

# Rotavirus *and* Rotavirus Vaccines

## Proceedings of the Sixth International Rotavirus Symposium

July 7–9, 2004  
Mexico City



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Proceedings  
of the  
Sixth International  
Rotavirus Symposium

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*edited by Bernice Wuethrich*

**Proceedings of the Sixth International Rotavirus Symposium**

The Albert B. Sabin Vaccine Institute  
Office of International Programs  
1718 Connecticut Ave., N.W.  
Suite 700  
Washington, DC 20009  
phone: 202-265-6515  
fax: 202-785-3849  
[www.sabin.org](http://www.sabin.org)

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# Foreword

The organizers of the Sixth International Rotavirus Symposium recognize the efforts of the Ministers of Health from participating countries and scientific experts from around the world who demonstrate dedication to children's health, particularly regarding the important issue of rotavirus disease.

Rotavirus can cause severe diarrhea and vomiting, resulting in dehydration that kills 500,000 children a year. Nearly every child in the world becomes infected by the time they are five years old. However, 80 percent of deaths occur in developing countries. Our goal during the meeting in Mexico, which is reflected in these proceedings, was to review progress toward safe, effective rotavirus vaccines and address the question of how to make sure they get to the world's poorest children. New data on the extent and burden of the virus in developing countries, and insights into its biology and pathology give this document added timeliness.

The symposium tackled pressing scientific, social, and economic issues confronting rotavirus prevention. We thank the convening organizations and supporters for making this historic meeting possible.

## Symposium Organizing Committee

**Ciro A. de Quadros, MD, MPH**

Albert B. Sabin Vaccine Institute

**Roger I. Glass, MD, PhD**

Centers for Disease Control and Prevention

**Jon K. Andrus, MD**

Pan American Health Organization

**José Ignacio Santos, MD**

Hospital Infantil de Mexico, Federico Gomez

**Duncan Steele, MD**

World Health Organization



# Executive Summary

With **two new vaccines** nearing the completion of clinical trials, the global rotavirus community finds itself at a **pivotal juncture** in the effort to overcome the devastating mortality **caused by rotavirus**.

The rapid introduction of safe, effective, and affordable rotavirus vaccines is urgently needed in developing countries, where nearly 500,000 children a year die from the disease, according to the most recent mortality estimates reported at the Sixth International Rotavirus Symposium.

The symposium marked a watershed in the decades-long effort to bring such vaccines into use. For the first time, scientists, policy makers, economists, public health experts and the donor community together tackled the scientific, social, and economic issues that must be resolved for rotavirus vaccines to become widely accessible to the children who need them most—those living in developing nations.

First discovered by Dr. Ruth Bishop in 1973, rotavirus is described as a “democratic infection” afflicting nearly all children, whether rich or poor, by the age of 5. Yet it is the world’s poorest children who are most likely to die from rotavirus. More than 80 percent of rotavirus deaths occur in developing countries where resources are scarce and health care systems inadequate. By breaking with past practices and focusing clinical trials and licensure efforts in middle- and low-income countries, the global health community would save lives and change the lives of children too chronically sick and weak even to attend school.

With two new vaccines nearing the completion of clinical trials, the global rotavirus community finds itself at a pivotal juncture in the effort to overcome the devastating mortality caused by rotavirus. Successful, widespread introduction of these vaccines will hinge on the answers to three fundamental questions:

- 1) **Efficacy:** will the new vaccines work equally well for children in lower income countries as in upper- and middle-income countries?
- 2) **Safety:** will a few adverse events lead to the withdrawal of the vaccines?
- 3) **Cost:** will the new vaccines be priced and financed in a way to ensure long-term affordability and sustainability?

Without sustained political and financial commitment at the global, regional, and national levels, rotavirus will continue to sicken and kill children around the world. Decisive action is urgently needed.

In a declaration signed by health officials from 16 Latin American countries during the symposium, delegates agreed “to continue to support immunizations in the region as a common good in the region and as the highest political priority” and “to facilitate the introduction of the rotavirus vaccine, as soon as it becomes available at affordable price for the countries in the region.”

Among the **most critical issues** in introducing new rotavirus vaccines will be the cost and financing of **their purchase**.

Surveillance networks have provided **new insights** into regional and **global disease burdens**, and contributed to an upwardly revised estimate of 608,000 under-five deaths from rotavirus **worldwide** every year.

## Rotavirus Surveillance Networks

Key to the success of rotavirus vaccine programs is the development of robust regional surveillance systems that can generate comprehensive and systematic data on the disease burden and accurately forecast vaccine demand. Researchers from Asia, Africa, and Latin America reported on the birth and growth of such networks in their regions. In each region, the networks have served as catalysts for harnessing and enhancing local scientific capacity and initiating collaborative partnerships.

Surveillance has already provided new insight into regional and global disease burdens, and has contributed to an upwardly revised estimate of 608,000 under-five deaths from rotavirus worldwide every year. It has revealed complex combinations of different vaccine strains in different regions and indicated the importance of new emerging strains. This information has already alerted the public health community to the importance of tracking the cross-reactivity of candidate vaccines.

Surveillance networks are vital to efforts to profile the disease—from assessing the effectiveness of vaccines and identifying serotypes, to estimating the economic burden of infection. Furthermore, they will be vital to the rapid identification and assessment of any adverse incidents and to the shaping of appropriate responses by the global health community. For all these regions, strong surveillance is critical in both pre- and post-vaccine licensure.

Ultimately, the surveillance data will be used in advocacy and communication efforts directed toward national governments, donors, health care workers, and the parents of newborns. Data emerging from these networks will serve as the evidence needed to aid decision makers facing tough choices when allocating limited resources.

## Understanding Risks and Benefits

As the introduction of new vaccines draws nearer, the global health community must seek agreement on key issues, including acceptable levels of risk for complications such as intussusception (a blockage of the intestines). Intussusception arose as a potential vaccine-related problem in 1999 and resulted in the withdrawal of RotaShield, the first “vaccine against diarrhea,” from the U.S. market.

Since that withdrawal, researchers have refined their understanding of the actual risk of RotaShield-related intussusception. That risk has been revised dramatically downward, from 1 in 2,500 vaccinated children to 1 in 20,000-40,000 cases. This compares to a risk of death from rotavirus itself of 1 in 250 for some of the poorest

**A viable road forward is emerging.**  
**Private-public** partnerships provide a **promising**  
and **innovative approach** to vaccine financing.

countries. Furthermore, as reported at the symposium, risk was strongly correlated with the age of the child at first vaccination. Those children vaccinated in the first three months of life had a dramatically lower risk of intussusception than children first vaccinated at 4-9 months of age. This finally led many at the symposium to recommend that the first dose of vaccination of the new vaccines be limited to infants under 90 days of age.

Today's new vaccines differ significantly from RotaShield, in ways that may well further reduce the risk of intussusception. Clinical trials have been designed to detect the higher risk threshold first attributed to RotaShield.

While testing for safety is an essential and standard aspect of vaccine development, the question arises, "What is an acceptable level of risk?" Health experts must closely consider the risks and benefits of rotavirus vaccination, which vary in light of the radically different mortality rates in poor versus wealthy nations.

## Vaccines and Financing

At the time of the symposium, two new vaccines, RotaTeq (Merck) and Rotarix (GlaxoSmithKline [GSK]), were nearing completion of Phase III clinical trials. Other potentially promising candidates, including bovine-human reassortant, neonatal, and parenteral vaccines, were in various stages of development. Whatever the unique properties of these vaccines, their introduction must be framed in terms of efficacy, safety, affordability, and sustainability.

Among the most critical issues in introducing new rotavirus vaccines will be the cost and financing of their purchase. While all agree that the vaccines must be affordable, there is as yet little agreement on just what that means. In Latin America, for example, many countries have difficulty affording the US\$3.86 per-dose price of a combination vaccine that protects against diphtheria, pertussis, tetanus, *Haemophilus influenzae* b, and hepatitis B. Children require at least three injections. At the same time, pharmaceutical companies that invest hundreds of millions of dollars to develop new vaccines cannot continue research and development if they are unable to profit from their investments. GSK described a multi-tiered pricing system (geared to upper-, middle-, and low-income countries, and to the public and private sectors within all countries) that could address some of the concerns of developing countries. However, as yet there are no clear commitments to deliver vaccine to the poorest nations, nor agreement on how to finance this over the long term. Not only must more resources be committed to rotavirus vaccine programs, but long-term enforceable financial commitments are also needed.

Nevertheless, a viable road forward is emerging. Private-public partnerships provide a promising and innovative approach to vaccine financing. Key players in these efforts include the Global Alliance for Vaccines and Immunization (GAVI), Pan American Health Organization (PAHO), United Nations Children's Fund (UNICEF), World Health Organization (WHO), Rotavirus Vaccine Program (RVP), the Albert B. Sabin Vaccine Institute (SVI), and private donors. In coordination with pharmaceutical manufacturers such as GSK and Merck, the global health community is within reach of introducing urgently needed rotavirus vaccines to the world's children.

Rotavirus is "a disease whose time has come." United action by the global community has the power to stop it.

**Rotavirus is "a disease whose time has come."  
United action by the global community  
has the power to stop it.**



# Introduction

The Sixth International Rotavirus Symposium, held July 7–9, 2004 in Mexico City, brought together 350 participants for far-reaching discussion of a disease that is responsible for 1 in every 20 child deaths in the developing world—about 5 percent of all deaths in children less than 5 years of age. Welcoming those gathered, Dr. Ciro de Quadros, Director for International Programs at the Albert B. Sabin Vaccine Institute, noted that the meeting had convened at a pivotal juncture in the effort to defeat rotavirus: two new life-saving vaccines were likely to be available in the near future. That fact highlights the need to address the availability of vaccines to children in developing countries.

## Critical Issues of the Day

Introductory speakers flagged a number of developments that would be discussed at the symposium:

- A new global estimate of the burden of rotavirus disease—608,400 children die from rotavirus every year, far more than the previous estimate of 440,000;
- Results from rotavirus surveillance networks in Africa, Asia, and Latin America, including economic analyses of the burden of the disease and the cost-effectiveness of new vaccines;
- A reassessment of the risk of intussusception (a blockage of the intestine) associated with RotaShield, a rotavirus vaccine used in the United States in the late 1990s;
- Progress in building the public-private partnerships needed to accelerate the development and introduction of rotavirus vaccines in poor countries where the need is greatest;
- The commitment of the Mexican Ministry of Health to introduce a rotavirus vaccine in 2005—the first country in Latin America to make such a commitment.

Dr. Julio Frenk Mora, Mexico's Secretary of Health, officially opened the symposium, noting that rotavirus "is a major, major public health priority" for Mexico and for the Americas. He urged the international community of scientists, clinicians, public health practitioners, policy makers, vaccine companies, and members of the donor community represented at the symposium to review thoroughly and share the latest developments in both scientific research and issues related to vaccine introduction. He shared Mexico's own

**If Ministers of Health were to introduce a rotavirus vaccine today, in one or two or three years they will actually see a measurable decline in hospitalizations, perhaps in deaths and clinic visits. During the term that they are in office, they will see these changes.**

—Dr. Roger Glass  
*U.S. Centers for Disease Control and Prevention*

Figure 0.1

## Rotavirus Facts

### **Rotavirus is:**

- Characterized by severe acute diarrhea associated with vomiting that can lead to dehydration, shock, and death.
- The single largest cause of diarrheal deaths in children aged 5 and under.
- A virus that kills more than 600,000 children every year—more than 80 percent in developing countries.
- Responsible for 75,000 hospitalizations and 15,000 deaths in Latin America.
- A disease unaffected by improvements in sanitation and health.
- A disease that is vaccine-preventable.

experience in dramatically reducing child deaths due to cholera and other diarrheal disease—all except those deaths due specifically to rotavirus. “This persistence of rotavirus is truly global,” he said. “The introduction of rotavirus vaccine is a high priority, and recognition worldwide of its importance has accelerated the efforts to develop vaccines.” (See Figure 0.1)

Dr. Jon Kim Andrus, Chief of the Immunization Unit of the Pan American Health Organization (PAHO), linked the effort to defeat rotavirus to the need to reduce inequities and, in particular, to reduce the gap in vaccine technologies among countries—a goal to which PAHO is committed. PAHO’s Revolving Fund, for example, works with countries throughout Latin America that have a strong commitment to childhood immunization. “We have been managing this for more than 25 years, again with the focus of reducing the inequities and establishing an equitable affordable price of vaccines for all children, particularly for those children who need them most,” Andrus said. In addition, “PAHO will continue to work hard in promoting the introduction of rotavirus vaccine,” he concluded.

Dr. David Bloom, an economist at the Harvard School of Public Health, described a broad economic context within which to view the introduction of rotavirus vaccine. He outlined an evolving economic theory that assesses the impact of health on a nation’s development and wealth, and the role played by vaccines. (See Sidebar 0.1)

## Why We Need a Rotavirus Vaccine

Dr. Roger Glass, Chief of the Viral Gastroenteritis Section of the Centers for Disease Control and Prevention, pointed out that rotavirus is a democratic disease in that it infects all children, whether rich or poor. Worldwide, there are over 100 million children afflicted with rotavirus every year, about 2 million seek



*Sidebar 0.1*

## **Health, Economics, and Poverty— Immunization as a Development Priority**

*Dr. David Bloom, Economist, Harvard School of Public Health*

New research reverses an old equation of economics: whereas economic theory recognizes that greater wealth contributes to greater health, Dr. Bloom described the more recent understanding that health itself creates wealth.

“This new research is revealing the centrality, the catalytic role, and the oomph that population health has on the related process through which national incomes increase and through which poverty and human misery are mitigated,” Bloom said.

Healthier work forces are more productive, have more energy, better mental health, less absenteeism, and less “presenteeism” (when people who are ill and distracted show up for work). Healthier individuals tend to invest more in education (since they have a better chance of recouping the cost of their investments), and education itself is a driving force of economic growth. Healthier children have better cognitive development, are more likely to attend school, and get more out of each day they spend in school. Healthier people with longer anticipated life spans are also more likely to invest and save for retirement. And there is evidence that healthy populations are powerful magnets for the attraction of direct foreign investment, which is yet another channel for a country’s accumulation of capital.

“Population health appears to be an exceedingly robust and powerful predictor of economic growth,” said Bloom. By rule of thumb, a 10-year gain in life expectancy translates into nearly 1 additional percentage point in annual income growth—a significant gain given that the world economy grows by 2 percent to 3 percent a year. Furthermore, “Ten-year life expectancy gains are within the grasp of many developing countries.”

A major means of increasing life expectancy is to lower the infant mortality rate through vaccination against childhood diseases. Bloom suggested that vaccination programs can be viewed as an instrument of economic growth. In one study, Bloom and his colleague David Canning analyzed the economic benefit that would be realized by full implementation of the program of the Global Alliance for Vaccines and Immunization (GAVI). GAVI aims to extend the use of the traditional childhood vaccines, increase coverage of under-used vaccines, and help finance the introduction of anticipated vaccines, including rotavirus, in 75 of the world’s poorest countries. To estimate the rate of return on full investment in this program, Bloom converted estimates of averted deaths due to immunization into increases in life expectancy. He then used economic models to translate the higher life expectancy—that is, improvements in health status—into the growth of wages and income per capita. They found that the rate of return on full investment in this program would be in the range of 12 percent to 18 percent, placing it on par with investment in basic education as an instrument of economic growth and development.

