappear, and there were only 1,118 diarrhea-related deaths in Mexico. The rate went down to 11.8/100,000—which means that the vaccine enabled Mexico to avert 675 deaths, a 35% decrease.

Results

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of Diarrhea-Related Deaths Baseline (2003–2006)</th>
<th>2008</th>
<th>Diarrhea-Related Rate of Death Baseline (2003–2006)</th>
<th>2008 no. of deaths/100,000</th>
<th>Absolute Reduction No. of Deaths</th>
<th>Rate of Death no. of deaths/100,000</th>
<th>Relative Reduction in Rate of Death (95% CI) %</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages (0-59 mo)</td>
<td>1793</td>
<td>1118</td>
<td>18.1</td>
<td>11.8</td>
<td>675</td>
<td>6.3</td>
<td>35 (29 to 39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤11 mo</td>
<td>1197</td>
<td>680</td>
<td>61.5</td>
<td>36.0</td>
<td>517</td>
<td>25.5</td>
<td>41 (36 to 47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>421</td>
<td>285</td>
<td>21.1</td>
<td>15.0</td>
<td>136</td>
<td>6.1</td>
<td>29 (17 to 39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-59 mo</td>
<td>175</td>
<td>153</td>
<td>2.9</td>
<td>2.7</td>
<td>22</td>
<td>0.2</td>
<td>7 (-14 to 26)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

* Baseline values are the sum of the monthly median numbers of diarrhea-related deaths during the 2003–2006 baseline period.
† P values were calculated with the use of a chi-square test.

Secretaría de Salud, México
The most significant decrease was in children under a year of age. While an average of 1,197 had died each year since 2000, the number fell to 680 in 2008—a 41% reduction. In children above two years of age, the reduction was only 7% and was not statistically significant.

While this analysis cannot provide definitive evidence, Richardson said, rotavirus vaccination was the only intervention added to Mexico’s public health programs in 2007. Between 2003 and 2009 there was a 66% reduction in diarrhea-related deaths of children under 11 months. A substantial decrease in mortality from diarrhea in older children suggests that the vaccine has blunted transmission of the disease and induced herd protection.

Impact of Rotavirus Vaccine Introduction in South Africa

Cheryl Cohen from the National Institute of Communicable Diseases in South Africa presented early results of rotavirus surveillance that followed the introduction of the Rotarix vaccine in South Africa in August 2009.

Vaccination against rotavirus began only a few months after introduction of the 7-valent pneumococcal conjugate vaccine; both programs are funded by the South African Department of Health.

The schedule calls for administration of Rotarix at 6 and 14 weeks. In the first year, coverage was less than 50%; data from early 2010 indicated uptake of 50-75%. Surveillance data is collected at four sites: the Chris Hani Baragwanatha Hospital in Soweto, outside Johannesburg; at Mapulaneng Hospital, on the Mozambique border; at a site in KwaZulu-Natal Province, and at the Dr. George Mukhari Hospital, whose Diarrheal Pathogens Research Unit has been conducting surveillance for rotavirus since 2003.

Rotavirus in South Africa is a very seasonal disease, usually peaking in May, with a second smaller peak a few months later. In summer months there is little rotavirus but quite a bit of other diarrheal disease. Rotarix was chosen in South Africa because at the time it was the only licensed rotavirus vaccine.

Data collected from the sentinel sites through June 2010 showed a major decline in rotavirus-positive stool samples in the 2010 rotavirus season, the first following the vaccine’s introduction. In vaccinated children, rotavirus was detected in 11% of stool samples during the surveillance period, while in the unvaccinated children the rate was 20%.

“These are very preliminary data but they do suggest an early vaccine effect,” Cohen said. “The number of positive samples is really lower this year.”

**FIGURE 3.6**

Cumulative Number of Samples That Test Positive for Rotavirus, NICD Rotavirus Surveillance Sites, South Africa, 2009 and 2010

Source of data: National Institute for Communicable Diseases (NICD) rotavirus surveillance 2009 and 2010
Monitoring “Replacement” Strains After Vaccination

As was noted previously, replacement disease, in the context of vaccination, comes about when a vaccine-targeted pathogen starts to disappear and its ecological niche is occupied by a strain that is less susceptible to immune factors stimulated by the vaccine. There are some suggestions of replacement disease due to pertussis vaccination, and more recently following the introduction of conjugate pneumococcal vaccine.

It is well known that rotavirus has tremendous genetic diversity within regions and from region to region. Theoretically, any of the known P and G complexes could recombine to form new viruses, assuming these recombinations created sustainable viruses.

Brazilian Experience with Serotype Shifts

Jailson Correia discussed a study of the phenomenon in Recife, Brazil, where he is a pediatrician and researcher. Rotarix, which consists of a single attenuated G1P8 strain of human rotavirus, was introduced in March 2006. Its impact on replacement disease was studied at the IMIP hospital in Recife. Pre-vaccine enhanced surveillance in the hospital had shown G1P8 to predominate, accounting for half of all samples taken in 2004 and 2005.

Strain G9P8 accounted for another 29% of cases, with smaller numbers containing G2P4 and G8P6 strains. In the year following universal introduction of the vaccine, the rotavirus-positive samples that also tested positive for the G1P8 strain dropped from about 50% to 6%, while G9P8 dropped from 29% to 23%. The G2P4 strain, meanwhile, increased from 3% to 51%. Toward the end of the period, G2P4 was the only strain recovered from stools.

Fluctuation in the prevalence of G2 strains was not new. From 1982 to 1995 they were the most important strains in much of Brazil. They became less significant from 1996 to 2005. But G2 strains were on the increase in Argentina and other parts of Brazil prior to the introduction of the vaccine. So it is possible that this increase was due not to vaccine pressures, but partly or entirely due to natural variation. With colleagues at the U.S. CDC, Brazilian researchers did a case-control study of G2P4-specific vaccine efficacy and found that it was above 25%.

In short, it is not clear yet whether differential vaccine effectiveness against different strains can contribute to strain replacement or replacement disease. It must be studied more; robust and continued surveillance is needed. But this is not a reason to delay vaccination, Correia said, because the benefits of the vaccine, and the need for it, outweigh concerns that are up to now theoretical. “During the time of my talk, 17 children died of rotavirus associated diarrhea,” he said.

“During the time of my talk, 17 children died of rotavirus associated diarrhea.”

— Jailson Correia, Pediatrician

“These are very preliminary data but they do suggest an early vaccine effect (in South Africa). The number of positive samples is really lower.”

— Cheryl Cohen, National Institute of Communicable Diseases, South Africa
Natural Molecular Evolution of Rotavirus Strains

To deepen the symposia’s understanding of the complex issue of rotavirus serotypes, Jon Gentsch of the CDC presented a background talk on natural evolution of rotavirus strains.

He said it is important to note that new rotavirus strains were known to emerge suddenly before the arrival of vaccines. For example, G9 strains, only rarely reported earlier, exploded in prevalence over the two decades prior to the vaccine’s introduction. Something similar occurred with G12 serotypes. Some strains are associated with animal rotaviruses but evolve and become more important human pathogens. For example serotype G8, a typical bovine rotavirus, has apparently reasserted with human rotaviruses to gain a foothold in Malawi.

By 2008, 19 different G genotypes and 27 different P genotypes had been sequenced and published, and additional genotypes have been recognized since. Using classification schemes based on the degree of genetic homogeneity among these types, researchers are able to track their evolution in detail. This is important for monitoring vaccination programs, Gentsch said, because it will help researchers understand how they impact the rotavirus genome—and provide clues on changes in vaccine effectiveness, if they occur. Full-genome sequencing will also allow researchers to look at interspecies transmission and how this impacts evolution of human rotaviruses.

Evidence suggests strongly that human rotaviruses have been derived by a direct interspecies transmission from animals. Studies of individual genes of human and animal rotaviruses have shown identical genomic profiles, molecular proof that interspecies transmission occurs and can create unique new human strains.

We should expect to see continuing emergence of new rotavirus strains, Gentsch said, but luckily, our vaccines appear to protect against strains other than the ones they contain.