Figure 0.2

## The State of Children's Health

### The Good

- The child mortality rate declined by nearly 60 percent from 1960 to 2002.
- Immunization coverage expanded from 5 percent to 10 percent of children in 1974 to about 75 percent of children by 1990.

### The Bad

- More than 10 million children age 5 and under died in 2002.
- Children aged 5 and under comprise about 10 percent of the global population, but account for about 20 percent of global deaths.
- Six to 7 million of the more than 10 million child deaths were preventable.
- About 10 percent of those preventable deaths were due to rotavirus infection.

### The Ugly

- Life expectancy gaps between rich and poor countries reach more than 40 years.
- Infant mortality rates vary by a factor of more than 50.
- The child mortality gap is growing. In 1960, child mortality was five times higher in developing countries than in industrial countries; it in 1990 was 10 times higher and in 2002, 13 times higher.

\* From the presentation by Dr. David Bloom, Harvard School of Public Health.

inpatient care, 25 million have outpatient visits, and about half a million deaths occur. "And those estimates will be revised upward with the next speaker," Glass said. (See Figure 0.2)

"Diarrheal diseases are really among the most common diseases of humans," he said.

A vaccine would save lives in developing countries where most deaths occur, and save hospitalizations, doctor visits, and costs in developed countries. In the United States, for example, there are approximately 60,000 to 70,000 hospitalizations a year for rotavirus.

Efforts at vaccine development began more than 20 years ago, and in 1998, RotaShield was licensed for use in the United States. "It was heralded as the first vaccine specifically targeted to diarrheal diseases," Glass said. But nine months after its introduction, 15 cases of intussusception were identified in vaccinated children, and RotaShield was voluntarily withdrawn from the market.

Since then, a scientific understanding of the exact risk of intussusception has evolved, and the initial risk assessment of 1 in 2,500 children vaccinated has been recalculated at less than 1 in 32,000. Glass described the results of a new study that Dr. Lone Simonsen would be presenting at the meeting: it found the risk of intussusception in children under 3 months of age as between 1 in 30,000 and 1 in 40,000. "And it is this problem of intussusception that is with us still today and which we hope to overcome with a new vaccine," Glass said.

New oral vaccines, while close at hand, still face hurdles. They involve questions of efficacy (particularly for children in the poorest developing countries), safety, and cost.

Population health **appears** to be an exceedingly **robust** and **powerful predictor** of economic growth. By rule of thumb, a 10-year gain in life expectancy **translates** into nearly 1 additional percentage point in annual income growth— a **significant gain** given that the world economy grows by 2 percent to 3 percent a year.

—*Dr. David Bloom*  
*Harvard School of Public Health*

Glass asked, “What can we do to speed up development and introduction of these vaccines? How can we ensure adequate supply at affordable cost?” Viewed globally, affordable cost means prices that will allow sustained introduction and adequate supply for the 130 million children born into the world each year.

Glass described the Rotavirus Vaccine Program (RVP), initiated by the Global Alliance for Vaccines and Immunization (GAVI), which is working to accelerate introduction of vaccines over the next five to 10 years to children in developing countries. To achieve this goal, Glass said four things are needed:

- 1) A number of live oral vaccines that are safe, effective, and affordable;
- 2) Surveillance networks that assess the disease burden, study emerging viral strains in different regions, monitor the impact of vaccines when they are introduced, track adverse vaccine-related events, and accurately forecast vaccine demand;
- 3) Strong advocacy and communications efforts with Finance and Health Ministers so that they have the information they need to introduce rotavirus vaccines; and
- 4) Backup vaccines, developed over time and based on different principles.

# Session I. Epidemiology and Disease Burden

Although rotavirus is the major cause of severe childhood gastroenteritis worldwide, researchers have lacked a complete picture of the actual extent. Hospital-based surveillance has been spotty, and estimates of global prevalence rely on reports that are often more than 15 years old. But today researchers in many parts of the world are stepping up their efforts to gain an updated picture of its prevalence. A number of the investigators leading those efforts in Latin America, Asia, Africa, and the United States reported on their findings. In addition to generating epidemiological data, researchers in Latin America, in particular, are beginning to assess the costs related to rotavirus disease. A revised global estimate of rotavirus mortality set the context for the entire session.

Dr. Umesh Parashar of the U.S. Centers for Disease Control and Prevention presented new data that suggest the number of annual rotavirus-related deaths of children under 5 is 608,400, or 39 percent of all diarrhea-related deaths. This is significantly more than the previous global estimate of 440,000 child deaths, or 22 percent of all diarrhea-related deaths. Whereas the new numbers were based on a rigorous review of studies published since 2000, the older estimate was based on studies conducted between 1986 and 1999, with the majority of studies dating back to the 1980s. Parashar's new analysis included 41 studies, 18 of them from low- and middle-income countries, and each with a minimum of 100 patients. It found that 39 percent of children with severe diarrhea were infected with rotavirus. Parashar therefore calculated the total number of rotavirus-related deaths as 39 percent of the 1.56 million annual child deaths due to diarrhea, or 608,400.

Parashar suggested several possible explanations for the higher rates in more recent studies, including the use of better detection methods and the possibility that improved hygiene and sanitation have reduced bacterial and parasitic diarrheas more than viral diarrheas. "If so, this highlights the need for vaccines to control these viruses," Parashar said. Whatever the underlying reasons, Parashar pointed out that the results have been consistent across many studies and regions.

## Regional Rotavirus Surveillance Networks

Several of the session's reports from regional rotavirus surveillance networks supported the higher global estimate of mortality. Researchers have recently established such networks in Asia, Africa, and Latin America. They aim to determine the disease burden of rotavirus and identify the viral strains circulating in any given area. But these networks yield more than just data on the disease. As Dr. Paul Kilgore of the Asian Rotavirus Surveillance Network (ARSN) pointed out, they are also helping to develop and to harness local scientific capacity, to form collaborative partnerships, and to lay the foundation for further surveillance and the

**In the past two decades,  
global diarrhea mortality of children has declined  
from an estimated 4.6 million annual deaths  
to 1.56 million. And the question is,  
has rotavirus mortality declined at the same pace?**

—Dr. Umesh Parashar  
*U.S. Centers for Disease Control and Prevention*

Figure 1.0

## Rotavirus Surveillance Networks: Key Infrastructure in Pre- and Post-Marketing Phases

### Surveillance networks:

- Generate data on disease burden and forecast vaccine demand that is critical to affordable pricing of vaccines.
- Profile rotavirus disease:
  - Track emerging serotypes and strains.
  - Measure the effectiveness of vaccines and cross-reactivity.
  - Document adverse vaccine-related events like intussusception.
  - Estimate the global economic burden of the infection.
- Harness and enhance local scientific capacity, encourage collaborative partnerships, and establish the basis for further studies.
- Provide “evidence” for use in advocacy and communication campaigns.
- In the future, serve as a means to monitor the impact of a vaccination program.

introduction of rotavirus vaccines. “One of the key benefits ... is that we are sharing expertise across the region,” Kilgore said. “This reduces our costs and helps build experience very quickly in the region. It has also built the foundation for training and infrastructure for additional studies to follow.” (See Figure 1.0.)

In Africa, the African Rotavirus Network (ARN) was created in 1998 to develop local research capacity, train scientists and lab technicians, gather baseline data, and initiate surveillance studies based on World Health Organization (WHO) protocol. In Asia, the ARSN, a hospital-based surveillance in nine countries, was established in 1999 using uniform WHO standards. In Latin America, researchers working with a surveillance study developed for the GlaxoSmithKline Biologicals (GSK) vaccine program have amassed a vast amount of epidemiological data, and three country-specific studies have been completed in the region.

## Rotavirus in Asia

Before the ARSN was established, rotavirus data across Asia were sparse. For example, the most recent rotavirus data from Indonesia dated back to 1983, and Vietnam had no laboratory-based testing for rotavirus. Since the ARSN was established in 1999, it has tested 11,000 hospitalized children. A review of the first two years of surveillance conducted in 36 hospitals in nine countries found that 45 percent of acute diarrhea cases were attributable to rotavirus, nearly double the previous estimates of about 25 percent. The results were based on reports from China, Thailand, Indonesia, Hong Kong, Taiwan, Korea, Malaysia, and Vietnam, a group of countries that made up the world’s first regional surveillance for rotavirus.

Kilgore reported that 11 of 21 countries in the region are now conducting ongoing surveillance. “But one of the key lessons in all of this has been that implementation of multi-country networks is very difficult. Standardizing methods requires a lot of attention,” he said. Nonetheless, “The ARSN has defined epidemiology in Asia as never before, and these novel findings have really been focusing attention on rotavirus where before we essentially had no data to show.”

## Rotavirus in Africa

Dr. George Armah, from the Noguchi Medical Research Institute in Accra, Ghana, reported on the work of the ARN. Prior to its establishment, few studies on rotavirus in Africa involving more than 100 patients had been published. “The other disheartening thing was that only five countries in the whole of Africa had done some genotyping or serotyping,” Armah said. Over the last six years, the network has held four rotavirus workshops, trained a core of laboratory technicians, and evaluated 14,000 stool samples, identifying 3,000 as positive for rotavirus. Nineteen countries are now involved in the network, up from 11 countries that participated in the first training workshop.

Overall, 50 percent of the strains identified in Africa are G1, with G4 and G8 being the least common. G9 strains emerged in Nigeria in 1998–99, while G2 and G3 strains occurred in West Africa in waves two or three years apart. West and Eastern Central Africa reported the most unusual viral strains. Throughout the continent, many infections were mixed, containing a number of different strains.

The ARN has planned ongoing surveillance, as well as some studies to determine the costs associated with rotavirus. It is also developing regional labs in Ghana, South Africa, and Kenya.

## Rotavirus in Latin America

In Latin America, investigators in 11 countries conducted a six-month surveillance of children under the age of 3 who were hospitalized with severe diarrhea. Dr. Miguel O’Ryan of the University of Chile reported on the study, performed for GSK prior to the execution of a large clinical trial of a rotavirus vaccine candidate. Surveillance took place between November 2002 and May 2003, with different start dates and surveillance periods in different countries. Of 6,300 samples tested, 49 percent were positive for rotavirus infection, with broad seasonal differences across countries, age prevalence variations, and different serotype patterns. (See Figure 1.1)

*Figure 1.1*

### Latin American Multi-Center Hospital-Based Surveillance Study of Children Less Than 3 Years of Age, January–June 2003

- 11 countries
- 8,031 children presented with GE episodes
- 78% of children required hospitalization
- 6,521 stool samples collected
- 49% rotavirus detection rate (3,122 children)
- 2 days: overall median duration of hospitalization
- 67% of caregivers financially affected by illness of child
- 1,240 strains serotyped:
  - G1 = 51%
  - G2 = 1%
  - G3 = 10%
  - G4 = 18%
  - G9 = 3%
  - Untypable = 17%

\*From the presentation by Dr. Miguel O’Ryan, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile

Figure 1.2

## Disease and Economic Burden of Rotavirus in Mexico: A Prospective Study of 119 Cases, March–June 2004

- US\$120-603 = average monthly family income
- US\$103.50 = direct medical costs per family
- 32 hours of 20-86% of monthly income = average loss of family work time
- 55% of families spent savings for treatment
- 47% of families borrowed money to pay for treatment

\*From the presentation by Dr. Romeo Rodriguez, National Center for Infant and Adolescent Health, Mexico.

The study assessed rotavirus-associated household costs. Of the 3,122 RV+ children, 27 percent mistakenly received antibiotic treatment before evaluation at the study center, and 77 percent required intravenous rehydration. Among caregivers of the sick children, 40 percent reported absenteeism from paid work.

Researchers reported on country-specific studies in Mexico, Brazil, and Venezuela. In Mexico, diarrheal morbidity dropped sharply in the 1990s following a 1991 cholera outbreak that led to improved sanitation and hygiene practices. Since 2000, however, the decline in diarrheal deaths has slowed. Based on the study, Mexican researchers have reached three conclusions:

- 1) The epidemiological pattern of diarrheal illness has shifted from bacterial and parasitic causes to viral causes, mainly rotavirus;
- 2) Rotavirus occurs year-round, peaking in the winter season; and
- 3) The economic burden of the disease is greatest among the poor, who are more likely to experience complications.

(See Figure 1.2)

In Brazil, rotavirus was first detected in 1976. Dr. Alexandre Linhares of the Evandro Chagas Institute in Belem has reviewed the results of studies since that time. Across Brazil, there are wide variations in the seasonality of the disease depending upon the region, and detection rates vary, ranging from 4.5 percent to 66 percent. The serotypes most commonly found include G1 (40 percent) through G4, but more unusual strains were noted, including G5, G8, and G10. G9 accounts for approximately 13 percent to 17 percent of cases.

Brazil was also part of the multi-center surveillance conducted in Latin America. This hospital-based study included 49 sites in the tropical city of Belem, where children under 3 years of age were treated for severe gastroenteritis. The seven-month study found positive rotavirus rates of 46 percent. Linhares reported that the Brazilian Ministry of Health will soon implement a two-year countrywide surveillance for hospitalizations and deaths among children under 5 years of age in five Brazilian states.

Dr. Irene Perez-Schael of the Central University of Venezuela reported on five years of rotavirus surveillance in the state of Caraboba and extrapolated the results to the rest of the country. In children 3 to 11 months of age, the accumulated rotavirus rate was 59 percent, with the most severe cases occurring in the 6 to 8 month

We have **increased awareness** in several countries to the point where they **are now** thinking about how a vaccine would be introduced **if it were available.**

—*Dr. Paul Kilgore*  
*Asian Rotavirus Surveillance Network*

age group. G1 was the most common strain detected (47 percent). The study noted the protective impact of breast-feeding against rotavirus infection. In all, Perez-Schael estimated that 1 of every 2,000 children in Venezuela will die due to rotavirus in the first year of life.

Perez-Schael also reported that from 1998 to 2004, 131 cases of intussusception occurred, with 87 percent of the cases in children under 1 and the majority between 3 to 9 months of age. Furthermore, the intussusception rate has increased in recent years. Although no cause for this trend has been identified, Perez-Schael noted that poverty in Venezuela has risen by 20 percent in this same period. The study did not detect an etiological connection between rotavirus and intussusception.

In conclusion, all presenters concurred that there is an urgent need to introduce a vaccine to combat rotavirus disease. Efforts are underway in all regions to expand surveillance and to develop data for presentation to key policy makers. In Asia, surveillance will be initiated in countries where there are currently no data: Cambodia, India, Sri Lanka, Laos, and Mongolia. The ARN plans to expand surveillance studies and develop regional labs. In Latin America, researchers will develop a comprehensive assessment of the economic costs of rotavirus infection and make these data available for decision making regarding the use of a rotavirus vaccine.

## Session II.

# Virology, Pathogenesis, and Immunity

Since Dr. Ruth Bishop, currently at the Royal Children's Hospital in Melbourne, Australia, discovered rotavirus in Australia in 1973, scientists have probed its wheel-like structure, identified its genes and proteins, and deciphered aspects of the human immune response to this pathogen. Yet mysteries remain, and symposium speakers shared current knowledge and presented new information on the diversity of rotavirus strains, subtleties of the immune response, the course of disease, and the possible causes of vaccine-related intussusception.

### Rotavirus Diversity

Recent studies show that rotavirus is both more diverse and more adept at change than previously thought. The early studies that examined strain diversity identified four globally important strains: G1, G2, G3, and G4. G-type itself is determined by the specific configuration of a protein on the outer surface of a rotavirus known as VP7. Together, these strains accounted for more than 90 percent of those circulating, and researchers therefore used them as the basis of first-generation reassortant vaccines that combined human and animal strains.

However, a new survey of 66 published studies documenting rotavirus diversity on six continents recognizes more than 40 strains based on the combination of their surface proteins, reported Dr. Jon Gentsch, a microbiologist with the U.S. Centers for Disease Control and Prevention. The survey shows how strain prevalence has changed over time and differs among regions. In the last eight years, for example, a new strain, G9, has emerged as globally important and now appears to be more common than G3. Regional differences are also striking: in Australia, G9 represents about 20 percent of the strains; in Brazil, G5 is most common; in Malawi, G8 accounts for 50 percent of the strains; and G6 is important in Hungary.

Rotavirus strains are also characterized by their P-type, a surface protein called VP4 in the outer shell of the virus that is another target for neutralizing antibodies. There have been two common P serotypes, known as P8 and P4. Gentsch reported that a third P serotype now appears to be globally important—and it is associated with a rotavirus strain that infects newborns. Studies show its prevalence at up to 26 percent, and Gentsch predicted that it will be increasingly recognized as one of three important P serotypes.

Finally, intensified surveillance has revealed a great deal of reassortment between common P and G types. “Overall, there are more than 40 of these combinations, and it keeps being revised upwards as time goes on,” Gentsch said.

### The Impact of Diversity on Vaccines

Given this great diversity, Gentsch questioned whether a vaccine based on G1 or other common strains of rotavirus would provide sufficient cross-protection against a number of emerging and rare strains, including some with unique molecular characteristics. Alternatively, he suggested that vaccines may need to be formulated to reflect the strain prevalence in different locations.

**Over mostly the last eight years or so,  
serotype G9 has been found as an emerging strain  
and is believed to be globally important.**

*—Dr. Jon Robert Gentsch  
U.S. Centers for Disease Control and Prevention*

The main disease associated with rotavirus, of course, is **gastroenteritis** but these rotaviruses also are etiologically or incidentally associated with **numerous other diseases**.

—Dr. Richard Ward  
*Cincinnati Children's Hospital*

New evidence of another type of rotavirus also called into question the potential effectiveness of vaccines based on a single strain, so-called monovalent vaccines. These vaccines assume that the immune response to that one strain will protect against subsequent exposure to other rotavirus strains. In fact, a significant body of evidence supports that approach. But Dr. Guillermo Ruiz Palacios of Mexico's National Institute of Science, Medicine and Nutrition presented evidence to the contrary. Tracking naturally occurring rotavirus infections in Mexico, he found that an initial infection with either G1 or G3 protected against subsequent infection against most—but not all—of the other major strains. The exception was the G2 strain. “So, there is a lot more to learn in terms of protection, and although there is heterotypic protection, this heterotypic protection does not seem to correlate with certain serotypes,” he concluded.

## Pathogenesis

Dr. Richard Ward of the Cincinnati Children's Hospital Medical Center described the full spectrum of illness that has been associated with rotavirus. Although it typically causes gastroenteritis, on rare occasions rotavirus has been reported to be associated with upper and lower respiratory infections, hepatic abscess, pancreatitis, diabetes, intussusception, and biliary atresia (an obstruction of the bile ducts that destroys the liver), Ward said.

He noted that of all the rotavirus strains tested in mice, only G3 strains such as rhesus rotavirus (RRV) have been shown to replicate outside the intestine and induce diseases such as hepatitis and biliary atresia. RRV is the same rotavirus strain that was used in the RotaShield vaccine, which was pulled from the market after being associated with a slightly elevated risk of intussusception in human infants. It is possible that intussusception can be induced by a limited number of G3 strains that are able to infect and replicate in tissues outside the intestine, Ward concluded.

## Immunity

Studies on protective immunity induced by rotavirus infection or by rotavirus vaccines help scientists to understand the full range of biological responses associated with protection against rotavirus infection. Ruiz-Palacios described the immune responses most strongly associated with protection against subsequent infections. He noted that contrary to most systemic viral infections such as mumps or measles, in which a single infection will fully protect against future re-infection, several bouts of rotavirus are necessary before a child is fully protected. With each additional rotavirus infection, the symptoms decrease in severity, and immunity increases. Scientists are able to use the level of antibody found in mucous membranes, IgA, as a measure of vaccine take—*i.e.*, to determine whether a vaccinated infant did become infected with the strain and develop an immune response.

Researchers are still investigating which rotavirus proteins elicit the strongest human immune response and whether those responses are homotypic (effective against just one strain of the virus) or heterotypic (effective against more than one viral strain). Dr. Harry Greenberg of Stanford University reviewed what is known about the immune response to rotavirus. He noted that an immune response targeting at least two viral proteins, VP4

and VP7, can produce both forms of immunity. “The type of immunity that you have when you are protected will depend on what type of antibody you have generated,” he said. He also reported preliminary new data by Dr. Mary Estes that indicate yet another rotavirus protein, NSP4, elicits an immune response in mice. However, this has not yet been studied in humans.

Greenberg also addressed the question of what arms of the immune system are at work in fighting rotavirus and how immune cells find their way to their targets. While T cells have a role in spreading the clearance of an infection, it is human B cells that are the key to overcoming rotavirus. But to attack the virus, B cells must first find their way to the site of the infection in the intestine. He described recent work that has identified some of the molecules and receptors that help B cells home in on their target: integrin  $\alpha 4\beta 7$  and at least two chemokine receptors, CCR9 and CCR10.

## Another surrogate of protection is breastfeeding, human milk.

—Dr. Guillermo Ruiz-Palacios  
National Institute of Science, Medicine and Nutrition, Mexico

### Breast-feeding: Protection Against Rotavirus

Breast-feeding helps protect against rotavirus infection, according to a new analysis presented by Ruiz Palacios. In a study of 400 babies, either breast- or bottle-fed, his team found that the benefits of breast-feeding vary with the age of the child. Of breast-fed babies under 6 months, half were fully protected from rotavirus infection. In all, cohort studies have shown a 40 percent protection conferred by breast-feeding during a baby’s first year of life. A protein in breast milk, lactadherin, seems to protect against symptomatic rotavirus infection.

### Discussion

*Viremia.* Several members of the audience commented on the possible impacts of viremia, the presence of virus in the bloodstream. New work shows that transient viremia is more common than previously thought and that, indeed, every natural rotavirus infection could potentially end up with at least evidence of the virus moving through the blood. However, speakers noted that, with few exceptions, viremia does not mean the virus will infect extraintestinal tissue.

*Extraintestinal Infection.* Another speaker made the point that although the G3 strain of rhesus rotavirus was associated with biliary atresia (destruction of ducts that carry bile from the liver) in the mouse model and that RotaShield contained the G3 rhesus rotavirus, it would be a mistake to extrapolate the results in mice to humans “in that 1.2 million doses of RotaShield were given, and there was not a single case of biliary atresia reported.”

Others noted that animal studies with the candidate quadrivalent vaccine RotaTeq found no extraintestinal infection. The same study found extensive extraintestinal infection with RotaShield in both mice and pigs without ever finding it in the blood.

*Other Conditions.* Asked whether there was a causal association between encephalitis and meningitis and the viremia of rotavirus, and if so, what may be the possible consequences of live viral vaccination, Ward responded that there is very little evidence that natural rotavirus infection causes such conditions. As far as the odds that any of these live virus vaccines might be associated with any of these diseases, “I don’t think there will be any association because I am not even convinced the wild type viruses are causing them on any regular basis ... In the end, I think rotaviruses cause severe diarrhea in normal situations.”

## Session III.

# Past Experience with Rotavirus Vaccines

Scientists continue to reassess the history of rotavirus vaccines even as that history continues to exert powerful influences on present-day efforts. This session was framed by an overview of rotavirus vaccine history, and prodded into the present by a re-analysis of the risk of intussusception associated with RotaShield.

## Twenty Years of Vaccine Experience

More than 20 years ago, Dr. Timo Vesikari of the University of Tampere Medical School in Finland tested the first rotavirus vaccine on humans. Vesikari presented “a personal view of history,” summarizing major steps in the development of rotavirus vaccines and lessons learned.

The discovery of animal rotaviruses, specifically the Nebraska calf diarrhea virus (NCDV), was crucial to the development of a rotavirus vaccine for children. In the late 1970s, using strains of the NCDV, the U.S. National Institutes of Health (NIH) demonstrated cross-protection against human rotavirus. RIT, a Belgian company, introduced the bovine vaccine RIT4237. Oral vaccination of 2-year-old children followed, producing an antibody response in approximately 70 percent of the subjects.

Researchers were interested in neonates, however, and were encouraged by an Australian study led by Dr. Bishop. It showed that children who had neonatal rotavirus infection were protected against severe rotavirus disease over a three-year period. A single-dose study of strain RIT4237 in newborns showed that vaccination just before the rotavirus epidemic season offered 100 percent protection against severe disease, although it did not impact the overall number of infections. In 1983, the vaccination of a group of 8- to 11-month-old children demonstrated that vaccine-induced immunity lessened the severity of rotavirus disease and that there might be cross-protection between strains. However, following an unsuccessful clinical trial of RIT4237 in Rwandan children, an article was published in *The Lancet* deeming RIT4237 a failure. “That was the killer, so to speak,” Vesikari recalled.

**Some of the problems and mysteries  
still remain unresolved.  
We don't really know the reason for failure in Africa  
and, in fact, in Asia.**

*—Dr. Timo Vesikari  
University of Tampere Medical School, Finland*

Another bovine vaccine, WC-3, entered clinical development just as RIT was withdrawn. While it provided protection in a U.S.-based study, it did not show adequate protection in children in Africa or Latin America. “This vaccine virus survives until today as the backbone of Merck’s current bovine-human reassortant vaccine,” Vesikari said. Then, in the mid-1980s, a rhesus rotavirus vaccine (RRV) was developed that contained lower concentrations of the virus and relied heavily on multiplication in the host to induce an immune response. While the RRV proved to be more immunogenic than the bovine vaccine, it was ultimately less protective.

The response of the international health community to these potential vaccines was muted, according to Vesikari. “Requirements were that rotavirus vaccines should protect not only against all severe disease but against all disease. This was a very strong argument, and it was very difficult to defend the concept that the prevention of severe disease is good enough,” said Vesikari.

Nonetheless, many principles of rotavirus vaccination that we know today were already established 20 years ago. Vesikari summarized these lessons:

- 1) Use a high titer vaccine;
- 2) Use a buffer to protect the vaccine against gastric acid; and
- 3) Avoid co-administration with oral polio vaccine (OPV), since OPV suppresses uptake of rotavirus vaccine.

“But some of the problems and mysteries still remain unresolved,” Vesikari said. “We don’t really know the reason for failure in Africa and, in fact, in Asia. Other vaccines have not been tested under those most challenging conditions . . . . We still don’t know what the mechanism of protective immunity is exactly, especially in terms of vaccine-induced immunity. And we still don’t know the role of serotype-specific immunity, what exactly it is, and how critical it is.”

## Understanding RotaShield

RotaShield, which was introduced to the U.S. market in October 1998, was composed of the rhesus rotavirus strain (representing serotype G3) and three rhesus-human reassortant strains. In less than a year, epidemiologists established a temporal relationship between RotaShield and intussusception, and the vaccine was withdrawn from the market.

At the session, Simonsen reported on an as-yet unpublished re-analysis of the increased risk of intussusception associated with RotaShield. She found that the age at which children were vaccinated was critically important to the risk of intussusception. She also determined the Population Attributable Risk (PAR) to be 1 intussusception event in 40,000 vaccinees—a dramatically lower risk than the previously accepted 1 in 10,000 (see Sidebar 3.1).

Yet the root biological cause of that elevated risk—whatever it actually is—remains unknown, making it “difficult to impossible to predict whether or not future vaccines will cause intussusception,” said Dr. Paul Offit of the Children’s Hospital of Philadelphia. Offit reviewed current knowledge regarding the biology of RotaShield-associated intussusception. He started from the generally accepted presumption that natural infection does not cause intussusception, suggesting that there must be a feature of the RotaShield vaccine that critically differs from natural infection. Offit said that the problem may lie with the RRV strain itself, since RRV is the only feature of RotaShield that differs from natural infection.

RRV has unique biological properties. Unlike human rotavirus, it is able to replicate in cell culture in the absence of trypsin, cause liver disease in certain strains of inbred mice, and cause diarrhea cross-species. Yet the link between these unique features and intussusception is unknown. Offit suggested that RRV in humans may lead to the release of a cytokine or cytokines that cause an increase in gut motility and gut edema, putting children at risk for intussusception. He concluded, “Because both RotaTeq and Rotarix contain human rotavirus surface proteins and do not possess certain biological features similar to RRV, I am going to go out on a limb and predict that neither will cause intussusception.”

## Discussion

*Risk Assessment and Perception.* Much discussion revolved around risk assessment and perception. “As we move ahead with rotavirus immunization in the U.S., we estimate that there are probably several thousand intussusceptions that occur naturally by chance alone, which means about five or six a day in the U.S. . . . When

### Sidebar 3.1

## **Reappraisal of Association Between Rotavirus Vaccine and Intussusception**

*Lone Simonsen, PhD, Senior Epidemiologist, National Institute of Allergy  
and Infectious Disease, U.S. National Institutes of Health*

The first licensed rotavirus vaccine, RotaShield, was used in the United States from October 1998 to July 1999, during which time 600,000 infants received approximately 1.2 million doses in a three-dose schedule. Case-control and cohort studies indicated a strong temporal link between the first dose of RotaShield and intussusception in the following three weeks. Scientists estimated that the Population Attributable Risk in a fully implemented RotaShield program would be one excess case of intussusception per 10,000 doses. While RotaShield was withdrawn from the market, its legacy remains. In terms of the fate of new rotavirus vaccines, "Risk perception is the key issue ... there is a need, first of all, to predefine the acceptable level of intussusception risk," said Simonsen.