Raul Velazquez of Mexico commented that it was important to have work such as that being done by Gentsch and his colleagues. “I think there is a major issue to know whether these changes of serotypes over the world are due to natural changing or vaccine pressure,” he said. “We don’t have any answer for this … and this is important because it’s related to efficacy or the effectiveness of the vaccines in the future.”
James Baggs, from the Immunization Safety Office at CDC, reported on the results of four years of monitoring rotavirus vaccines for evidence of adverse events in the United States. The CDC has focused on potential links to intussusception, the telescoping of the bowel that was linked to the first rotavirus vaccine, RotaShield, and prompted its removal from the market.

On the Lookout for Intussusception in the United States

Vaccine safety surveillance studies by the CDC are based primarily on two databases.

One is the Vaccine Adverse Event Reporting System (VAERS), a nationwide passive reporting database using self-reports from drug companies, doctors, patients, and others. VAERS found no overall link to intussusceptions, but did find a relative risk of 1.71 in the seven days after the first dose of the three-dose RotaTeq vaccine, which dominated the U.S. market during the reporting period. This risk finding did not quite reach statistical significance. Also, there are many limitations to the VAERS data because it is a passive system. Traditionally it has been thought to underreport vaccine reactions, but it may also receive flurries of purported adverse event reports that come in response to media stories.

The CDC also employs the Vaccine Safety Datalink (VSD), a collaboration with eight managed care organizations that has been used to answer vaccine safety questions since 1990. The network captures 9 million people, about 3% of the U.S. population. A new VSD project called rapid cycle analysis has been used to provide quick answers to safety questions about new vaccines. The VSD now updates data on all vaccines and every outcome each week. For each vaccine, CDC chooses a number of specific outcomes to monitor.

For RotaTeq, the CDC undertook a rapid cycle analysis from May 2006 to May 2008 to monitor for an increased risk of intussusception and other adverse events. It found no increased risk of intussusception and 0 cases of the disorder following the first dose or within 7 days of any dose among the 207,621 doses of vaccine administered to the group under study.

**FIGURE 3.6**

**VSD Rapid Cycle Analysis of RotaTeq® Vaccine, May 2006 – May 2008**

**Major Findings**

- Five cases of IS with 30 days after RotaTeq® in the computerized data
  - Did not exceed expected
  - No cases within 7 days of vaccination
  - 207,621 doses included

- Only 2 cases validated after medical record review
  - Neither case occurred following dose 1

- Results provide no evidence that RotaTeq® receipt is associated with an increased risk for IS or other pre-specified adverse events
In a separate review, the CDC used VSD data to examine outcomes from a total of nearly 840,000 doses, including 328,000 first doses. This study found an overall risk ratio of 0.81 in the 30 days following RotaTeq. Looking at dose one only, the CDC found no increased risk 1-7 days after administration of the vaccine, but did find a 1.46 increased risk of intussusceptions in the 30 days following dose 1. However, the confidence intervals were too wide to give significance to this number.

Looking at the VSD data from 2001 to 2009—RotaTeq was introduced in 2006—there is no change in the rate of intussusceptions in hospital settings, but a trend line upward in outpatient intussusception rates, perhaps beginning in 2008. However, it is important to understand that the natural rate of intussusceptions has increased over time, which makes the comparison of historical data tricky.

In summary, the U.S. post-marketing experience in VAERS and VSD provide no evidence that RotaTeq is associated with an increased risk for intussusception either in a 30 day window or the seven day window following vaccination. There is continued surveillance of this effect. At this time the VSD has limited data on Rotarix. An early analysis of VAERS showed no increased risk.

Intussusception in Australia

Dr. Julie Bines, pediatric gastroenterologist at the University of Melbourne, provided an update on the Australian safety monitoring experience.

Some 87% of eligible infants in Australia received at least one dose of a rotavirus vaccine before four months of age in 2009, and 84% received a complete course. The mixture of Rotarix and RotaTeq used in various Australian states offered an opportunity to compare the safety profile of the two vaccines.

Surveillance included passive adverse event reporting through the Therapeutic Goods Administration, the Australian version of the FDA, and a number of active intussusception studies, including one conducted through the Australian Pediatric Surveillance Unit (APSU).

All pediatricians and pediatric surgeons in Australia were sent e-mails or report cards over the first two years of the vaccines’ introduction, asking them to indicate whether they had seen a case of intussusception. If they indicated yes, there were sent a questionnaire and asked to validate the diagnosis according to the Brighton Criteria. They also were asked to provide immunization data, clinical presentation and outcome information.

A second study looked at adverse events to vaccination at four sentinel sites in four states, two of which had adopted Rotarix and two RotaTeq.

Dr. Bines presented data from both studies for the first 18 months following introduction of rotavirus vaccines. Researchers calculated the expected rates of intussusceptions based on historical data from 1994 to 2006. Over this period of time there was a decline in the incidence rate of intussusception in children under 2. The data showed 200 cases of intussusceptions in the four sentinel states—including eight recurrent episodes, which were removed from the study. Of the remaining 192 cases, 92 occurred in vaccinated children. These included 23 cases of intussusception in the first 21 days following rotavirus vaccination.

In Victoria state, where 66,000 children received RotaTeq vaccine, there was no difference between expected and observed cases after the completion of the three-dose series. However, there were three cases within the first week of the first dose, against an expected rate of 0.6 cases, and six cases within the first three weeks of the first dose, against a background rate of 1 or 2.

Similarly, for the Rotarix vaccine, there was no overall difference between the expected rate and the actual rate over the first nine months of life in vaccinated and unvaccinated children. Again, there was a small increase over the expected rate in the first week after the first dose of Rotarix, and in the first three weeks after that first dose.

The background rate was calculated as the average rate from 2001 to 2006. However as noted, the pre-vaccination rate of intussusceptions was going down over this period. Because of this fact and the potential for underreporting—not all intussusceptions are admitted to the sentinel hospital in Victoria—health officials do not believe that they have overestimated the relative risks, Bines said. However, the number of cases is very small, and the confidence intervals are great.
“Why might the Australian experience differ from the US experience?” asked Bines. She said the vaccine was new, with a fairly limited period of time of observation, for a rare condition with a small number of cases. Methodologies used for reporting in post-marketing surveillance in Australia are quite different than those used in the United States. Australia has relatively high background rates of intussusception, as do Vietnam and Hong Kong, when compared to the United States. The explanation for this is unclear, but the data are sound.

The results of these studies, Bines said, merit further continued post-marketing surveillance for intussusceptions, particularly in regions with different baseline intussusception rates compared to the U.S.

**Variation in “Baseline” Intussusception Rate in Infants in Different Regions**

<table>
<thead>
<tr>
<th>Country</th>
<th>IS Hospitalization Rate per 100,000 Infants</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panama</td>
<td>30.0</td>
<td>1998-2002</td>
<td>Saez-Lorens et al</td>
</tr>
<tr>
<td>United States</td>
<td>33.6</td>
<td>2001-2004</td>
<td>Tate et al</td>
</tr>
<tr>
<td>Venezuela</td>
<td>35.0</td>
<td>1998-2001</td>
<td>Perez-Schaed et al</td>
</tr>
<tr>
<td>Switzerland</td>
<td>38.1</td>
<td>2003-2006</td>
<td>Buettcher et al</td>
</tr>
<tr>
<td>Latin America</td>
<td>51.0</td>
<td>2002</td>
<td>Abate et al</td>
</tr>
<tr>
<td>Chile</td>
<td>51.0</td>
<td>2000-2001</td>
<td>O’Ryan et al</td>
</tr>
<tr>
<td>New Zealand</td>
<td>65.1</td>
<td>1998-2002</td>
<td>Chen et al</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>66.0</td>
<td>1994</td>
<td>Gay</td>
</tr>
<tr>
<td>Taiwan</td>
<td>68.4</td>
<td>1999-2001</td>
<td>Ho et al</td>
</tr>
<tr>
<td>Denmark</td>
<td>68.8</td>
<td>2001</td>
<td>Kolsen-Fischer et al</td>
</tr>
<tr>
<td>Australia</td>
<td>81.0</td>
<td>2000</td>
<td>Justice et al</td>
</tr>
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<td>Hong Kong</td>
<td>88.2</td>
<td>1997-1999</td>
<td>Nelson et al</td>
</tr>
<tr>
<td>Vietnam</td>
<td>302</td>
<td>2003</td>
<td>Bines et al</td>
</tr>
</tbody>
</table>

**Rotavirus Vaccination and Immune Deficiencies**

Because many infants in Africa are HIV-positive, researchers have attempted to determine the impact of rotavirus vaccination on children with any type of immune syndrome.