Simonsen reported on the results of an extended analysis of the CDC case-control study that first examined intussusception and RotaShield. The most striking finding links age at first vaccination with the risk of intussusception. While children from birth to 1 month have very low rates of naturally occurring intussusception, the rate jumps in the 4- to 10-month age range. Likewise, during the mass vaccination of U.S. infants with RotaShield, the majority of first-dose-associated cases of intussusception occurred in children 4 months of age or older or those who were in the "catch-up" immunization category.

Of the 43 first-dose RotaShield-associated intussusception cases identified, only eight (19 percent) occurred among infants who were less than 90 days of age, an age group that had received the majority (61 percent) of all first doses. Thus, the practice of "catch-up" immunization of older infants who received their first dose at 3 to 7 months of age contributed disproportionately to the number of RotaShield-associated intussusception cases.

Also of interest was the declining number of intussusception cases during the RotaShield use period. This decline coincided with the fact that, initially, 60 percent of first doses were given to older infants, whereas toward the end of the program, only 30 percent of first doses were given to older infants. In a fully implemented vaccine program, "catch-up" immunizations would have eventually been eliminated, lowering significantly the risks of intussusception.

In all, Simonsen found that with a two-dose neonatal vaccination schedule, the Population Attributable Risk would be 1 in 40,000 vaccinees—a result consistent with accepted severe events with other vaccines. "Clearly risk-benefit analyses are always in favor of RotaShield," said Simonsen.

In considering the introduction of new rotavirus vaccines, Simonsen exhorted researchers to pre-define acceptable levels of risk for intussusception, to consider closely the disease burden of rotavirus in poor versus wealthy nations, and to examine how the evidence of "harvesting" affects risk assessments. She argued that a study of intussusception in post-licensure surveillance systems would be more cost-effective than in pre-licensure studies.

we start a vaccination program and we start to accumulate these children with chance intussusception events in the week or two following the first or second immunization, what should we do?” one participant asked.

*Surveillance Networks in Post-Licensure Phase.* Panelists responded that there must be in place excellent post-licensure surveillance systems that can very quickly assess the incidents of intussusception following vaccination. In addition, the public health community needs to agree on the definition of safety and an acceptable level of risk in the United States. “The definition of safety is that the benefits have to outweigh the risks ... But the ACIP [the U.S. Advisory Committee on Immunization Practices] is moving away from a medical definition of safety to a more of a legal definition of safety, which is an absolute safety that no adverse event is acceptable, and that is a very, very dangerous place to go.”

There was a sense that the system was broken when it came to RotaShield, in part because the process of data analysis and interpretation lay too close to the policy implications. “Sometimes it is like we are all talking into these waves, and we are just battling each other instead of just looking at it because it’s data.”

**If there is going to be one take-home message from this year,  
it is that ... **you can’t talk** about intussusception **risk**  
without talking about **age**.**

—Dr. Lone Simonsen  
U.S. National Institutes of Health

## Session IV.

# Results with New Rotavirus Vaccines

Lead investigators for the world's two most advanced rotavirus vaccine candidates—Merck's RotaTeq and GSK's Rotarix—presented the results of their clinical trials to date. Both vaccines were in the midst of Phase III clinical trials, each of which had more than 60,000 children enrolled. Investigators representing a wide range of other vaccines presented their findings, including on neonatal, inactivated, and hexavalent vaccines. The session also reviewed global regulatory issues being raised by the new vaccines.

### RotaTeq: History and Progress

Dr. Penny M. Heaton, Director of Biologics-Clinical Research at Merck Research Laboratories, described RotaTeq as an attenuated live oral vaccine given in three doses. It is a bovine-human reassortant vaccine that contains five antigens: G1, G2, G3, G4, and P1. Heaton said of Merck's decision to develop a polyvalent vaccine, "We wanted to make sure that we were giving children a chance to make antibody to as many different strains as possible, as early on as possible." The five RotaTeq strains represent over 80 percent of the strains that are responsible for rotavirus gastroenteritis worldwide.

Merck began working on RotaTeq in 1991 after licensing the vaccine from Fred Clark and Paul Offit at the Children's Hospital of Philadelphia and the Wistar Institute. Clinical trials have since shown that the vaccine is well-tolerated and that efficacy is about 70 percent against any rotavirus gastroenteritis and 100 percent against severe rotavirus gastroenteritis for the first post-vaccination rotavirus season in Phase II studies. The company developed a safe liquid vaccine buffer to eliminate the need of feeding ahead of vaccination, carried out dose-ranging studies, and began developing its manufacturing process and constructing its manufacturing facility. But company plans to conduct final trials in about 2,000 children were dramatically altered in 1999, when the reports of RotaShield's association with intussusception came out. Instead, Merck launched a rotavirus efficacy and safety trial (called REST) of more than 60,000 children based in the United States and in European countries.

The trial's safety premise is that RotaTeq will not increase the risk of intussusception relative to a placebo within 42 days after any dose. Nonetheless, Merck decided only to enroll children in countries that had the highest standards of care available to treat any possible cases of intussusception, said Heaton. An independent Data and Safety Monitoring Board monitors any possible cases of intussusception as they occur and determines if the child had received the vaccine or the placebo. "We will stop the trial early if we detect an increased risk," Heaton said.

Merck is also evaluating other non-serious adverse experiences such as fever, vomiting, diarrhea, and irritability; vaccine safety when given with other routine childhood immunizations; the protection it offers against rotavirus strains not included in the vaccine formulation; and its effectiveness in reducing hospitalizations and emergency department visits for rotavirus.

**We wanted to make sure that we were giving children a chance to make antibody to as many different strains as possible, as early on as possible.**

*—Dr. Penny Heaton  
Merck Research Laboratories*

## We believe that we will bring a **safe** and **efficacious** vaccine on the **market first** to those who **need it most**.

—*Dr. Beatrice de Vos, GlaxoSmithKline Biologicals*

“We could never prove the absence of risk pre-licensure .... However, we do think it is feasible to show that this vaccine is clinically acceptable for licensure, and then we can shift the safety evaluation to the post-licensure setting.”

### Rotarix: History and Progress

Dr. Beatrice de Vos, Director of Clinical Development at GSK, described Rotarix as a live attenuated vaccine given in two doses and derived from a single strain of human rotavirus (G1[P8]). De Vos said that scientists first detected the vaccine’s parent strain in 1989, when it was circulating among infants in Cincinnati, Ohio. Those infants appeared well-protected against rotavirus infection the following season. Furthermore, GSK chose a G1 strain because it is the most prevalent strain worldwide.

GSK tested the vaccine in over 9,400 subjects in Phase I and Phase II clinical trials, primarily in the United States, Latin America, and Europe, following the timing of local routine childhood vaccination schedules. Throughout these early trials, there was no significant difference between vaccine and placebo recipients in the incidence of serious adverse events or of other less severe symptoms such as fever, diarrhea, and vomiting. No deaths related to vaccination were reported.

De Vos reported that different regions experienced generally similar levels of vaccine efficacy—about 73 percent against any rotavirus gastroenteritis and up to 90 percent against severe rotavirus. Nonetheless, de Vos said that the rates of vaccine take (indicated by the strength of the immune response) did vary along with differences in the age of first vaccination. De Vos said that GSK is working to understand the impact of a child’s age, including the possible effects of maternal antibodies and of breast-feeding.

According to de Vos, GSK also found that Rotarix worked in settings with multiple serotypes, such as G9 in Brazil, where the vaccine elicited cross-protective efficacy of up to 83 percent against severe rotavirus due to non-G1 serotypes. Furthermore, the studies have shown Rotarix to be effective when administered with other standard childhood vaccines, and it did not hinder their uptake, including that of oral polio vaccine. On the other hand, a trial in South Africa found that co-administration of rotavirus vaccine and oral polio vaccine limited uptake of the rotavirus vaccine after the first dose, but uptake returned to normal after the second dose.

Phase III trials involving over 70,000 infants, mostly in Latin America, are nearing completion to validate the safety and efficacy of the vaccine and to assess the risk of intussusception or other serious adverse events. Smaller trials are being conducted in Asia and Africa.

De Vos described the “holistic approach” that GSK took in preparing for the Phase III clinical trial, including working with local investigators in 11 Latin American countries to collect health and economic data, carry out disease-burden studies, and conduct both strain surveillance and surveillance to gauge the background rate of intussusception. That rate varied depending on the country, and surveillance also showed that children tended to get intussusception at a slightly younger age in Latin America than in the United States. GSK conducted the intussusception surveillance so that they would have a baseline against which to understand the data they collect on their Phase III clinical trial.

GSK is basing its assessment of vaccine safety on the occurrence of intussusception during the 31 days after each vaccine dose, and a Data Safety Monitoring Board reviews the whole program every three months to

detect any possible signal that the vaccine is triggering intussusception in infants. The study will also evaluate how well children are protected against rotavirus for two years after receiving the vaccine.

While the study was still underway at the time of the symposium, de Vos reported that surveillance had been completed for all vaccinees post-dose 1 and for the vast majority post-dose 2. An Independent Data Monitoring Committee that was continuously monitoring for safety had detected no sign that the vaccine was associated with intussusception.

De Vos concluded her talk by saying, “We believe that we will bring a safe and efficacious vaccine on the market first to those who need it most.”

## Discussion

*Environment and Vaccine Efficacy.* Most questions addressed issues of vaccine take under different conditions. One participant questioned whether Merck was concerned that children in developing countries may respond differently from children in the developed countries where the majority of clinical trial subjects were enrolled, and another asked whether Merck had data on strain-specific efficacy. Heaton replied that most of the trials have been in areas where G1 is dominant, so they have little data on other serotypes. However, the current large-scale clinical trial is studying efficacy and vaccine take in different regions or among different populations. In the southwestern United States, for example, REST has enrolled children in the Navajo and White Mountain Apache nations. Replying to a question about interaction between RotaTeq and oral polio vaccine, Heaton said that Merck planned to study that in the future.

Asked which children were not responding well to their vaccine, de Vos replied, “It is a very interesting question but difficult to answer.” They are examining factors such as the quality of maternal antibodies (which differs between populations), breast-feeding, and the possibility that infection with multiple enteric viruses in South African infants affects vaccine take.

*Transmission of Excreted Virus.* Yet another participant asked whether there were data on the transmission of excreted virus to unvaccinated children. Heaton replied that because RotaTeq has such low shedding rates—only about 4 percent to 5 percent of infants shed after the first dose and then only in very small amounts—studying transmission was very difficult. “It would take over 10,000 infants just to show that the transmission rate was less than 1 percent,” she said. De Vos replied that between 15 percent and 50 percent of vaccinated children will shed live virus, depending on the strength of the individual’s immune response. Based on the genetic stability of vaccine strains recovered from the stool of vaccinated children, de Vos said that GSK believes it can wait to study such transmission in the post-licensure period.

*Socio-Economic Status of Children Vaccinated.* Finally, one participant asked whether the companies have data on vaccine take in children of low social economic status in developing countries and whether significant numbers of poorer children were enrolled in the trials. Both de Vos and Heaton replied that they will be analyzing any trends related to socio-economic status.

## Other Vaccine Approaches

*A Bovine Vaccine for Broad Protection.* In the early 1990s, alongside the development of the rhesus rotavirus vaccine (RRV), scientists at NIH were working on a similar vaccine that incorporated a bovine virus along with three human rotavirus strains. Dr. Albert Kapikian of the NIH described a proposal to use that bovine-human reassortant vaccine as the basis for a hexavalent vaccine containing six strains of rotavirus. It would be aimed at providing the broadest possible protection against rotavirus infection.

Clinical tests in the late 1990s had shown that the bovine reassortant had similar efficacy to and fewer side effects than RRV (later marketed as RotaShield). Specifically, the bovine vaccine did not cause a transient, low-grade fever that affected about one-third of the subjects who received the RRV.

## For the developing countries of the world **we need** a vaccine **that can protect** against these unusual serotypes of 8 and 9.

—Dr. Albert Kapikian  
U.S. National Institutes of Health

The existing tetravalent bovine vaccine includes strains G1, G2, G3, and G4. Kapikian proposed adding G8 and G9 to increase protection in areas where these newer strains are emerging, such as India and parts of Africa. Kapikian also recommended a revised rotavirus vaccination schedule that would potentially eliminate the danger of intussusception, since infants are most vulnerable to intussusception at 4 to 9 months of age. The revised schedule would set the first dose at 0 to 4 weeks of age and the second dose at 4 to 8 weeks of age, with no “catch-up” vaccination in older, more susceptible infants.

Kapikian reported that the NIH Office of Technology Transfer had received license applications for the bovine rotavirus vaccines from companies in the United States, China, India, and Brazil. In addition, the NIH recently approved the prospective grant of an exclusive license for the human bovine reassortant rotavirus vaccine to a U.S. company for use in the United States, Canada, and Europe only. “So we really are anticipating that these vaccines will move ahead,” Kapikian concluded.

*Bringing Back RotaShield.* Since RotaShield was voluntarily withdrawn from the market in July 1999 when the U.S. Vaccine Adverse Event Reporting System (VAERS) identified a number of intussusception cases in vaccinated infants, more than 50 scientific publications and presentations have reported on evaluations of the vaccine. Dr. Leonard Ruiz, President and Chief Executive Officer of BIOVIRx, Inc., highlighted the changing scientific story of RotaShield and described his company’s plans to again market the vaccine. In 1999, statistical projections indicated that 1,500 to 1,600 additional cases of intussusception could occur in the United States if the total birth cohort were vaccinated with RotaShield. By 2001, the projection was between 300 and 700 cases, and in 2003 a new analysis indicated that the total number of cases of intussusception had not increased when the vaccine was used. Other studies have shown that use of RotaShield did not conform to the manufacturer’s recommended dosage schedule, which specified that the first dose be given at 2 months of age. Rather, approximately 50 percent of the first doses were given to infants older than 3 months, during the age of greatest susceptibility to intussusception. Consequently, 80 percent of the intussusception cases associated with RotaShield occurred in infants older than 3 months. In addition, “RotaShield really still represents the standard in clinical efficacy,” Ruiz said.

Given these new insights, BIOVIRx has licensed the vaccine and aims to gain regulatory and marketing approvals and to target a low per-dose price in order to make the vaccine universally available. Ruiz said his company has “the opportunity for a flexible pricing strategy” and noted the importance of delivering a cost-effective vaccine to the developing world.

During the discussion period, Ruiz said that BIOVIRx will first seek U.S. Food and Drug Administration (FDA) approval and then approach the Advisory Committee for Immunization Practices in the United States to rescind the withdrawal of its recommendation for RotaShield. Asked about how he would overcome the stigma attached to RotaShield, Ruiz acknowledged this as a serious challenge and replied that his approach would be to promote the scientific papers and findings about RotaShield that have been produced since 1999. He also said the company would consider conducting further clinical trials to assess possible vaccine side effects other than the risk of intussusception.