One syndrome that appears to have a negative interaction with rotavirus vaccination is severe combined immunodeficiency (SCID), a rare, multifaceted dysregulation of the immune system. It occurs in the United States at the rate of about 1 in every 40,000 cases. In most developing countries it is not even diagnosed, because many of these children die early in life without much explanation.

It is known that rotavirus causes severe, unremitting chronic diarrhea in SCID children, with persistent prolonged rotavirus shedding, said Madhi of Witwatersrand University. There are even case reports of systemic illness when the child’s gut is unable to contain the infection.

In a recent issue of the New England Journal of Medicine, investigators reported on three SCID children who continued to shed live rotavirus particles up to a year after vaccination. In one of the cases, the vaccine strain was disseminated to another person.

Normally, the virus is shed for about three or four days after vaccination. On the basis of this finding, SCID has been listed as a contraindication for vaccination against rotavirus. Unfortunately, the syndrome usually
only presents at four to six months of age. By then most children would already have been vaccinated against rotavirus. Screening for SCID is almost impossible; in the cases reported in the NEJM, post-vaccine rotavirus infections led to diagnosis.

**HIV’s Impact on Rotavirus Disease**

HIV shares some similarities with SCID in terms of immuno-suppression. The incidence of HIV in many countries in Southern Africa is around about three to five cases per 100 live births, despite efforts to stop maternal-child transmission. Around 50,000 children are born HIV-infected in South Africa alone each year. Obviously, understanding the safety of the vaccine in this particular population is of paramount importance.

There is data indicating the risk of diarrheal disease in HIV-positive children. In a recent Kenya study, the burden of acute gastroenteritis in HIV-infected children was around five times higher than in HIV-negative children. In Kenya and in two other studies where this issue has been examined, the prevalence of rotavirus detection in HIV-infected children with severe gastroenteritis was slightly lower than for HIV-negative children. However, rotavirus disease causes about two times as many serious illnesses in HIV-infected children. In short, while rotavirus is less frequently discovered as the cause of acute diarrhea in HIV-positive children, the overall burden of the virus in this group is still proportionally higher.

Studies in Malawi have shown that the clinical course of rotavirus illness in HIV-infected children is fairly normal, except that HIV-infected children have more prolonged asymptomatic shedding of the virus, for up to about four weeks post-diarrheal disease. Following infection with wild-type rotavirus, seroconversion rates for IgG and IgA were similar between infected and uninfected children.

**Rotavirus Vaccination in HIV-positive children**

A key issue, of course, is whether the rotavirus vaccine is effective in combating the disease in HIV-positive children, and whether a live virus it can cause or accelerate rotavirus illness in these children. A study in South Africa by Duncan Steele, who leads PATH’s rotavirus initiative, addressed this issue, focusing on Rotarix. This is a significant issue, because in the vaccine studies conducted in Malawi and South Africa, about 5% of the children included were HIV-positive.

HIV-positive children in the South Africa trial were randomized to receive placebo or Rotarix in a three-dose schedule, with seroconversion rates measured at two months after the third dose. Most of the children in this study had not received antiretroviral drugs by the time the titers were measured. In this study group, 70% of the HIV-infected children had normal CD4 counts at the time of immunization, but two months after the third dose of vaccine, 60% of the children had already progressed to moderate to severe AIDS.

There were no relevant differences between the control and vaccine groups in the amount of severe fever, diarrhea or vomiting within seven days of each dose of vaccine. There was also no difference in terms of the change of CD4 count or CD4 percentage between the vaccinated and placebo arms. The vaccine does not appear to have caused progression of AIDS in these children.

As for the vaccine’s immunogenicity, the seroconversion rate in children with HIV two months following the third dose of vaccine was 57%, which viewed as a response to the vaccine. By comparison, in the placebo group, only 18% seroconverted, evidently because of infection with wild-type rotavirus over this period. In the parallel group of South African children who were not HIV-infected, indications of vaccine efficacy or the “take rate” after three doses of the vaccine was 67%. There were only 50 HIV-positive children in the vaccinated group, but the results were statistically significant.

The proportion of HIV-positive children shedding rotavirus vaccine after the first dose of vaccine was around 37%, but only one of these 50 children shed vaccine virus after a third dose of vaccine. This child continued shedding virus for 60-75 days post-vaccination, indicating that even in some select HIV-infected children perhaps with severe immune suppression, there’s an inability to actually control replication of attenuated rotavirus vaccine as well.

In short, these results indicate that Rotarix is generally safe and immunogenic in HIV-positive children. Thus far, there is a lack sufficient data indicating the degree of efficacy against rotavirus disease in these children.
Global Perspectives on Rotavirus Vaccine Safety

Melinda Wharton of the National Center for Immunization and Respiratory Diseases at CDC spoke to the gathering as a member of the WHO Global Advisory Committee on Vaccine Safety (GACVS). This group, established in 1999 to provide independent scientific assessments to WHO, has reviewed safety data from rotavirus vaccination since 2006.

In June 2007 the committee concluded that safety data from RotaTeq and Rotarix was reassuring in regard to intussusception, adding that it would be important to continue monitoring for the disorder as developing countries introduced the vaccines. The committee also discussed the occurrence of Kawasaki disease among the recipients of RotaTeq. The committee felt there was at best a hint of a signal linking the disorder to RotaTeq, and a later meeting concluded there was no strong evidence of a causal association.

At a December 2008 meeting, the committee ruled out an intussusception risk on the order of magnitude that had been found with RotaShield. But it determined that post-marketing data from the two newer vaccines was insufficient to confidently rule out a much lower-magnitude risk.

It has been hypothesized that giving rotavirus vaccines outside the recommended age range could be associated with an increased risk of intussusceptions, but no data directly support this hypothesis. Even if there were a theoretical small increase in risk, the benefits of vaccination would exceed any risk of intussusception.

Therefore, at its June 2009 meeting, the global safety committee recommended expanding the age eligibility for vaccination beyond 32 weeks, the age limit recommended by the WHO Strategic Advisory Group of Experts (SAGE), in order to maximize coverage of the vaccines, especially in countries with high rates of childhood mortality from diarrheal disease.

Porcine Circovirus and Rotavirus Vaccines

The WHO Global Advisory Committee on Vaccine Safety reviewed the porcine circovirus (PCV) contamination issue in March 2010 and again in May. After being informed by an academic investigator that DNA sequences of PCV1 were detected in two commercially available batches of Rotarix in the United States, GlaxoSmithKline did its own testing and confirmed the presence of PCV1 DNA throughout the entire production process of the vaccine.

On March 22, the U.S. FDA recommended that clinicians in the United States temporarily suspend the use of Rotarix vaccine while the agency gathered additional information.

The Global Advisory Committee, which met by teleconference on March 25th, supported the safety of Rotarix based on large clinical trials pre-licensure and an extensive post-licensure experience.

At an FDA advisory committee meeting on May 7th, 2010, GSK documented the lack of evidence that the virus could undergo productive infection in human cell lines. The company also presented an analysis of specimens from clinical trials and found no evidence for infection of infants with porcine circovirus type 1. Merck later found much smaller amounts of PCV in its rotavirus vaccine.
Safety Data: Future Needs

Although data support the safety and effectiveness of both Rotarix and RotaTeq, ongoing evaluation is needed to provide additional data for the expanded age groups. Any national immunization programs that elect to extend age eligibility for the first dose of rotavirus vaccine to infants aged greater than 15 weeks, or the last dose beyond 32 weeks of age, should initiate monitoring for effectiveness and safety, Wharton said.

Rates of intussusception in unvaccinated children are higher among older infants, so even if there is no causal relationship, cases of intussusception in temporal association with vaccination will be more likely to occur in infants who are vaccinated when aged more than 15 weeks. It is essential to monitor intussusception in these infants with correct interpretation of the data.

“Fundamentally, decisions about use of vaccines are decisions about risks and benefits,” Wharton said. When considering possible risks from intussusceptions, as well as emerging theoretical risks such as PCV and small risks such as the harm the vaccine may cause children with rare immune deficiencies like SCID, it’s important to keep this fact in mind, she said.