*Neonatal Vaccines.* Dr. Bishop described the development of rotavirus vaccines for newborn infants. “Perhaps now we need to consider neonatal vaccination as a strategy, particularly as one that may overcome this intussusception problem,” Bishop said. The candidate neonatal vaccines are based on strains of rotavirus

that enter newborn nurseries in hospitals, where they become established. They can persist over many years and are to some extent unique. Studies in Australia, and more recently in India, have shown that exposure to these neonatal strains can protect against severe diarrhea with future rotavirus infection. There is also evidence that protection extends to other strains. In addition, Bishop said that widespread infection in newborns appears to reduce the prevalence of severe diarrhea in young children in the surrounding communities.

Phase I and II trials of a neonatal vaccine in Australia showed an immune response of 46 percent in infants, associated with a protective efficacy of 56 percent against rotavirus the following winter. Bishop said that one problem in the study was that the vaccine culture constrained the strength of the dose. Since then, the vaccine's immunogenicity has been improved, and Bishop hopes to conduct further trials.

**Perhaps now we need to consider neonatal vaccination as a strategy, particularly as one that may overcome this intussusception problem.**

—Dr. Ruth Bishop  
*Royal Children's Hospital, Melbourne, Australia*

*Alternatives to Oral Live Vaccines.* While scientists have mostly focused on creating live virus vaccines that can be given orally to induce an immune response that closely mimics a natural rotavirus infection, other researchers are pursuing work with parenteral vaccines. These are vaccines that can be injected or inhaled and that do not directly target the gastrointestinal tract. Rather than using live virus, parenteral vaccines under development include those using killed virus, expressed antigens, virus-like particles, and viral DNA.

Dr. Baoming Jiang of the U.S. Centers for Disease Control and Prevention described the potential obstacles confronting other oral live vaccines, including the continuing doubts about whether such vaccines would work as well for children in poor countries of Africa and Asia as they do for children of middle- and upper-income countries. He noted that, because of the RotaShield experience, “a few intussusceptions could rapidly blow away the oral vaccines.” In contrast, parenteral vaccines have some advantages: “We have no worry about intussusception or perceptions. They are cheaper to develop ... and can be added to existing parenteral vaccines to make a combo vaccine,” he said. Baoming pointed to promising data that showed that parenteral rotavirus vaccines protected against rotavirus in rabbits, mice, and piglets.

Baoming described his work with macaques. It identified serum antibody response as a strong correlate of protection against which to assess the protective effects of parenteral rotavirus vaccines. As a next step, Baoming said, “We really need to move forward to test this in humans. We need a good vaccine company like Merck or GSK to develop this kind of program.”

Dr. Osamu Nakagomi of Nagasaki University in Japan described his work testing a virus-like particle (VLP) vaccine in newborn piglets. The vaccine candidate used purified virions of a G1 strain, which were inactivated and then inoculated three times into piglets. A week after the final immunization, the inoculated piglets and a control group were challenged with human rotavirus. In the week following the challenge, the immunized piglets had a serum immune response and did not shed infectious virus, while the control group shed virus. Following the trial, all the animals were sacrificed and examined for pathological changes. The control group suffered greater damage from rotavirus in their intestines than did the immunized group. Nakagomi concluded that the results provide a promising basis on which to pursue further research.

*Figure 4.1*

## New Regulatory Approaches

In the past, vaccines were developed and used first in the industrialized world. When they later reached developing countries, regulatory authorities there often based their decisions on those already taken in industrialized countries. Therefore, the phenomenon of vaccine development targeted first for the developing world—such as for rotavirus or malaria—raises new regulatory challenges. Dr. Liliana Chocarro of the World Health Organization (WHO) described initiatives for new regulatory mechanisms to address these challenges.

One example of these initiatives is in the actions taken by the European Union's European Medicines Evaluation Agency (EMA). Consistent with the old way of doing things, the EMA will not license new vaccines produced in Europe that targeted only developing country markets. Therefore, there is no clear regulatory oversight for these products, especially in those developing countries that lack the internal expertise to evaluate vaccines.

To address this, WHO and the EMA have now agreed that the EMA will issue scientific opinions that evaluate new vaccines as if it were issuing a license for that product. WHO will then consider this scientific opinion valid when deciding whether to pre-qualify a new vaccine to be supplied through United Nations' agencies.

WHO is also working with developing countries to strengthen their regulatory authorities. Chocarro described a proposed Network of Regulatory Authorities of Developing Countries. ‡ Its objective would be to strengthen developing countries' procedures and expertise for the evaluation of clinical trial proposals and clinical trial data.

‡ Nine countries and WHO formalized the Developing Countries Vaccine Regulators Network on September 17, 2004. Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa, and Thailand participated in the Network's founding.

\* From the presentation by Dr. Liliana Chocarro, World Health Organization

# Session V. From Vaccines to the Expanded Program on Immunization

The cost of taking a vaccine from the laboratory to the market requires considerable investment by companies. At the same time, the final vaccine cost is important for countries considering introducing a new vaccine. These issues came to the fore in this session as speakers addressed many critical questions. How will the value of rotavirus vaccines be established? How much will they cost? Who will finance them, and how will they be introduced? How will their value be communicated? From cost-benefit analysis to the value of public-private partnerships, the session explored the issues that will be central to actual implementation of rotavirus vaccines in national immunization programs.

## Cost Is Key

Dr. Dagna Oriana Constenla from Emory University spoke to the question of how to assess the actual value of rotavirus vaccines. “From a health perspective, vaccination appears to be a great investment. However, is it a great investment in terms of economics?” she asked. Constenla described a preliminary cost-effectiveness study of the vaccine in eight Latin American countries: Argentina, Brazil, Chile, the Dominican Republic, Honduras, Mexico, Panama, and Venezuela. The study evaluated the disease burden of rotavirus in those countries, the health costs associated with this burden (although not the societal costs, such as household costs), and the cost-effectiveness of a rotavirus vaccine over a range of vaccine prices. Based on GSK’s candidate vaccine, the study assumed an efficacy rate of about 85 percent in preventing rotavirus-associated deaths, hospitalizations, and outpatient visits. It then applied all of these data to a hypothetical annual birth cohort in each country over a five-year period.

The study estimated that the health costs associated with all rotavirus related deaths, hospitalizations and outpatient visits for the eight countries over five years would be just under US\$7,000 per 1,000 children below the age of five. Extrapolated to all low-and middle-income countries in Latin America and the Caribbean, universal rotavirus vaccination would avert 4,100 deaths, 135,000 hospitalizations, and 1.8 million outpatient visits, saving the region US\$53 million. (See Figure 5.1.)

But would universal rotavirus vaccination result in actual cost-savings? To do so, the cost of a two-dose vaccine course would need to be less than US\$10, Constenla reported. “Although an intervention may not save money in addition to improving health, it can still be considered a good health investment,” she said. But this depends in part on the budget available and the priorities of each country—so cost-effectiveness itself needs to be related to a decision context.

*Figure 5.1*

### Facts and Figures in Vaccine Financing

- Governments in poor countries spend on average US\$6 per capita of public funds on the health care system.
- Of this amount, an average of 4 percent goes to immunization programs.
- Donors spend about 4 percent of official development assistance on the health care sector.

\*From the presentation by Dr. Ruth Levine, Center for Global Development

Figure 5.2

## Who Is Who in Vaccine Financing

*United Nations Children's Fund (UNICEF)*: works with about 100 poor countries to forecast demand for different vaccines. It pools the data and issues tenders for about 3 billion doses a year, covering some of the immunization needs of about 40 percent of the world's children but only about 10 percent of the world's expenditures on vaccines. Vaccines procured by UNICEF are financed by donors, private contributions, and developing country governments.

*Pan American Health Organization (PAHO)*: provides technical assistance on vaccine-preventable diseases to member states in the Americas by working closely with national vaccine programs to refine strategies to protect the achievements of routine immunizations, polio eradication, measles eradication, and neonatal tetanus elimination, to meet new goals for rubella elimination, and to introduce new and under-utilized vaccines. PAHO also serves as a bulk purchasing agent for vaccines and syringes for participating countries through its Expanded Program of Immunization (EPI) Revolving Fund. Vaccines procured by PAHO are financed by member states through the capitalization of the Fund, currently at a level of approximately US\$30 million.

*Global Alliance for Vaccines and Immunization (GAVI)*: is a public-private partnership focused on increasing access to vaccines among children in poor countries. Partners include national governments, UNICEF, WHO, the World Bank, the Bill & Melinda Gates Foundation, the vaccine industry, public health institutions, and non-governmental organizations.

*Vaccine Fund*: is the financing entity created to support GAVI's immunization goals, providing financial support directly to low-income countries to strengthen their health delivery and immunization services and to purchase new and under-used vaccines.

\* Derived from presentation by Dr. Ruth Levine.

## Fixing the Broken System of Vaccine Financing

From Constenla's and other presentations, at least one thing was clear. "Without money flowing, no lives will be saved by the vaccines that you are working so hard on," said Dr. Ruth Levine of the Center for Global Development in Washington, D.C. Levine reviewed the main players in the current system of vaccine financing, the challenges and problems in that system, and recent developments in financing newer vaccines in the poorest countries. She said that the most important reform of the global system of vaccine financing would be switching from short-term financial commitments to purchase vaccine in developing countries to long-term enforceable commitments. (See Figure 5.2)

Problems endemic to the old way of doing business include weak forecasting of demand for specific vaccines. "With lots of built-in unpredictability in the current system ... we collectively pay too much for many vaccines," said Levine. This is partly due to rapid changes of many kinds within developing countries, but also because there are few consequences for getting it wrong. "If the demand forecasts are incorrect, there is inconvenience, there is some embarrassment, but there are no direct consequences to the people who were responsible for the forecasts," Levine said. Another major problem is that funding commitments are typically

What happens with respect to rotavirus,  
in terms of the **speed** at which the product is adopted  
and the extent to which the international system of financing  
can provide **security** to industry...  
will have long-term consequences for the future of vaccines  
that will benefit the developing world.

—Dr. Ruth Levine  
*Center for Global Development*

short term due to budgeting systems. The major exception is grants made by the Vaccine Fund of GAVI, which provide five- to eight-year financial commitments.

Compounding the situation is the high, and in some cases rising, price of many new vaccines, particularly combination vaccines. Countries that have introduced the newer vaccines—such as for hepatitis B and *Haemophilus influenzae b* (Hib)—are finding that immunization is an ever-larger share of their health-care spending. For example, it cost Kenya about 4 percent of its government health budget in 2000 to finance the introduction of a new combination vaccine and to expand coverage with routine immunizations. This proportion will rise to about 20 percent of its budget by 2007. Therefore, the challenge is to sustain the increased spending associated with introducing new vaccines.

There is also the challenge of competing health demands. Kenya, for example, received a three-year grant from the Global Fund to Fight Aids, TB and Malaria, after which the government is expected to provide sustaining funds for the program. “You can see that it is almost head-to-head competition between what will be needed to sustain the Global Fund program and what would be needed to fulfill the ambitions of the immunization program,” Levine explained.

“There is a lot of momentum now to develop a much better functioning system of immunization finance, and through the Vaccine Fund, the potential [is there] to do it,” Levine said. What is most needed is a simple instrument of long-term contracting that is legally enforceable and extends up to 10 years. The system must have legal consequences for either inaccurate forecasting or failure by industry to deliver the vaccine it commits to. The concept of risk-sharing is key to the success of a new system. Industry would have to accept some quantity risk and price concessions in exchange for longer term funding commitments. Sponsors, for their part, would have to accept some initial price risks. Contracts, for example, would involve negotiating a price in advance, based on a price trajectory that starts high (so that companies can cover their R&D spending and make a profit), and then tails off to a lower level over a number of years. Finally, it would require a consistent effort to build demand within developing countries and to increase overall financing for health and immunization. “I can’t stress that last part enough,” Levine said. To lay the groundwork for such changes, a major advocacy effort is needed.

## Advocacy and Communications

John Wecker described such a major advocacy effort underway by RVP. The program is a public-private partnership established with a US\$30 million grant from GAVI to accelerate the development and introduction of late-stage rotavirus vaccines. Wecker contrasted RVP’s goals of delivering rotavirus vaccines to the children who need it most with other experiences in vaccine introduction: “It has taken almost 15 years from the time

that hepatitis B vaccines were made available in the industrialized world to their availability on a wide-scale basis in the developing world, 10 years in the case of the Hib vaccine” he said. “As we look forward to the introduction of new rotavirus vaccines, we have to do something differently.”

Wecker described three novel activities conducted by RVP. First is the collection and generation of information that will aid decision makers in choosing whether to commit resources to rotavirus vaccine introduction. Decision makers need reliable surveillance data and information on disease burden as they weigh their health priorities. RVP is working with its partners to collect information on system costs and vaccine cost-effectiveness. “We need to recognize that for national governments to be able to make committed decisions to introduce these new vaccines, we need to establish what is the cost per immunized child,” Wecker said. System costs include infrastructure, education of health care workers, and community awareness campaigns. RVP is also partnering with vaccine manufacturers to conduct clinical trials in the poorest countries, generating data on disease efficacy and safety in those settings.

Second is development of a stable marketplace through working with both the demand and supply sides of the equation. On the demand side, analysis of the new data will allow an accurate description of vaccine value. According to Wecker, communicating that value will create demand. Similarly, for donors to make a financial commitment to support vaccine introduction in low-income countries, they need to understand that they will get a return on their investment. “That return is the lives of children saved,” Wecker said.

On the supply side, RVP is working with manufacturers to better match their manufacturing capacity to that demand in order to ensure an adequate supply for all who want and need the new vaccines.

Third, RVP will be working with a series of early adopter countries to prepare for the introduction of rotavirus vaccines. Then, when the vaccines are actually available, these countries will be prepared to move quickly. Their experience will be documented to serve as models for other countries.

Wecker said that he has been asked why RVP is willing to risk money and resources when the new vaccines have not yet even been proven viable. “Only by taking that risk now will we have the opportunity to meet our commitment to accelerate the availability of vaccines in the developing world,” Wecker said. “Someone once said that you cannot leap a 20-foot chasm in two 10-foot jumps. You have to make that commitment.”

Decision makers are not the only ones who will need to understand the value of rotavirus vaccines. Ultimately, consumers in developing countries will also need to get their children vaccinated. Therefore, the mother or father of the child to be vaccinated must understand the life-saving potential of rotavirus vaccines.

Dr. Heidi Larson of the United Nations Children’s Fund (UNICEF) discussed broad strategies for communicating with the consumer in developing countries. “We have to understand who we are talking to,” she said. “We didn’t do this adequately with polio, and now we are in trouble.”

Once again the global rotavirus community finds itself  
on the **brink of success** and our shared vision is **clear:**  
to **reduce** the number of children who die each year around  
the world due to rotavirus infection through  
the **use of these new vaccines.**

—Dr. John Wecker  
*Rotavirus Vaccine Program*

In addition, Larson said that the global environment for vaccines has changed significantly in the last year. “Immunization is not immune to a world that is defined by growing distrust in just about every public institution,” Larson said. Trust is a huge issue in vaccines. It comes up around issues such as the content of vaccines, who manufactured them, and where. In this climate, small adverse events become big national media events. In addition, “The better job you do in immunization, the less apparent is the need for vaccine,” Larson said.

Larson said that the key to building trust in any new vaccine is to communicate as much as possible before a vaccine is introduced. “Along with communicating the benefits, we need to be clear about risks,” she noted. To “sell” rotavirus vaccines, the public health community will have to overcome the fact that the disease and its impact are not well-known. When it is known, it may be known for earlier problems with RotaShield. “But we do have a story to tell,” Larson pointed out. “The story is that rotavirus is killing over half a million children every year ... and that it does not discriminate between rich and poor—any child anywhere can get it, and the poor die from it much more.”

In introducing rotavirus vaccines, the public health community needs to understand that parents have two main questions: is it safe for my child? and is it worth the risks? Parents need to understand that rotavirus prevents the most serious type of diarrhea, but there are other causes as well. They need to see the evidence that intussusception is being investigated and addressed and that attention is being paid to other possible side-effects. And they need to know that the vaccine is not enough; it is still important to have clean water and good sanitation.

In conclusion, Larson said, “The good news is that we have huge opportunities right now ... There is a significant revitalization in the global health and development community on immunization.” In addition, a huge global child survival effort is centered on achieving the Millennium Development Goal of reducing child deaths by two-thirds. “What better way than a rotavirus vaccine?” Larson asked.

## Discussion

*Communications and Advocacy.* Most of the discussion focused on questions of communications and advocacy work. One participant questioned why Africa and Asia were being left out of the current advocacy work and large-scale clinical trials when those are the regions hardest hit by rotavirus. Wecker responded that although the process has begun in Africa and Asia, there is a lot more work to do. In particular, a public-private partnership known as (RAPID) is evaluating Rotarix in clinical trials in Bangladesh and South Africa, and RVP is discussing a similar effort with the Merck vaccine candidate. This work includes an important advocacy component within the affected countries.

Panelists and audience members grappled with questions of how to refocus the attention of the press from headline diseases like SARS that have limited impact—or the rare vaccine-related adverse event—to the life-saving benefits of vaccines. Larson pointed out that the media are paid to find tension, and adverse events are a perfect tension. “We have to create different kinds of tension that actually lead to positive messages,” she said. Possible angles include personalities, numbers, and new data. Others noted that every community will need to

**The most critical question will soon be:  
Now that we have a vaccine, how are we going to use it?**

—Dr. *Ciro de Quadros*  
*Albert B. Sabin Vaccine Institute*

give a human face to the disease, as well as the importance of distinguishing between communications and marketing when talking to the public about rotavirus. The key, Larson said, is for communications to be research-driven.

De Quadros noted the strong participation of the press at the symposium itself: “In my whole career, I have never attended a meeting with so much press, people with so much information and good information ... My hope is that this will filter down now to every country because the action is really at the country level.”

*Public Discussion of the Risks and Benefits of Vaccines.* Combating the media’s focus on negative events begged a bigger question: the need for a public discussion about the risks and benefits of vaccines and how they may differ in different settings. In Bangladesh, for example, rotavirus kills 1 in every 250 children, while in the United States it kills approximately 1 in every 100,000 children. But in both places the risk of an adverse event with vaccination may be 1 in 30,000—yielding vastly different risk-benefit ratios. “Is it possible to have different risk-benefit ratios for the approval of any kind of health care intervention?” asked one participant. He stressed the need for an open dialogue to discuss such questions and to combat fears that inferior products were being dumped in developing countries or that clinical trials in developing countries mean that poor people are being used as guinea pigs. Without such a dialogue, a future adverse event similar to intussusception could again eliminate “the opportunity to use these potentially life-saving vaccines in developing countries.”

# Session VI. Roundtable— Perspectives on Vaccine Introduction: The Role of Public-Private Partnerships

The roundtable discussion was informed by perspectives of representatives of industry, the donor community, the global health community, and Ministers of Health in Latin America. Co-chaired by Dr. Roberto Tapia, the Mexican Vice Secretary of Health, and Dr. Jon Andrus of PAHO, this session served as a forum for stimulating discussion of the challenges involved in vaccine introduction, including the pivotal issue of affordability. While each person had his or her own point of view, all agreed that the development of effective partnerships between the private and public sectors is essential to the introduction of rotavirus vaccines in poor nations, where children are at greatest risk of dying from severe rotavirus gastroenteritis.

Concluding the conference, representatives of 16 Ministries of Health across Latin America presented a declaration dedicating their countries to prioritizing universal vaccination. The declaration called for immunization to continue receiving support “with the highest political priority, as a public good for the region.” (See Figure 6.1)

## Dr. Elaine Esber, Merck Research Laboratories

Providing comments on behalf of Dr. Adel Mahmoud, President of Merck, Dr. Esber said that the “staggering disparity” in global vaccine efforts is threatening the goal of eradicating or controlling many infectious diseases. In the least developed countries, this disparity has involved sporadic and inconsistent immunization efforts, crumbling health care delivery systems, and insufficient leadership.

Esber called for national and regional level consensus for a commitment to three key prerequisites for successful vaccine programs:

- Immunizing the majority of susceptible individuals to achieve “herd” immunity;
- Ensuring the sustainability of community-based immunization efforts; and
- Harnessing the political will of policy makers to close the vaccine gap.

“This meeting is a milestone in the chapter of rotavirus, where the message is ‘Let’s get going with what it takes to stop mortality due to rotavirus,’” Esber said.

Efforts to close the gap will require billions of dollars in funding over a period of several decades to expand the immunization programs of WHO and UNICEF and to introduce new GAVI-funded vaccines. “It will require

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where the message is ‘Let’s get going with what it takes  
to stop mortality due to rotavirus.**

—Dr. Elaine Esber  
Merck Research Laboratories

political will, national, and multinational commitments,” she said. “The seriousness of the task has to be matched with the magnitude of the local investment in health. Governments must place disease prevention at high levels.”

For its part, Esber said that Merck has put in place costly multi-country programs to address safety and efficacy concerns and that the company is committed to providing a high-quality, safe, and effective vaccine for low- and middle-income countries at an affordable price. “This is a commitment from the highest management levels at Merck,” Esber said. Merck plans to file its vaccine, RotaTeq, with the FDA in late 2005 and simultaneously submit applications for its registration in other countries, including Mexico.

Public-private partnerships, emphasized Esber, are critical to efforts to close the global vaccine gap and to reduce rotavirus morbidity and mortality. “No single source or entity,” said Esber, “can make it happen on their own.”

**We have to communicate, communicate, communicate.**

—*Dr. Steve Wiersma*  
*World Health Organization*

## Dr. Steve Wiersma, World Health Organization

Dr. Wiersma outlined three key issues involved in introducing rotavirus vaccines:

- Establishing a clear demand for vaccine through establishing the burden of disease;
- Ensuring a supply of safe and effective registered vaccines at affordable prices with available financing; and
- Developing the capacity of health care delivery systems to distribute vaccines, monitor their use, demonstrate their impact, and track any adverse side effects.

Of particular importance in establishing the burden of rotavirus disease is emphasizing the cost-effectiveness of immunizing children. But consensus on the need for a rotavirus vaccine “can’t be something that we impose from high levels,” Wiersma said. “It must occur at a grassroots level, all the way up through the chain” that rotavirus is an urgent public health priority.

Wiersma also noted the importance of effective communication around rotavirus vaccination so that the public develops a full understanding of both its benefits and limitations. “Putting a face on the disease,” said Wiersma, “is an extremely important concept and something we don’t always do very well.”

Wiersma suggested that one of the biggest obstacles to effective communication might be the word “rotavirus” itself. “Should we really be promoting a diarrhea vaccine?” he asked. He pointed out that there is precedent for this in other public health campaigns. For instance, “We do not really have a meningitis vaccine, although that’s what the public thinks we have. We have vaccines against some very specific etiologic agents for meningitis.” The same is true for pneumococcal and hepatitis vaccines. Wiersma urged the public health community to discuss the pros and cons of promoting vaccines for rotavirus versus diarrheal disease.

## Dr. Tore Godal, Global Alliance for Vaccines and Immunization

Dr. Godal assessed GAVI’s progress since its inception four years ago, continuing challenges, and steps GAVI is taking to further accelerate the introduction of rotavirus vaccines in developing countries.

In reviewing the results of GAVI’s work, Dr. Godal contrasted the organization’s experience with two underutilized vaccines, hepatitis B and Hib. Whereas “very, very significant progress” has been made with

## **Immunization** is back at a more **central stage** in overall development.

—Dr. Tore Godal

*Global Alliance for Vaccines and Immunization*

hepatitis B vaccine, progress had been limited with the Hib vaccine. According to WHO, more than 40 million children in Vaccine Fund-supported countries had been immunized against hepatitis B by the end of 2003. With respect to overall vaccine coverage, some 4.8 million additional children were immunized in 2003 as compared to 2002. Despite these advances, “We have a very big challenge that we must not put under the carpet in the face of good progress,” Godal said.

Based on its four years of experience, GAVI has reached several conclusions relevant to the introduction of a rotavirus vaccine:

- It is possible to achieve rapid scale-up in poor countries with certain products;
- Global immunization targets can be achieved by providing countries with non-targeted funding, that is, leaving it up to the country to decide how to allocate the funds to achieve their goals;
- Financial incentives that reward success can result in increased access to vaccines; and
- GAVI has gained “real life” experience in planning for the sustainability of immunization programs.

Looking to the future, Godal said that the GAVI Board of Directors is “very excited” that developments in the rotavirus field are moving faster than anticipated. He reported that the board would be implementing two new projects to accelerate the introduction of a rotavirus vaccine in the poorest countries. The two projects are based on a report from the Management Committee of the Accelerated Development and Introduction Plans (ADIPs). First, a GAVI group will explore with GSK the feasibility, including technical, scientific, and cost implications, of an early introduction of rotavirus vaccine in eligible countries. Second, RVP will explore opportunities to participate in the testing and pilot introduction of the GSK vaccine in settings where income levels are low and the health infrastructure is limited.

Dr. Godal also noted that GAVI’s major donors have requested the development of a long-term strategy (until 2015) that will include a plan to phase out funding to targeted countries and to initiate new financing mechanisms for the purchase of vaccines. “Immunization is back at a more central stage in overall development,” asserted Godal.

### **Dr. Steve Landry, Vaccine Fund/Co-Chair of the GAVI Financial Task Force**

Dr. Landry presented an overview of the Vaccine Fund, its initial strategy for accelerated introduction of vaccines, and the implications for rotavirus. The Vaccine Fund is the funding arm of GAVI and is registered as a U.S.-based charitable organization dedicated to providing equal access to childhood immunizations. With donations from the Bill & Melinda Gates Foundation, other private foundations, and nine different countries, the Vaccine Fund has raised US\$1.3 billion.

“Our entire strategy is based on one very fundamental assumption ... that the financial responsibility ultimately has to be transferred to governments together with their local partners,” Landry said. “Without that, the entire house of cards collapses.”

**“Our entire strategy is based on one very fundamental assumption ... that the financial responsibility ultimately has to be transferred to governments together with their local partners.”**

—*Dr. Steve Landry*  
*Co-Chair of the GAVI Financial Task Force*

GAVI’s original strategy for the introduction of new and underutilized vaccines was based on the idea that Vaccine Fund support would be catalytic, providing five years of free vaccines, with the countries gradually moving toward self-financing. GAVI also assumed that the price of vaccines would drop and that governments and their partners would increase spending incrementally on vaccines in a smooth transition away from Vaccine Fund support.

In actuality, vaccine prices did not drop as anticipated, particularly for newer products. While governments and their partners did increase spending, on average by 46 percent, the resource requirement doubled in the same time period. Landry noted that the vaccine financing gap is directly related to the product being introduced. More mature products, for example, monovalent hepatitis B vaccine, are the least expensive, while less mature products, such as the Hib vaccine, are the most expensive. High prices for newer vaccines, explained Landry, is a premium paid to the industry to recoup their legitimate research and development costs.

In charting a road forward, the Vaccine Fund has sought new strategies to address the financing gap. It is currently investigating an approach in which the Vaccine Fund will continue to provide five years of free vaccines, as initially planned, but spread out over a 10-year period. In that timeframe, countries will phase in their contributions at the estimated mature price of the product rather than the actual higher market value. GAVI and the Vaccine Fund will provide the compensatory financing. New vaccines “are global public goods,” asserted Landry. “Those should be covered by the international community. The long-term cost of the vaccines is probably most appropriately covered by governments together with their partners.”

The GAVI Board identified four questions to be investigated before implementation of the new financing plan:

- 1) What will be the plan’s annual cost and the total cost to GAVI and the Vaccine Fund?
- 2) Will the new plan meet the needs of developing countries?
- 3) What will be the impact of the plan on the short and long-term price of vaccines?
- 4) How will the plan be implemented?

“We are trying to learn from the experience with Hib, hepatitis B, and yellow fever. We are trying to translate that into the strategies that we will use to support the introduction of rotavirus, pneumococcus, and other new vaccines,” Landry concluded.

## Dr. Jean Stephenne, GlaxoSmithKline Biologicals

Dr. Stephenne noted that the Mexico City meeting represented the establishment of a new and innovative model for vaccine introduction. In the past, vaccines were only made available in poor nations after 10 to 20 years of use in Europe and the United States. In the case of rotavirus, the vaccine industry and the global

**Our rotavirus vaccine is a new model ...  
because we have involved  
developing countries **right** from the **beginning**.**

—Dr. Jean Stephenne  
*GlaxoSmithKline Biologicals*

scientific community have committed to accelerating the introduction of the vaccines in developing countries where mortality is highest and the potential impact is greatest. In addition, “It is a new model in the way the industry is doing its clinical plan because we have involved developing countries right from the beginning,” Stephenne said.

While the vaccine industry has been criticized in the past for failing to do research for vaccines for developing countries, Stephenne said this is no longer true. In addition to rotavirus, vaccines are in development for dengue, malaria, pneumonia, tuberculosis, and human papillomavirus. “So now the pressure is no longer on the industry,” he said. The new challenge is, “Will we find the money to purchase these vaccines? Will we find the funds to make sure that these vaccines are available in the developing countries?”

He observed that the greatest obstacle to making vaccines available where they are needed most is in the financing and implementation of vaccine programs in developing countries. The production of a large quantity of vaccine, for example, requires at least five years of advance planning. Thus, GSK has committed to producing a few tens of millions of doses of rotavirus vaccine for Europe, Latin America, Asian countries, and the United States. But it has not committed to producing hundreds of millions of doses for the poorest countries because, without financial commitments, it does not know there is a market in those countries.

Issues of supply and demand must be addressed before production and pricing can be determined, and GSK must recoup money invested in vaccine development.

Stephenne said there were two simple concepts that determine price: “Price is a function of volume ... and there is no free lunch.” He noted that the new vaccines are expensive to produce and to develop and that the vaccine industry needs a reasonable price.

He noted two important developments in GSK’s vaccine strategy: it will implement a three-tier pricing scheme for high, middle, and low-income countries, which will include a private market price even in the poorest countries, and it will build a manufacturing network around the world much like that of the auto industry.