“The Global Advisory Committee is on record that we think expansion of the age restrictions could be undertaken.”

-- Melinda Wharton, WHO

Discussion of Vaccine Safety Issues

A participant from Kenya said that it was likely, given the logistical challenges in Africa, that a child would receive Rotarix from one facility and RotaTeq from another. The question was whether there are studies about how the two vaccines interact.

Umesh Parashar said he was not aware of any evaluations of mixed schedules of the two vaccines. But on a biological basis, he said, it was probably recommended that any child who received one RotaTeq vaccine should receive three because it is on a three-dose schedule regardless of whether the child also got a Rotarix vaccination.

A participant from Mexico asked whether any of the HIV-positive children in the Rotarix trial had viremia from the vaccine virus.

Madhi said the studies did not look for post-vaccine viremia, but none of the 250 HIV-positive children had contracted diarrheal illness from a rotavirus vaccine strain.

An unidentified African participant noted that many countries lack capacity for post-introduction surveillance and wondered: What is being done to ensure countries can detect adverse effects?

Melinda Wharton said WHO has projects underway to try to help build surveillance capacity. Many individual countries probably won’t be able to conduct intensive vaccine safety studies, but they should be able to respond to safety concerns, she said.

An unidentified participant from Pakistan asked about the possibility of revising age limits for the rotavirus vaccines. Since it’s unlikely that large-scale trials of these vaccines will be held in the future, does this mean countries are stuck with the age limits forever?

Wharton said that the Global Advisory Committee felt that, especially in countries with high mortality rates, the risks of expanding age limits were minimal at worst, while the benefits might be great. While SAGE did not take this position, “the Global Advisory Committee is on record that we think expansion of the age restrictions could be undertaken.”

An unidentified participant said that it was his understanding that not all intussusception cases are detected, and some may resolve spontaneously. He asked whether it was possible that a small percentage of cases of intussusception were being missed in children who had been vaccinated in the previous seven days.

Bines of Australia said that a small percentage of intussusceptions, perhaps 10%, resolve without surgery or other intervention and thus might not be counted in safety studies. On the other hand, even if these cases represented a higher number of vaccine-related intussusceptions, the net benefit of the vaccines was still clearly very high.
A Sudanese participant asked whether it might be better to focus on clean water rather and improving hygiene to reduce rotavirus morbidity and mortality, rather than vaccination.

Parashar said that clean water, better sanitation and vaccination were part of a package of tools to fight not just rotavirus but other infections as well. Still, “even in settings where there is good access to clean water, and reasonable environmental hygiene, in high-income counties, you still get this infection very early in life in almost all infants,” he said. “Even in settings with good hygiene and sanitation, you won’t really fully prevent this disease, and that’s really been one of the drivers for vaccination as an effective prevention strategy.”

“Even in settings with good hygiene and sanitation, you won’t really fully prevent this disease, and that’s really been one of the drivers for vaccination as an effective prevention strategy.”

— Umesh Parashar, CDC

A speaker from Gambia said that especially in the African region, the protective level of the rotavirus vaccines was still low. “I hope there are plans to do more to improve the vaccine, to have a higher efficacy level,” the speaker said.

Parashar reiterated that while the level of efficacy was lower in low income country settings, the take-home point is that “even with the reduced protection, because the burden of disease is so much higher and the rate of disease is so much higher in developing country settings like Africa relative to developed settings, you actually will prevent a lot more severe disease in terms of numbers of cases prevented per thousand vaccinated children despite that somewhat lower efficacy.” He added, “you do still want to find ways to make these vaccines work even better, but what you have today is fairly good.”
SESSION V: The Rotavirus Vaccine Pipeline

The second day of the session focused on the rotavirus vaccine pipeline—vaccines under development now, and the prospects for rotavirus vaccines that may be less expensive, easier to produce, more immunogenic, and in general more appropriate for African or certain Asian settings.

To be sure, even if the efficacy of current vaccines’ against severe rotavirus diarrhea was only 60%, if these vaccines were made available around the world, and 70% of children received them, in 15 years it would be possible to save the lives of 1.7 million children.

A strong rotavirus vaccine pipeline, and strong markets for the vaccine are crucial to getting existing and future rotavirus vaccines to those who need them, said Deborah Atherly, an economist from PATH.

To date, 24 countries have introduced rotavirus vaccine, representing a birth cohort of 14 million children. Of those 24 countries, none are among the world’s poorest, though nine are in the World Bank-defined “lower-middle” area.

The endeavor to get rotavirus vaccines to the poorest countries is aided by the fact that much of the intellectual property for rotavirus vaccines is public and has been transferred to vaccine makers in many countries, Atherly said.

Supply, Demand, and Lower Vaccine Prices

The development of a pipeline of new rotavirus vaccines has obvious advantages in terms of increasing supply to meet demand, and lowering prices. Within 10 years, by 2020, GAVI forecasts a demand for about 200 million doses of rotavirus vaccine in 65 countries. If every country in the world introduces rotavirus vaccines at a coverage rate commiserate with other vaccines, demand could rise to more than 300 million doses. The current market is about 30 million doses.

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FIGURE 5.1

Vaccine Efficacy Against Severe Rotavirus GE in the First Year of Life, by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Vaccine</th>
<th>Countries</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Rotarix™</td>
<td>Malawi, South Africa</td>
<td>61.7</td>
<td>44.0, 73.2</td>
</tr>
<tr>
<td>Africa</td>
<td>RotaTeq®</td>
<td>Ghana, Kenya, Mali</td>
<td>64.2</td>
<td>40.2, 79.4</td>
</tr>
<tr>
<td>Asia</td>
<td>RotaTeq®</td>
<td>Bangladesh, Vietnam</td>
<td>51.0</td>
<td>12.8, 73.3</td>
</tr>
</tbody>
</table>

The GSK and Merck vaccine courses currently sell for US $120 to $200 in the industrialized countries. In South Africa, the price for the GSK two-dose course is more than US $20. The PAHO Revolving Fund for Vaccine Procurement, which contracts with vaccine manufacturers on behalf of the countries of Latin America and the Caribbean, is paying US $15 a course for Rotarix, US $16.50 for RotaTeq.

GSK and Merck are meeting current demand, and they have offered discounted or tiered pricing for developing countries. It’s estimated, Atherly said, that Merck and GSK could ramp up to 120-150 million doses per year, or even higher, with some capital investment. Whether the companies will make these decisions while offering the vaccines at prices affordable to the newer markets is not clear.

New Players on the Horizon

Thus it is fortunate, Atherly said, that over the next five to seven years as many as six new suppliers, from India, China, Indonesia and Brazil, may enter the market. Between them, the six companies could produce somewhere between 200 and 400 million doses per year. With more producers, price should fall.

For example, prices dropped when new suppliers entered the market for Haemophilus influenzae type b (Hib) and hepatitis B vaccines. Prices fell by 40%, while demand more than doubled. A similar trend occurred with the introduction of new Hib-containing pentavalent vaccines in 2008. Demand has more than doubled, and prices were expected to decline 40% by 2012.
Affordable vaccines are essential to donors, as evidenced by the impact of the economic downturn on GAVI’s funding, which is causing delays in vaccine introduction. Even if countries obtain vaccines through GAVI, sustaining their use after GAVI assistance expires requires that they be affordable within the context of an individual country’s budgetary limitations.

Also, many of the non-eligible developing countries that will need to self-fund introduction of rotavirus vaccine currently spend less on health per child than an entire course of rotavirus vaccine would cost, Atherly noted.

Thus, a healthy and globally diverse industry is vital to ensuring an uninterrupted and sustainable supply of affordable vaccines. Self-producing countries such as India or China may strongly prefer local production.

Atherly said that achieving the right balance between supply and demands is a difficult task.

“If we give subsidies and build the demand but there is no supply or we build up supply and there is no demand, then it’s a problem,” she said. “We need to make sure everyone is looking at what the others are doing.”

New Rotavirus Vaccines in Development

Dr. Georges Thiry, director of PATH’s Advancing Rotavirus Vaccine Development project, presented an outline and details on some of the leading rotavirus vaccines currently under development.