**We need to encourage the right of our children to safe,  
effective, affordable, and competitive vaccines in the market.  
Our countries have been undertaking important efforts  
to face these rights responsibly.**

—Dr. Rosario Quiroga  
*Vice Minister of Health, Bolivia*

According to Stephenne, three critical issues must be addressed to finalize price and supply:

- 1) The funding gap in the ability of poor countries to purchase needed vaccines and the prioritization of vaccines on the part of national governments;
- 2) Liability issues; and
- 3) Long-term commitments from vaccine purchasers.

## Dr. Rosario Quiroga, Vice Minister of Health, Bolivia

Dr. Quiroga presented a declaration of health officials from 16 countries in the Americas who together called for the new rotavirus vaccines to be made available to infants and for immunization to continue receiving support “with the highest political priority, as a public good for the region.” She concluded the session by reading the statement drafted by the representatives of the Ministries of Health at the Sixth International Rotavirus Symposium (see Figure 6.1).

Setting the context of that joint statement, Dr. Quiroga discussed the role of the public sector in Latin America in fulfilling the goals of universal immunization set out in the Expanded Program on Immunization (EPI). She observed that EPI is “one of the most democratic public health programs.” With 90 percent of children now covered, the Americas region has witnessed the eradication of polio and the control of measles and other childhood diseases. The second objective of EPI was to attain self-sufficiency in vaccine production and in access to new-generation vaccines. The third objective was to promote financial and technical sustainability in vaccine programs through the development of institutional structures such as scientific committees to draft vaccine policies.

Despite strong progress in fulfilling the objectives, much remains to be done to combat child mortality. Rotavirus vaccines could also critically assist Latin America in meeting the Millennium Development Goal of reducing infant mortality by two-thirds by 2015, Quiroga said.

She observed that issues of equity and social inclusion are of special importance in considering rotavirus vaccines: “Would it be proper that only in some countries, such as Mexico, the introduction of rotavirus vaccine is being considered, but not in Bolivia? We think that the vaccines need to be seen as a common good.” She also noted that the introduction of every new vaccine in the EPI schedule strengthens training, human resources, and communication.

**We think that the vaccines need to be  
seen as a **common good**.**

*—Dr. Rosario Quiroga  
Vice Minister of Health, Bolivia*

**Considering:**

That out of the 600,000 deaths caused by rotavirus annually,  
82% are in developing countries;

**Agree:**

To continue to support immunizations as a common good in  
the region and as the highest political priority ...

# Declaration

by Representatives of Ministries of Health in the Americas‡

*Sixth International Rotavirus Symposium*

*Mexico City, Mexico*

*July 7–9, 2004*

## Considering:

- That rotavirus is one of the most frequent causes of severe gastroenteritis in the world, causing acute diarrhea mainly among those who are 3 to 35 months old;
- That out of the 600,000 deaths caused by rotavirus annually, 82% are in developing countries;
- That rotavirus treatment is costly and it has an important economic impact in Latin America where it causes an average of 15,000 deaths and 75,000 hospitalizations a year;
- That two promising vaccines are soon to enter the market;
- That rotavirus vaccines will reduce rotavirus mortality 60% or more through the inclusion in the national immunization schedules in our region;
- That this new technology shall be made accessible to infants to avoid vaccination-preventable diseases.

## Agree:

- To continue to support immunizations as a common good in the region and as the highest political priority;
- To show achievements in public health as a result of universal vaccination;
- To look for mechanisms within the national budgetary processes for negotiation with the highest-level officials so as to ensure sustainability of the current vaccination programs and the introduction of new vaccines;
- To call upon PAHO and its Revolving Fund for the acquisition of vaccines to work together with bilateral and multilateral agencies, the Global Alliance for Vaccines and Immunization and the manufacturers of vaccines to facilitate the introduction of the rotavirus vaccine, as soon as it becomes available at affordable price for the countries in the region.

‡ *Argentina, Bolivia, Brazil, Ecuador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Peru, Paraguay, Saint Vincent, Suriname, Trinidad and Tobago, and Venezuela.*

\* Presented by Dr. Rosario Quiroga, Vice Minister of Health, Bolivia

# Symposium Speakers

<b>Jon Kim Andrus</b> * ‡ <i>Pan American Health Organization, US</i>	<b>Ruth Ellen Levine</b> * <i>Center for Global Development, US</i>	<b>Guillermo M. Ruiz Palacios</b> * <i>Instituto Nacional de Ciencias Médicas y Nutrición, Mexico</i>
<b>George E. Armah</b> * <i>Noguchi Medical Research Institute, Ghana</i>	<b>Alexandre Linhares</b> * <i>Instituto Evandro Chagas, Brazil</i>	<b>Leonard P. Ruiz</b> * <i>Biovirx, Inc., US</i>
<b>Ruth Frances Bishop</b> * <i>Murdoch Children's Research Institute, Australia</i>	<b>Osamu Nakagomi</b> * <i>Nagasaki University, Japan</i>	<b>Lone Simonsen</b> * <i>NIAID/National Institutes of Health, US</i>
<b>David E. Bloom</b> * <i>Harvard University, US</i>	<b>Paul Offit</b> * ‡ <i>The Children's Hospital of Philadelphia, US</i>	<b>Duncan Steele</b> ‡ <i>World Health Organization</i>
<b>Liliana B. Chocarro</b> * <i>World Health Organization, Switzerland</i>	<b>Dagna Oriana Constenla</b> * <i>Emory University, US</i>	<b>Jean Stephenne</b> * <i>GlaxoSmithKline Biologicals, Belgium</i>
<b>Ciro de Quadros</b> ‡ <i>Albert B. Sabin Vaccine Institute, US</i>	<b>Miguel O'Ryan</b> * <i>Facultad de Medicina, University of Chile</i>	<b>Roberto Tapia Conyer</b> <i>Subsecretaría de Prevención y Protección de la Salud, Mexico</i>
<b>Beatrice de Vos</b> * <i>GlaxoSmithKline Biologicals, Belgium</i>	<b>Umesh D. Parashar</b> * <i>Centers for Disease Control and Prevention, US</i>	<b>F. Raúl Velázquez</b> * <i>Hospital de Pediatría CMN-Siglo XXI, IMSS, Mexico</i>
<b>Elaine C. Esber</b> <i>Merck &amp; Co., Inc., US</i>	<b>Irene Perez Schael</b> * <i>Instituto de Biomedicina, Venezuela</i>	<b>Timo Vesikari</b> * <i>University of Tampere, Finland</i>
<b>Julio Frenk Mora</b> * <i>Secretaría de Salud, Mexico</i>	<b>Rosario Quiroga</b> * <i>Ministry of Health, Bolivia</i>	<b>Richard Leo Ward</b> * <i>Cincinnati Children's Hospital Medical Center, US</i>
<b>Jon Robert Gentsch</b> * <i>Centers for Disease Control and Prevention, US</i>	<b>Romeo Rodriguez</b> * <i>National Center for Infant and Adolescent Health Tec. Secretary, Mexico</i>	<b>John Wecker</b> * <i>Rotavirus Vaccine Program, US</i>
<b>Roger Glass</b> * ‡ <i>Centers for Disease Control and Prevention, US</i>	<b>Tore Godal</b> * <i>Global Alliance for Vaccines and Immunization, Switzerland</i>	
<b>Harry B. Greenberg</b> * <i>Stanford University, US</i>	<b>Penny M. Heaton</b> * <i>Merck &amp; Co., Inc., US</i>	
<b>José Ignacio Santos</b> ‡ <i>Hospital Infantil de México, Federico Gomez, Mexico</i>	<b>Baoming Jiang</b> * <i>Centers for Disease Control and Prevention, US</i>	
<b>Albert Kapikian</b> * <i>Laboratory of Infectious Diseases/NIAID/NIH, US</i>	<b>Paul Evan Kilgore</b> * <i>International Vaccine Institute, Korea</i>	
<b>Steve Landry</b> * <i>The Vaccine Fund, US</i>	<b>Heidi Jane Larson</b> * <i>UNICEF, US</i>	

‡ organizer  
\* speaker

# Symposium Participants

<b>A</b>	<b>Kutzi Arriaga</b> MSD, Mexico	<b>M. K. Bhan</b> Indian National Science Academy, India	<b>Ana Carvalho</b> Albert B. Sabin Vaccine Institute, US	<b>H. Fred Clark</b> The Children's Hospital of Philadelphia, US
<b>Hector Jose Abate</b> SLIPE/SAR, Argentina	<b>Melissa Arvay</b> Centers for Disease Control and Prevention, US	<b>Robin Biellik</b> PATH, Rotavirus Vaccine Program, France	<b>Enrique Casanueva</b> Hospital Universitario Austral, Argentina	<b>Ralf Leo Clemens</b> GlaxoSmithKline Latin America & Caribbean, Brazil
<b>Arturo Abdelnour Vasquez</b> Costa Rica	<b>Edwin Jose Asturias</b> Universidad del Valle Guatemala, Johns Hopkins School of Public Health	<b>Carlos Blancas Jimenez</b> Escuela Superior de Medicina, Mexico	<b>José Luis Castañeda</b> Instituto Nacional de Pediatría, Mexico	<b>Jose Cofre Guerra</b> Hospital Luis Calvo Mackenna, Chile
<b>Camilo J. Acosta Rodriguez</b> GlaxoSmithKline, US	<b>B</b>	<b>Rebeca Borgaro Payró</b> Hospital Inovamed Cuernavaca, Mexico	<b>Erika Castañon Acosta</b> Nutricion, Mexico	<b>Norma Beatriz Coluchi</b> Laboratorio Central de Salud Pública, Paraguay
<b>Felipe Aguilar Ituarte</b> Hospital Infantil de México	<b>Javier Báez Villaseñor</b> Facultad de Medicina, Universidad Nacional Autónoma de México	<b>Paulo Candia Braga</b> GlaxoSmithKline, Brazil	<b>Eduardo Castillo Gonzalez</b> Merck & Co., Inc., Mexico	<b>Juan Contreras Martinez</b> IBT, Universidad Nacional Autónoma de México
<b>Yvonne Aida Maldonado</b> Stanford University, US	<b>Beni Naraine Balkaran</b> Ministry of Health, Trinidad y Tobago	<b>Filemon Bucardo</b> University of Leon, Nicaragua	<b>Juan Enrique Castrejón</b> Merck & Co. Inc., US	<b>Iris Contreras</b> IMSS, Mexico
<b>Christopher Alan Singer</b> US	<b>Zita Lucia Barajas</b> Hospital Médica Sur, CIBBIOTEC, Mexico	<b>José Cruz Bugarín González</b> Birmex, Mexico	<b>Alma E. Cerna</b> IMSS, Mexico	<b>Maria Coreño</b> IMSS, Mexico
<b>Maria Alè de Pedrozo</b> Ministerio de Salud Pública y Bienestar Social, Paraguay	<b>Maria Angélica Barbosa</b> Ministerio de Salud Pública y Bienestar Social, Paraguay	<b>Dante Busato</b> GlaxoSmithKline, Argentina	<b>Rocio Cervantes Rosales</b> Birmex, Mexico	<b>Adely Correa</b> GlaxoSmithKline, Chile
<b>A Jennifer Allen</b> Merck & Co., Inc., US	<b>Patricia Barcenas</b> Birmex, Mexico	<b>Diana Carolina Caceres</b> INS, Colombia	<b>Yolanda Cervantes</b> GlaxoSmithKline, Mexico	<b>Adriana Cravioto</b> Merck, Mexico
<b>Celia Alpuche Aranda</b> Mexico	<b>Patrick Noel Barrett</b> Baxter Vaccine Ag. Austria	<b>Julio Cardenas Rodriguez</b> Merck, Mexico	<b>Patricia Cervantes Powell</b> Aventis Pasteur, Mexico	<b>Luz Cruz</b> Mexico
<b>Juanita Angel</b> IGH Pontificia Universidad Javeriana, Colombia	<b>Oswaldo Barrezueta</b> Pan American Health Organization, Venezuela	<b>Helio Pinheiro Carneiro</b> Seu Filho e Você Magazine, Brazil	<b>Ana Elena Chevez</b> Ministerio de Salud Pública, Centro Nacional de Biologicos, El Salvador	<b>George Curlin</b> National Institutes of Health, US
<b>Graciela Ania</b> Piensa, Mexico	<b>Ines Barron</b> Birmex, Mexico	<b>Rita Cassia Carmona</b> Adolfo Lutz Institute, Brazil	<b>Roberto Chuit</b> Ministerio de Salud, Argentina	<b>Leonor de Cozzarelli</b> Inst. Nacional. de Higiene y Medicina Tropical Leopoldo Izquieta Perez, Ecuador
<b>Carlos Aranza Donis</b> Hospital General de Tlanepantla, Mexico	<b>Aurora Bautista-Marquez</b> Instituto Nacional de Ciencias Médicas y Nutrición, Mexico	<b>Veronica Carrion</b> Secretaria de Salud, Mexico	<b>Ana Maria Cibrian Tovar</b> GlaxoSmithKline, Mexico	<b>Juan del Monte Toledo</b> Instituto Nacional de Ciencias Médicas y Nutrición, Mexico
<b>Nancy Arias</b> IBT, Universidad Nacional Autónoma de México				