Thiry noted that a third rotavirus vaccine already exists. In 2000, China approved a one-dose oral vaccine produced by Lanzhou Institute Biological Products. It is a monovalent live-virus vaccine produced from a sheep rotavirus. About 10 million doses were administered between 2000 and 2008, and an additional 5 million doses in 2009. The vaccine has been produced solely for China’s domestic market.

Six other live attenuated vaccines have advanced to clinical testing, including Phase 3 trials, which is the last step before licensure. A G9P11 monovalent vaccine under development by Bharat Biotech in India contains a VP4 element of bovine origin. Phase 2 trials have been completed, and Phase 3 trials are being prepared in India.

Murdoch Childrens Research Institute in Australia is developing a G3P6, Vero cell-grown strain in Indonesia.
which is in Phase I. POLYVAC, a Vietnamese firm, has developed a G1P8 human strain through Phase I studies under the name Rotavin.

The International Medica Foundation has taken the license to Wyeth’s quadrivalent RotaShield vaccine and revived it. The vaccine is being produced by IDT Biologika, a German-based contract manufacturer. The vaccine is in Phase IIb trials in Ghana.

(According to information on the International Medica Foundation’s Web site, the safety concerns regarding the potential link between RotaShield and intussusceptions can be addressed by maintaining strict requirements on age of administration. “Recent scientific evidence supports the safety of RotaShield when it is administered to infants at the appropriate age and it is not associated with intussusception.” For more information, see http://www.intl-medica.org/rotashield.asp)

Four different manufacturers are collaborating to develop a bovine reassortant vaccine. These are Shantha Biotechnics and Serum Institute of India, Instituto Butantan in Brazil, and Wuhan Institute of Biological Products in China. The vaccine is a human-bovine reassortant based on a virus developed by Albert Kapikian at the U.S. National Health Institute and licensed in 2006. A Phase 2b study in Finland demonstrated 90% efficacy. It was being tested in clinics in Brazil and India in 2010.

Lanzhou Institute of Biological Products is also developing a reassortant strain, based on their sheep (ovine) virus. They have replaced the G10 with G2, G3, and G4, to make a trivalent candidate that is being tested clinically.

**Additional Vaccine Candidate, and a Timeline**

While predicting the outcome of any medical product still undergoing clinical testing is very risky, Thiry said there might be as many as five additional rotavirus vaccines licensed by 2015, and another four vaccines by 2017.

In addition to the live-virus vaccines listed above, four different U.S. research centers—at the CDC, Baylor College of Medicine, Cincinnati Children’s Hospital, and the National Institute of Allergy and Infectious Diseases—are conducting early experiments with inactivated rotavirus or rotavirus subunits. The inactivated products could in theory be licensed perhaps in the 2017-2020 range.

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**FIGURE 5.4**

Advancing Rotavirus Vaccine Development (ARVAC)
Various technologies are being evaluated that could reduce the need for cold storage, minimize packaging costs and optimize the ease of administration. Adjuvants, which can increase the immune stimulating properties of vaccines, are being considered for some of the inactivated vaccines. Genetic engineering of rotavirus also presents possibilities in the future design of vaccines as well.

“If we give subsidies and build the demand but there is no supply or we build up supply and there is no demand, then it’s a problem. We need to make sure everyone is looking at what the others are doing.”

— Deborah Atherly, PATH

Portrait of the Push to Provide More Rotavirus Vaccines

International public-private collaborations are greatly accelerating the development of new rotavirus vaccines, particularly vaccines that could be relatively inexpensive and more easily stored and administered.

A good example is a new vaccine candidate that has been developed from a rotavirus strain associated only with asymptomatic infections or mild diarrhea. Nita Bhandari from the Society for Applied Studies in India, said the vaccine, known as 116E, is currently in Phase II trials under license to Bharat Biotech International Limited, in Hyderabad.

The vaccine candidate, a G9P11 serotype, was isolated at a hospital in New Delhi from children with no symptoms of rotavirus. Follow up indicated the infected children were protected from severe rotavirus diarrhea for up to two years. PATH and the government of India are participating in the vaccine’s development, with the assistance of Glass and other U.S. scientists.

A study presented by Dr. Bhandari was designed to evaluate the safety of the 116E rotavirus vaccine candidate. For the study, the vaccine was administered three times orally at four week intervals and at two dosage levels. The test subjects were healthy infants 8 to 20 weeks of age. A secondary objective was to evaluate the immunogenicity of the vaccine.

Children enrolled in the study were recruited from an urban setting and given routine childhood vaccines—DPT, polio vaccine and hepatitis B—at 6, 10 and 14 weeks of age. The test article (vaccine or placebo) was given at 8, 12 and 16 weeks. Infants were followed up on a daily basis for 14 days after each of the three administrations, and there was a weekly follow-up visit on days 21 and 28.

A total of 1,165 infants were screened, 187 were enrolled in one arm of the trial and divided into placebo and vaccine groups. Similarly, for the other arm, testing a different dosage, 238 infants were eligible for enrolment and 182 were enrolled (and also divided into placebo and vaccine groups).

The vaccine appeared to be generally safe, there were no intussusceptions reported, and there was evidence of immunogenicity after one dose. Given the encouraging results, multicenter trials were planned and expected to begin by the end of 2010.
Making the Most of Existing Vaccines

Duncan Steele of PATH noted that a number of factors interfere with the efficacy of current rotavirus vaccines. If these obstacles could be removed, the vaccines would provide better immunity and save more lives, said Steele. Experience with several live oral vaccines has shown that the immune response to these vaccines is blunted by nutritional deficiencies, maternal and trans-placental antibody levels, and by other microbial infections that interfere with the immune response in a variety of ways. Some of these problems, such as parasitic infections or gut diseases, are only going to change when there is global socioeconomic improvement and children live in more sanitary conditions.

Efficacy Quandary: Maternal Antibodies and Breastfeeding

Maternal antibodies—antibodies passed to the fetus during pregnancy—clearly play a role in vaccine efficacy. Studies in Mexico, Finland, and South Africa all showed that a relatively high level of maternal rotavirus antibodies is associated with an impaired response to rotavirus vaccination.

In a Mexican study by Guillermo Ruiz-Palacios and Dick Ward, children who developed antibodies against rotavirus or “seroconverted” after vaccination had a geometric mean concentration of anti-rotavirus immunoglobulin A (IgA) of about 170. The level in the children who did not respond to the vaccine was significantly higher, almost 360. In a South Africa study, the children who ended up failing to seroconvert after vaccination were the ones whose mothers had higher IgA levels before the rotavirus season. During the season, all the mothers have these higher antibody levels. Though maternal antibody probably plays a role in the poor immune responses seen in infants in developing countries, Steele said, there is little that can be done about that.

Breastfeeding is another component of the equation. Breast milk contains rotavirus antibodies, as well as factors such as rotavirus-specific proteins called lactadherins. In-vitro studies show that breast milk can neutralize rotavirus, which leads one to question whether breast milk would weaken a rotavirus vaccine. Studies are underway to determine the impact these neutralizing factors have when a breastfed baby receives a live oral rotavirus vaccine.

But even if it turns out that breastfeeding blunts the impact of the vaccine, Steele said, addressing this problem would be extremely complicated. WHO strongly encourages breastfeeding, especially for children with diarrheal disease. It would be difficult to alter this recommendation, for example, by asking that mothers suspend breastfeeding during the vaccination period.

Julie Bines asked whether specific neonatal strains of rotavirus would persist despite the presence of high circulating maternal antibodies. Steele said that neonatal strains, such as the 116E strain that is under development as a vaccine, have been demonstrated to persist in young children less than 28 days of age. They seem to be able to replicate despite the high levels of maternal antibodies.

“I think it points out there certainly is a potential for improvement, with Rotarix vaccine, by looking at an alternative schedule from the two dose schedule.”

— Shabir Madhi, University of Witwatersrand
Improving Efficacy by Delaying or Adding Doses

Steele discussed whether an additional dose could be added, for example, to the two-dose Rotarix schedule. At present, WHO recommends that the GSK vaccine be given concurrently with DPT1 and DPT2; that is, at 6-8 weeks of age and at 10-12 weeks, but never after 32 weeks.

Data during trials in South Africa and Malawi showed the vaccine’s efficacy in terms of serology increased with a third dose of the vaccine. This also occurred in studies in Bangladesh. An evaluation of the efficacy of two versus three doses in these very small studies indicated not much effect in Malawi, the more resource-poor environment.

A much larger effect is seen when two doses are given at older ages. For example, in Vietnam when doses were given at 9 and 13 weeks, anti-rotavirus IgA antibody seropositivity rates were 62.5%, compared to 81% when the vaccines were given at 13 and 17 weeks. In South Africa, seropositivity was 36% when the vaccine was given at 6 and 10 weeks, but 61% when the vaccine was given at 10 and 14 weeks.

However, many children in developing countries already receive their vaccines past the recommended date, and it might be counterproductive to recommend that children be vaccinated later rather than earlier – especially when, as has been clearly shown, the rate of serious rotavirus infections in younger children is quite high, Steele said. While later immunization might improve immune response and efficacy, it might not produce a net benefit in terms of serious illness prevented and lives saved.

The issue of age for optimal immunization leads to another question, which is whether a later booster vaccine should be considered. The data from studies in Africa and Asia indicate waning immunity for both Rotarix and RotaTeq. If a booster dose was to be given, the best time might be at age 9 months, with the measles vaccine.

Studies would need to show whether there are interference or safety concerns with co-administration of these two vaccines. In addition, the studies would have to be large to pick up an impact from the booster shot, because in general the burden of disease is much lower in the second year of life, Steele noted.

Finally, Steele said, supplementing vaccination with probiotics or micronutrients might increase efficacy. A study conducted in 1995 with a rhesus monkey-derived rotavirus vaccine showed improved seroconversion in the group of children who received Lactobacillus casei.

Potential Benefits of Killed-virus Vaccines

Baoming Jiang of the U.S. CDC, who is co-developing a killed-rotavirus vaccine, discussed ways in which his and other vaccines in development might offer ways to skirt problems posed by live oral rotavirus vaccines.

All live-virus vaccines evaluated so far have been far less efficacious in the developing world, as noted previously, a fact that holds true for oral polio and cholera vaccines as well, Jiang noted. Maternal antibodies and breast milk play a role, as do gut overgrowth, malnutrition, and simultaneous infections with diseases like HIV, malaria, and tuberculosis. In the industrialized world, mixed infections are very rare.

In developing countries they are common. Co-infections lower the rate of rotavirus replication in the gut.
While there may be ways to improve administration of the oral live vaccine, Jiang said, it may be advantageous to administer injectable vaccines.

"I think we realize that we should not put all the eggs in one basket," he said. The advantages of an injectable vaccine are many. First, such vaccines probably would not carry the risk of intussusceptions or vaccine contamination, eliminating some safety concerns and thus making development cheaper, with a trial size of 5,000 possible, rather than the 70,000 or so required for Rotarix and RotaTeq. Killed or subunit vaccines could be combined with other, existing vaccines, lowering administration cost.

Injectable Rotavirus Vaccines Under Development

Jiang mentioned three non-replicating injectable rotavirus vaccines currently under development.

A VP6/VP8 vaccine, with proteins expressed in different bacteria, is being worked on at Tufts, Cincinnati Children’s Hospital, and at NIH. Mary Estes at Baylor College is developing a virus-like particle that has shown protection in animal studies. Jiang and Roger Glass were working on an inactivated, Vero cell-grown vaccine that also has shown protection in animal models.

Estes’ vaccine contains three different VLP formulations with morphology similar to the proteins of the native virus. These VLPs have induced antibody production levels from 30% to 100%, depending on the formulation and the model. These particles also have been studied with the use of adjuvants.

Jiang and Glass have been pursuing inactivated vaccine for almost ten years. They have developed two major candidate strains and a patented heat inactivation method that maintains the structure of the capsid proteins, Jiang said. Animal studies have been conducted in mice, macaques, and in gnotobiotic (germ-free) piglets. A single 0.2 mcg shot formulated with alum induces antibody response. A challenge of vaccinated piglets was successful, Jiang said.

Now, Jiang said, his laboratory is looking for partners, with the objective of developing a stand-alone vaccine for use in low-income countries by about 2015. Eventually, the vaccine would be combined in a multivalent shot for global use. Jiang said he was working to get a partnership.
with a developing world manufacturer through engagement with PATH and the Gates Foundation. Julie Bines pointed out, in reference to Jiang’s talk, that intussusception might be caused by a systemic inflammation rather than a mucosal response, so an injectable vaccine would not preclude the necessity of looking for intussusceptions in vaccinated children.

**Discussion of Boosting Vaccine Efficacy and New Vaccine Development**

Manish Patel asked whether adding a third dose of Rotarix had increased the duration of protection in the Malawi trial.

Shabir Madhi said that the estimate of efficacy over the first two years of life was about 85% for the three-dose approach, compared to 39% for two doses. The seroconversion rate also was much greater with the three-dose schedule compared to the two-dose. “I think it points out there certainly is a potential for improvement, with Rotarix vaccine, by looking at an alternative schedule from the two-dose schedule,” Madhi said.

An unidentified participant noted that the interaction between the OPV and rotavirus vaccines was not synergistic. He asked whether rotavirus vaccination would compromise the polio eradication initiative.

Duncan Steele said that several studies have looked at the interaction of giving a live oral polio vaccine together with both RotaTeq and Rotarix. In no case did co-administration of rotavirus affect the polio antibody response. After the first dose there is an impact on the rotavirus antibody, he said, but after the second dose the levels are the same as in a rotavirus-only group. “It has been looked at, it’s been evaluated by WHO, and it’s not a problem,” he said. Roger Glass noted that early on in the polio eradication campaign, scientists had addressed the effect of maternal antibody by raising the titer of the vaccine. He asked whether GSK had ever thought about raising the titer—effectively boosting the dose—of its rotavirus vaccine to improve efficacy in developing countries.

Bernd Benninghoff of GSK responded, “At the current time we are not developing or we are not looking into this one.” While altering the schedule was being investigated, “there’s nothing about elevating the dose.” Jason Mwenda of WHO asked whether there were any plans to test any of the new vaccines under development in Africa.

George Thiry said the Indian, Brazilian and Chinese firms working on rotavirus vaccines would try to get approval in their countries first. After WHO qualification for the global market, new studies would be considered, including in Africa.

Brendan Flannery asked Thiry about the WHO prequalification process for rotavirus vaccines and whether PATH would assist vaccine developers in their efforts to secure WHO approval.

Thiry said that PATH, with Gates Foundation support, is helping to fund vaccine development by Bharat Biotech and the four manufacturers who are developing a bovine reassortant rotavirus vaccine. PATH provides technical support including regulatory, clinical and manufacturing development. There already have been meetings with the WHO prequalification group, he said. The first aim is to achieve approval in the country of manufacture, the second with WHO.
SESSION VI: Late Breaking Research on Rotavirus

During an open session, Gagandeep Kang, professor of gastroenterology and microbiology at Christian Medical College in Vellore, India, presented a study that was aimed at determining the degree of protection provided by first and subsequent rotavirus infections. The study was funded by the Wellcome Trust and conducted in Vellore, in the southern Indian state of Tamil Nadu. Kang said that after collecting the data, his team had spent three years analyzing it “because we were so scared by what we found that we weren’t sure we ought to publish it.”

The data seemed to contradict earlier understandings of immunity produced by natural rotavirus infections. The Indian study was prompted by a 1996 study conducted in Mexico and published in the *New England Journal of Medicine* that showed a reduction in the occurrence and severity of subsequent rotavirus infections in Mexico.

The urban slum areas where the study was conducted in Vellore have an infant mortality rate of 38 per 1,000 live births, with 23% of these deaths caused by diarrheal disease. Kang and his colleagues recruited a birth cohort, followed it intensively for three years, tested the children for infections, and evaluated their sera for anti-rotavirus IgA and IgG. Much to their surprise, their findings question the notion that after an initial infection, subsequent rotavirus infections should decrease in frequency and severity.

Of the cohort of 452 children, 79 dropped out of the study—44 moved, 30 refused to continue, and 5 died. The withdrawals did not significantly affect the outcome. The remaining 373 children experienced a total of 1,856 diarrheal illnesses, resulting in 1,300 clinic or hospital visits and 43 hospitalizations. Of the five deaths, three were caused by diarrhea-related illness.