# LIST OF PARTICIPANTS

## D

**Alejandra Diaz Alvarado Leyva**  
*GlaxoSmithKline, Mexico*

**Cristina Diaz Vega**  
*Merck, Mexico*

**Daniel DiStefano**  
*Merck & Co., Inc., US*

**Beatriz Dobashi**  
*Secretaria Municipal de Saúde, Brazil*

**Maria Ines Costa Dourado**  
*Universidade Federal da Bahia, Brazil*

**Bozena Drewicz**  
*GlaxoSmithKline, Mexico*

**Anh Duc Dang**  
*National Institute of Hygiene and Epidemiology, Vietnam*

## E

**Leticia Echartea Gonzalez**  
*Merck, Mexico*

**Margalit Edelman**  
*Merck Co., Inc., US*

**Vanessa Elharrar**  
*Pan American Health Organization, US*

**Alejandro Ellis**  
*Ricardo Gutierrez Children's Hospital, Argentina*

**Daniel Epstein**  
*Pan American Health Organization, US*

**Celia Escandon Romero**  
*IMSS Oportunidades, Mexico*

**Tania Espinosa**  
*Glaxo, Mexico*

**Tania Espinosa Sierra**  
*Mexico*

**Jose Felix Espinoza**  
*University of Leon, Nicaragua*

**Ernesto Esquivel**  
*IBT, Universidad Nacional Autónoma de México*

**Fernando Esquivel**  
*Universidad de Morelos, Mexico*

## F

**Andrea Falaschi**  
*SLIPE / SAP, Argentina*

**Zhao-Yin Fang**  
*Institute of Virology, China CDC*

**Jose Carlos da Silva Felner**  
*GlaxoSmithKline, Brazil*

**Victor Fernandez Patiño**  
*Censia, Mexico*

**Ana Maria Ferrari**  
*Facultad de Medicina, Universidad de la República, Uruguay*

**Juana Flores de Jesus**  
*Instituto Nacional de Ciencias Médicas y Nutrición, Mexico*

**Carlos Flores Menendez**  
*Pan American Health Organization, El Salvador*

**Adriana Forero**  
*GlaxoSmithKline, Colombia*

**Manuel Franco**  
*IGH Pontificia Universidad Javeriana, Colombia*

**Ana Paula Fuentes**  
*General Physician and Family Medicine, Mexico*

## G

**Guido Gaona**  
*Burson-Marsteller, Mexico*

**Pilar Garcia**  
*Fleishman, Mexico*

**Salvador Garcia**  
*Pan American Health Organization, US*

**Salvador Garcia Jimenez**  
*Pan American Health Organization, El Salvador*

**Rosa Garcia Loperena**  
*Instituto Nacional de Ciencias Médicas y Nutrición, Mexico*

**Miguel Leonardo García**  
*Unidad de Medicina Experimental, Universidad Nacional Autónoma de México*

**María García López**  
*Birmex, Mexico*

**Herlinda Garcia Lozano**  
*Indre Secretaria de Salud, Mexico*

**Angela Gentile**  
*Ricardo Gutierrez Children's Hospital Argentine Society of Pediatric, Argentina*

**Rolland Gianotti**  
*Seu Filho e Você Magazine, Brazil*

**Oswaldo M. Gola**  
*GlaxoSmithKline, Mexico*

**Jorge Alberto Gomez**  
*Argentine Institute for Infectious Disease, Argentina*

**Cesar Gomez Altamirano**  
*Centro Nacional para la Salud de la Infancia y Adolescencia, Mexico*

**Miguel Gomez Zarco**  
*Merck Sharp and Dohme, Mexico*

**Elizabeth Gomez**  
*Universidad Autónoma de Santo Domingo, Dominican Republic*

**Julieta Góngora Rodriguez**  
*Hospital Médica Sur, Cifbiotec, Mexico*

**Silvia Gonzalez Ayala**  
*School of Medicine, Sor María Ludovica Children Hospital La Plata, Argentina*

**Luis Gonzalez Gomez**  
*Star Medica Morelia, Mexico*

**Jim Gray**  
*Health Protection Agency, UK*

**Mario Gudiel**  
*Sistema Integral de Asistencia en Salud, Guatemala*

**Maria de Lourdes Guerrero**  
*Instituto Nacional de Ciencias Médicas y Nutrición, Mexico*

**Gonzalo Gutiérrez**  
*Instituto Mexicano del Seguro Social, Mexico*

**Jean Pierre M. Guyot**  
*GlaxoSmithKline, Belgium*

## H

**Harold Hamana**  
*Burson/Marsteller, US*

**Michelle Ann Harris**  
*SERHA, Ministry of Health, Jamaica*

**Gutla V.J.A. Harshavardhan**  
*Bharat Biotech International Limited, India*

**Luz Hederra**  
*Instituto de Salud Pública, Chile*

**Sandra Hermelijn**  
*Pan American Health Organization, Suriname*

**Beatriz Hernandez**  
*IMSS Oportunidades, Mexico*

**Elizabeth Hernandez**  
*Universidad la Salle, Mexico*

**Adolfo Hernandez Garduño**  
*Hospital General de México*

**Omar Hernandez Vargas**  
*Investigación en Rotavirus, Mexico*

**Marte Hernandez Porras**  
*Instituto Nacional de Pediatría, Mexico*

**Luc Hessel**  
*Aventis Pasteur, France*

**Itzel Yolanda Hewitt**  
*Ministerio de Salud, Panama*

**Johan Heylen**  
*GlaxoSmithKline Biologicals, Belgium*

- Akira Homma**  
*Bio-Manguinhos/Oswaldo Cruz Foundation, Brazil*
- Angela Howard**  
*Merck Pharmaceuticals, US*
- I**
- Volga Ana Iñiguez**  
*University Mayor San Andres, Bolivia*
- Bruce Innis**  
*GlaxoSmithKline, US*
- Rene Ireta**  
*Universidad Nacional Autónoma de México*
- Pavel Isa**  
*Instituto de Biotecnología, Universidad Nacional Autónoma de México*
- J**
- Ana Jimenez Burgos**  
*Mexico*
- Elias Jimenez Fonseca**  
*Hospital CIMA-San Jose; Neeman ICIC, Costa Rica*
- Jessica Jirash**  
*Burson Marsteller, Mexico*
- Kari Johansen**  
*Swedish Institute for Infectious Disease Control, Sweden*
- Nancy Justiniani**  
*Hospital General de México*
- Hugo Lobato**  
*MSD, Mexico*
- Marta Heloísa Lopes**  
*Faculdade de Medicina da Universidade de São Paulo, Brazil*
- Vanessa Lopez Guerrero**  
*IBT de la Universidad Nacional Autónoma de México*
- Angelica Lopez**  
*Birmex, Mexico*
- Susana Lopez**  
*Instituto de Biotecnología de la Universidad Nacional Autónoma de México*
- Hermilo Lopez Coello**  
*Birmex, Mexico*
- Expedito Luna**  
*Secretariat of Health Surveillance - Ministry of Health, Brazil*
- Maria Edilia Luna Cruz**  
*Instituto Nacional de Ciencias Médicas y Nutrición, Mexico*
- M**
- Raymond A. MacDougall**  
*Albert B. Sabin Vaccine Institute, US*
- Mercedes Macias**  
*Instituto Nacional de Pediatría, Mexico*
- Maria de Lourdes Sousa Maia**  
*Ministry of Health, Brazil*
- Rene Keilhauer**  
*Merck Sharp & Dohme, Mexico*
- Peter Khoury**  
*Baxter Bioscience, US*
- Carl Kirkwood**  
*Murdoch Children's Research Institute, Australia*
- Pablo Kuri-Morales**  
*Ministry of Health, Mexico*
- L**
- Claudio Franco Lanata**  
*Instituto de Investigación Nutricional, Peru*
- Hilda Laurani**  
*CHLAEP, Uruguay*
- Kathleen Marie Laya**  
*GlaxoSmithKline, Brazil*
- Jose Paulo Gagliardi Leite**  
*Oswaldo Cruz Foundation, Brazil*
- Paulo César Ieno**  
*GlaxoSmithKline, Brazil*
- Eleonora Leone**  
*Burson-Marsteller, Argentina*
- Sonia Beatriz Lescano**  
*Ministerio de Salud de la Nación, Argentina*
- Cecilia Loaiza**  
*Instituto de Atención Pediátrica/Universidad de Ciencias Médicas, Costa Rica*
- Omar Enrique Malespin**  
*Ministerio de Salud, Nicaragua*
- Eliane Mara Cesario Maluf**  
*Sociedade Paranaense de Pediatría, Brazil*
- Mario Martinez**  
*Pan American Health Organization, Mexico*
- Gerardo Martínez-Aguilar**  
*Instituto Mexicano del Seguro Social, Mexico*
- Amanda Martinez Rojo**  
*Digemid-Minsa, Peru*
- Cesar Octavio Mascareñas**  
*Aventis Pasteur, Mexico*
- Dean D. Mason**  
*Albert B. Sabin Vaccine Institute, US*
- Christopher Mast**  
*Merck & Co., Inc., US*
- Guadalupe Mateos C.**  
*Secretaria de Salud, Mexico*
- Norma Matias**  
*Centro Nacional Salud Infancia y Adolescencia, Mexico*
- Sean McElligott**  
*Merck & Co., Inc, US*
- Livia Medina**  
*GlaxoSmithKline Biologicals, Belgium*
- Jorge Medrano Galoc**  
*Ministerio de Salud, Peru*
- Edgar Mendez**  
*Departamento Regulación de los Programas de Atención, Guatemala*
- Luz Mendez Hernandez**  
*Instituto Nacional de Ciencias Médicas y Nutrición, Mexico*
- Reinaldo de Menezes**  
*Bio-Manguinhos, Fiocruz, Brazil*
- Marize Miagostovich**  
*Oswaldo Cruz Foundation, Brazil*
- Nanjari Milla**  
*Instituto Salud Pública, Chile*
- Lewis Miller**  
*Albert B. Sabin Vaccine Institute, US*
- Dario Pinto Miranda**  
*Ministry of Health, Brazil*
- Eunice Miranda**  
*GlaxoSmithKline, Belgium*
- Enrique Molina**  
*Esp. Científicas de Laboratorio, Mexico*
- Ida Molina**  
*Secretaria de Salud, Honduras*
- Ana Irma Monroy**  
*Birmex, Mexico*
- Maria Montes Cerda**  
*SIFBIOTEC, Mexico*
- José Cassio Moraes**  
*Ministry of Health, Brazil*
- Graciela Morales**  
*Merck Sharp & Dohme, Mexico*
- Marisela Morales**  
*Birmex, Mexico*
- Ruben Morelos Ramirez**  
*Secretaria de Salud, Mexico*
- Sarbello Moreno Espinosa**  
*Instituto Nacional de Ciencias Médicas y Nutrición, Mexico*
- Jorge Moreno Martinez**  
*Hospital Infantil Privado, Mexico*
- Antonio Morris**  
*GlaxoSmithKline, Chile*
- Joaquín Mould**  
*IMSS, Mexico*
- N**
- Miguel A. Nakamura**  
*Secretaria de Salud, Mexico*
- Armando Nava**  
*GlaxoSmithKline, Mexico*
- Maria Soledad Navarrete**  
*GlaxoSmithKline, Chile*
- Christopher B Nelson**  
*World Health Organization, Switzerland*
- Thomas Netzer**  
*Merck Vaccine Division, US*
- Irma Nieves**  
*Birmex, Mexico*

# LIST OF PARTICIPANTS

**Gloria Niño de Rivera**  
*GlaxoSmithKline, Mexico*

**Hermes Niño Leal**  
*Departamento Nacional de Planeación, Colombia*

**Sergio de Andrade Nishioka**  
*Anvisa, Brazil*

**Ernesto Nuñez**  
*University of Concepción, Chile*

**O**  
**Mariana Alves de Oliveira**  
*GlaxoSmithKline, Brazil*

**David Ortega Becerril**  
*GlaxoSmithKline, Mexico*

**Francisco Ortiz Garcia**  
*IMSS Oportunidades, Mexico*

**Juan Carlos Ovalle**  
*GlaxoSmithKline, Mexico*

**P**  
**Roberto Palacios**  
*Hospital Médicasur, Cifbiotec, Mexico*

**Juan C. Palma**  
*GlaxoSmithKline, Mexico*

**Franco Paredes**  
*Hospital Infantil, Mexico*

**Eric John Patzer**  
*Aridis, US*

**Noris M. Pavia Ruz**  
*School of Medicine, Universidad Nacional Autónoma de México*

**Jose Alberto Peña**  
*Merck & Co. Inc, US*

**Mary Edith Penny**  
*Instituto de Investigación Nutricional, Peru*

**Carlos M Perez**  
*Catholic University of Chile*

**Javier Perez**  
*Censia, Mexico*

**Analia Cristina Perez**  
*Ministry of Health ANMAT, Argentina*

**Luis Perez Gonzalez**  
*GlaxoSmithKline, Mexico*

**Patricia Perez Reyes**  
*IMSS Oportunidades, Mexico*

**Fernando Gabriel Pilara**  
*GlaxoSmithKline, Argentina*

**Luis Podesta**  
*Ministry of Health, Peru*

**Marisela del Carmen Poot**  
*Lartac, Mexico*

**Pierre Pothier**  
*Faculte de Medicine Moleculaire, France*

**Sheldon Poujade**  
*GlaxoSmithKline, Costa Rica*

**David Prado**  
*GlaxoSmithKline, Guatemala*

**Sai D. Prasad**  
*Bharat Biotech International Limited, US*

**Marylin Puerto Solis**  
*Universidad Autónoma de Yucatán, Mexico*

**Q**  
**Julio Quero**  
*MSD, Mexico*  
**Arnoldo Quezada**  
*Sociedad Chilena de Pediatría, Chile*

**R**  
**Maria Lucia Racz**  
*University of São Paulo, Brazil*

**Patricia Ramirez**  
*Instituto Nacional de Pediatría, Mexico*

**Chantal Marie Rassenfosse**  
*GlaxoSmithKline, Belgium*

**Isaias Raw**  
*Fundação Butantan, Brazil*

**Cesar Rengifo**  
*Glaxon, Colombia*

**Ana Luisa Renteria**  
*GlaxoSmithKline, Mexico*

**Leticia Reyes Gonzalez**  
*Nutrición, Mexico*

**Andres Reyes Vera**  
*Merck, Mexico*

**José Geraldo Leite Ribeiro**  
*Secretaria de Estado da Saúde Minas Gerais, Brazil*

**Luis Alberto Rios Nogales**  
*GlaxoSmithKline, US*

**Carlos Daniel Rios**  
*Hospital del Niño, Panama*

**Maribel Rivera Medina**  
*Hospital Escuela, Honduras*

**Jesus Federico Rivera**  
*Investigación en Rotavirus, Mexico*

**Luis Alberto Rodriguez**  
*ANMAT, Argentina*

**Beatriz Romero**  
*Birmex, Mexico*

**Monica Romero**  
*Birmex, Mexico*

**Raul Romero-Cabello**  
*Hospital General de México*

**Denisse Rosales**  
*Facultad de Ciencias de la Universidad Nacional Autónoma de México*

**Marina Alejandra Rossi**  
*Instituto Nacional de Medicamentos (Iname/Anmat), Argentina*

**Luisa Consuelo Rubiano**  
*Centro de Investigaciones de Infectología Pediátrica, Colombia*

**S**  
**Rosa Salas**  
*CAREC, Trinidad y Tobago*

**Ana Maria Salgado**  
*Birmex, Mexico*

**Efrain Salgado Gama**  
*Pediatrician, Mexico*

**Belen Maria Salinas**  
*INSALUD, Universidad de Carabobo, Venezuela*

**Elia Sanchez**  
*Secretaria de Salud, Mexico*

**Monica Sanchez**  
*GlaxoSmithKline, Mexico*

**Nervo Sanchez**  
*GlaxoSmithKline Biologicals, Brazil*

**Adriana Santiago Echauri**  
*Birmex, Mexico*

**Eduardo Savio**  
*Universidad de la Republica, Facultad Medicina, Cátedra Clínica Enf. Infecciosas, Uruguay*

**Erendira Sequeiros**  
*Hospital Infantil Privado, Mexico*

**Alan Shaw**  
*US*

**Amauri Gomes da Silva Filho**  
*GlaxoSmithKline, Brazil*

**Luiz Jacintho da Silva**  
*Secretaria Estadual da Saúde, Sao Paulo and Unicamp, Brazil*

**Evan S. Simpson**  
*Rotavirus Vaccine Program, US*

**Coimbra Sirica**  
*Burness Communications, US*

**Hyacinth D. Smith**  
*Vaccines Infectious Diseases Centre, University of the West Indies, Jamaica*

**Maria Solis Mejia**  
*GlaxoSmithKline, Mexico*