The children in this study were ill for an average of more than two months each year. And only 20 children in the group avoided experiencing a diarrhea illness in the three years of follow-up. There were 28 children who had several episodes, and about half had diarrhea before they were four months old.

Diarrheal disease peaked between three and seven months of age. It declined significantly in the second year of life. In terms of severity, rated on the Vesikari score, 148 of the 1,856 episodes were severe to very severe.

Pathogens could be identified in 36% of the episodes, and rotavirus was the leading pathogen found in these samples.

In general the rotavirus-positive diarrheas were more severe than those caused by other infections. While 2% of all diarrheal episodes were hospitalized, 4% of all rotavirus diarrheas were hospitalized. Rotavirus was detected in 28% of diarrhea hospitalizations, but in only 13% of diarrhea episodes treated at home.
Many of the children with negative stool samples had rotavirus infections as shown by serology, Kang said. The researchers identified a total of 1,103 rotavirus infections and 282 rotavirus diarrheas that resulted in 221 clinic visits, 12 admissions, and two deaths.

**Severe, Repeated Rotavirus Infections: Not rare?**

The children in the Vellore cohort were infected with rotavirus on average much faster than the children in the Mexico study. After six months, 53% were infected, compared to 34% in Mexico. By 12 months, 83% of the Indian children were infected, compared to 67% in Mexico. By two years, the percentages in the two cohorts were the same.

The most striking difference between this study and the one in Mexico was the number of re-infections. While in Mexico, symptomatic infections decreased as time went on, that wasn’t quite the case in the Indian study. In Kang’s study, some 24% of the children had two infections, 23% had three, 12% had four, and 20% had five or more infections. In addition, while 30% of primary infections were symptomatic, so were 26% of the fifth infections. The percentage of children who experienced only one infection was relatively small at 16%.

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**FIGURE 6.1**

- 59% (16%) children had only one documented infection, 92 (24%) had two, 86 (23%) had three, 45 (12%) had four, and 70 (20%) had five or more infections
- 30% of the primary infections were symptomatic, 26% among the fifth infections

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The most striking difference between this study and the one in Mexico was the number of re-infections. While in Mexico, symptomatic infections decreased as time went on, that wasn’t quite the case in the Indian study. In Kang’s study, some 24% of the children had two infections, 23% had three, 12% had four, and 20% had five or more infections. In addition, while 30% of primary infections were symptomatic, so were 26% of the fifth infections. The percentage of children who experienced only one infection was relatively small at 16%.
The severity of subsequent infections was also higher in the Vellore cohort. While no child in the Mexico study had moderate-to-severe diarrhea after two infections, more than a fifth of the children who had three or more rotavirus diarrhea episodes in Vellore had moderate or severe illness during the third, fourth or fifth episode. Children whose first rotavirus infection was symptomatic were twice as likely to have a second rotavirus infection than those whose first infection did not cause illness. And well-nourished six-month-olds were significantly less likely to have diarrhea and rotavirus infection than malnourished children.

In short, the protection that children in this cohort got from natural infection was much lower than the authors of the study expected. Also, the severity of the disease in subsequent infections declined more slowly than they would have expected. Presumably, host factors play a role in determining the outcome of these infections.

In a question session after Kang’s presentation, Raul Velazquez, who conducted the Mexican study, noted that the Indian researchers had not collected stool samples as frequently as was done in the Mexican study. He speculated that the lower number of samples might have lowered the numbers of infections they found. But Dr. Kang said more frequent examinations were done on a nested cohort. The only difference was that some asymptomatic infections were missed.

**HIV in Vaccinated Children in Kenya**

Geoffrey Nyambane gave a presentation on a study of HIV-positive children within the Phase III clinical trial of Merck’s RotaTeq vaccine held in Ghana, Mali and Kenya from April 2007 to March 2009. The Kenyan arm of the study was the only one to specifically examine HIV-related questions.

The study’s first objective was to assess serious adverse events within 14 days of any dose of RotaTeq or placebo in Kenya. The second objective, which used a nested cohort, was to closely examine reports of vomiting, diarrhea, and elevated temperature within 42 days of vaccination in a subset of subjects screened for HIV infection.

In the rural Kenyan study site, an area with an HIV prevalence rate of 15% among adults, 1,308 infants were randomly assigned to vaccine and placebo groups. Home visits for the nested cohort occurred on the 3rd, 5th, 7th, 14th, 21st and 42nd day following any vaccination. There were no pre-specified safety outcomes or hypotheses.

Serious adverse events were reported among 3.1% (20) of 649 vaccine recipients 3.3% of placebo recipients. The most common non-fatal events reported in both arms of the study were pneumonia and gastroenteritis. Clinical staff had been trained to look for and diagnose intussusceptions, but no cases of the disorder were reported in Kenya - or in the other African sites.

A total of 297 participants from the original study were scrutinized in the intensive safety surveillance cohort. In this group, serious adverse events were reported among 9.5% of vaccine recipients and 15% of the placebo recipients. The results were not statistically significant. The most common serious adverse events were, again, pneumonia and gastroenteritis, as well as malaria.

Sixty-six deaths were reported in this study group--36 vaccine recipients and 30 in the placebo group. The leading cause of death in both vaccine and placebo recipient was gastroenteritis. There were 13 among vaccine recipients, 10 in the placebo group, a non-significant result. Adverse events of any kind were reported in 93% of the vaccine group and 98% of the placebo group. Gastroenteritis, vomiting and diarrhea were slightly higher in the vaccine group, but again not at levels of statistical significance.

All participants in the study were offered HIV counseling and testing, and 89.2% accepted the services. Of those tested, 19 vaccine recipients and 11 placebo recipients were infected with HIV. All the infected children were treated with anti-retroviral drugs.

Among these 30 infants, 5 of the vaccine recipients and 1 of the placebo recipients had a serious non-fatal adverse event. A total of 11 HIV-infected infants died—eight of the vaccine recipients and three of the placebo group. Of the eight vaccine-recipient deaths, two were related to gastroenteritis, while two of the three placebo group deaths were related to gastroenteritis. These results also lacked statistical significance. No effort was made to determine whether the deaths in the HIV group were caused by any rotavirus strains.
Overall, the number of HIV-infected participants in the trial was small, which limited the conclusions regarding safety of the vaccine among this group. More study is needed.

**Pivoting to Policy: Making a Case for Rotavirus Vaccination**

In a policy-related presentation, pediatrician Tony Nelson of the Chinese University of Hong Kong noted that while it was important to strengthen the evidence base to guide decisions whether to introduce rotavirus vaccines, it was also worth examining what motivates decision makers.

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**FIGURE 6.2**

**What Decision-Makers Want to Support New Vaccine Use**

- Proven local disease burden
- Proven safe and effective vaccine
- Convincing health economics
- Limited negative effect on existing vaccines
- Support from clinical opinion leaders
- No blocking from GPs and parents
- Funding from external sources


Clearly, decision-makers need certain things before introducing a vaccine: proof of local disease burden, proof that the vaccine is safe and effective and will not have a negative impact on other vaccines, convincing cost-benefit analysis, expectations that physicians and parents will support the vaccine, and, of course, a way to pay for it.

A recent report by McKinsey& Company for the Gates Foundation and PATH used network analysis to look at the decision-making process. It stressed the importance of providing disease-burden data, and also of improving connectivity by communicating early in the process with the Finance Ministry and community groups.

Of the 24 countries that have introduced the internationally available rotavirus vaccines (this does not include China), 14 are in Latin America. Palau is the only Asian-Pacific country that has embraced the new vaccines, although Asian scientists and public health officials have developed significant data showing a high burden of disease. So how does the decision-making process differ between Latin America and Asia?

Advocacy and peer pressure have pushed the vaccine along in Latin America, Nelson said. In 2004, at the 6th International Rotavirus Symposium, representatives from Latin American health ministries called for PAHO and GAVI to facilitate rapid introduction of the vaccines at an affordable price. This level of advocacy does not exist in...
Asia, Nelson said. Additionally it also is worth noting that initial vaccine studies were mainly done in the Americas and Europe, offering tangible evidence of the vaccine’s impact there. Based on the geographic limitations of these early vaccine studies, an initial WHO rotavirus vaccination recommendation in 2007 left out Asia and Africa.

Decisions also are influenced by internal considerations within health ministries, Nelson said. For example, a new vaccine program means more work for the frontline staff, which could come at the expense of work in other areas. In addition, decision makers may worry that if they act too quickly to introduce a new vaccine, adverse events may appear that cause bad publicity and force them to respond. So it’s quite often easier to sit and do nothing.

A Gates Foundation-funded initiative called SIVAC (Supporting National Independent Immunization and Vaccination Advisory Committees) is seeking a more orderly, evidence-based decision-making process in GAVI-eligible and middle income countries by establishing National Immunization Technical Advisory Groups (NITAGS). Nelson said it is also important for vaccine advocates to focus on what motivates politicians to take action.

“We need to start thinking about messages and strategies that link programs and policies that improve equity and reduce poverty to our politicians’ inner subconscious and selfish desires,” he said. Perhaps, he joked, one could use statements like, “market research indicates that swing voters also want their neighbors’ children vaccinated against rotavirus.”

The Mysteries of Vaccine Decisions

Brendan Flannery from PAHO mentioned that Guyana, a GAVI-eligible country in South America, surprised international health officials when it decided to self-fund its rotavirus vaccine introduction. GAVI officials were taken aback and visited the country to ask the Minster of Health why he did not accept GAVI funding. The reason, he said, was that he had already gone to the Ministry of Finance and Congress to request funds. To go back and say they were not needed would have damaged his credibility, after having said that the GAVI funds might not be secure. So GAVI supported Guyana in strengthening its overall immunization program.

Mike McQuestion, Director of Sustainable Immunization Financing at the Sabin Vaccine Institute, introduced his project, which is currently working in 15 countries to form national budgets for immunization programs. McQuestion said he has learned from speaking with health and finance ministry officials and members of parliaments that there is a great deal of ignorance about how health budgets are formed. The National Immunization Technical Advisory Groups can play an important role in bridging this gap by guiding decision-makers through the evidence they need to evaluate vaccines as investments for improving public health.

Flannery said the good news is that, while the process can be complicated, after a particular vaccine is added to a national immunizations schedule it usually becomes a permanent fixture of the health care system.

“Once they happen, they tend to be irreversible,” he said. “So once a country gets these new vaccines in use, they’re going to find out a way to keep it there.”

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— Brendan Flannery, PAHO
SESSION VII: Next Steps for Rotavirus Vaccine

To introduce a roundtable discussion on vaccine introduction, John Wecker, Program Leader of PATH’s Vaccine Access and Delivery program, challenged participants at the conference to come up with simple messages about rotavirus vaccines that can be effectively conveyed to decision-makers. Will this intervention save lives? Is this a good use of my money? Is this a decision I should take?

A number of issues were raised about how to make the case for rotavirus vaccines. The following are highlights from the discussion:

• Rotavirus vaccines save lives. There is strong evidence from surveillance in countries that have introduced rotavirus immunizations, particularly Mexico, that the vaccines reduce mortality and the effect is almost immediate. And while there is not a lot of data from Africa, the evidence available indicates a potential to prevent many deaths.

• Rotavirus vaccines reduce hospitalizations. The vaccines appear capable of reducing hospital admissions for diarrhea by 50%.

• Know your audience. Messages should be tailored to the situation in a particular country or region. For example, the focus in Africa should be on the ability of the vaccines to prevent death, not on pure efficacy against infections. However, in other countries, such as South Korea, where there are not a lot of deaths from rotavirus, the main benefit is the ability of the vaccines to prevent hospitalizations.

• Intussusception risks can confuse. Discussing the data on intussusception risk is difficult because some scientists would say there is no risk, others might indicate a minor risk. As one participant noted, “When you go in front of the decision-makers, they’ve got all of our experts there, each one is saying something different. That kills the program. We’ve got to figure out a way of doing this better as scientists.”

• Put risks in context. Rotavirus vaccine risks should be discussed in relation to other vaccines. As Tony Nelson noted, “no vaccine is 100% safe. Rotavirus is no different than oral polio or flu vaccine.”

• Stress benefits beyond rotavirus. There is potentially a strong argument to make for the vaccine’s ability to reduce all causes of diarrhea by 25%.

• Don’t let waning immunity be a cause for delay. Waning immunity in the second year of life may not be significant because 80% of diarrhea deaths occur in the first year of life.

• Be an advocate for all rotavirus health interventions, not just vaccines. Advocacy for vaccines should occur in tandem with advocacy for wider use of oral rehydration and zinc supplementation to treat diarrheal diseases. This approach frames the discussion of rotavirus vaccines as part of a suite of interventions, which is likely to get a more receptive audience within Health Ministries suspicious that vaccine advocates may have ties with industry.

• Cost considerations require evidence of value. Price remains a barrier so government officials need to be convinced of the value of the vaccines and have options for funding their introduction.

• New vaccines in pipeline could cause confusion. Wecker noted that one complicating factor in seeking rapid expansion of rotavirus immunization is the potential for new rotavirus vaccines to be available as early as 2013 that could be cheaper than existing products. He wondered, “Do we wait until that happens, or do we move on what we know today in terms of the effectiveness, the safety of these vaccines, and the number of children we know are dying out there?” Wecker pointed out that there is a “chicken and egg” dilemma in that the best way to drive prices down is by
boosting demand, but if countries wait to see if the price is going to fall, that decision alone could keep prices relatively high.

- Focus on the link to Millennium Development Goals. Rotavirus vaccines should be put forward as a way for Health Ministers to achieve the childhood mortality reductions set forth in the UN Millennium Development Goal (MDG) 4.

- Use past vaccine successes to make case for rotavirus. An EPI manager from Ghana said that when talking about new vaccines, advocates can make a strong case by pointing to the success of existing immunizations. For example, Ghana started its measles control program in 2002 and since 2003, no child in Ghana has died of measles.

- Build a broad advocacy coalition. It is critical to assemble a diverse group of stakeholders to endorse vaccine introduction. In almost every country, successful adoption of a new vaccine involved alliances with pediatric associations.
In his concluding remarks, Duncan Steele summarized the findings discussed at the symposium. He noted that in seven African and Asian countries where 12,500 children were enrolled in rotavirus vaccine trials, the vaccines prevented about 23% of all serious diarrheal illnesses. In Malawi and South Africa, it prevented 30% of all diarrhea-related hospitalizations.

Rotarix prevented three serious bouts of gastroenteritis per 100 children in an African setting. In all countries into which it has been introduced so far, the vaccine has done better than expected at reducing disease. There has been a herd effect on illnesses in older children who do not receive the vaccine. Particularly striking was the reduction in deaths seen after introduction in Mexico. If the vaccine proved 60% efficacious, on average, in preventing deaths, it could prevent 1.5 million deaths by 2025 if it was introduced across the world.

“The efficacy data from these seven countries with both vaccines in 12,500 kids is that the vaccines are going to make a significant impact when we roll them out.”

“If we look at experiences in the slightly more developed countries, like Rotarix in El Salvador, there has been a dramatic decline in serious disease, with a 79% decline in hospitalized rotavirus diarrhea in children under 5 years old at seven hospitals in that country.”

In Mexico, there was a 41% reduction in infant deaths caused by diarrheal disease after introduction of Rotarix.

“We can keep talking about the vaccines, or we can start using them, and if we start using them we will prevent a significant burden in terms of diarrheal mortality due to rotavirus and diarrheal hospitalizations. It’s really a time for a call for action.”

“Call to Action

We the Participants of the 9th International Rotavirus Symposium agree to:

1) Continue to support immunization as a common public good worldwide, an economic necessity and a vital political priority;
2) To encourage increased vaccine research and expanded surveillance for vaccine-preventable diseases;
3) Encourage the joint collaboration of national governments, bilateral and multilateral agencies, the GAVI Alliance, and the manufacturers of vaccines to facilitate and accelerate the introduction of rotavirus vaccines worldwide;
4) To advocate for and raise awareness among public and policy makers of the burden of rotavirus-related diarrheal disease and the value of vaccination;
5) To call upon political leaders and decision-makers from developing countries to increase financial support to their national immunization programs; and finally
6) To call upon political leaders and decision-makers from developed countries and global immunization partners to scale-up financial support to the GAVI Alliance.”

— Duncan Steele, PATH
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