ACKNOWLEDGEMENTS

The Program Committee would like to thank the following for their support toward the organization and success of this meeting:

Bill & Melinda Gates Foundation

Bharat Biotech

US Centers for Disease Control and Prevention

Christian Medical College, Vellore

Fogarty International Center, US National Institutes of Health

GlaxoSmithKline

Indian Council of Medical Research

Merck Pharmaceuticals

PATH

ROTA Council

Sabin Vaccine Institute

Serum Institute of India, Ltd.

World Health Organization
11th INTERNATIONAL ROTAVIRUS SYMPOSIUM 2014
Building on Evidence: The Case for Rotavirus Immunization
3-5 September
New Delhi, India

CONVENED BY

Bill & Melinda Gates Foundation

Centers for Disease Control and Prevention, US

Christian Medical College, Vellore

Fogarty International Center, US NIH

Indian Council of Medical Research

PATH

ROTA Council

Sabin Vaccine Institute
INTRODUCTION

The 11th International Rotavirus Symposium brought together over 650 people from 56 countries in New Delhi, India, from 3-5 September, 2014 to examine new surveillance data and studies demonstrating the effectiveness and impact of vaccination for rotavirus, a leading cause of severe and fatal diarrhea in children under five years of age worldwide.

The new evidence included post-introduction surveillance in early-adopter countries in Africa, and definitive studies of impact in Latin America, North America and Northern Europe.

The Symposium came at a fortuitous time and place: two months prior, the Government of India had licensed the indigenously developed and produced ROTAVAC vaccine, and is now set to begin roll-out of the vaccine to the country’s birth cohort of 27 million children. Deaths from rotavirus in India reach almost 80,000 a year, contributing about one-fifth of global childhood mortality from rotavirus.

Roger Glass, with the Fogarty International Center, National Institutes of Health, USA, and a member of the Symposium’s Scientific Program Committee, set out the charge to the meeting:

• What can be done to improve current vaccines
• New vaccines are in the pipeline.

Throughout the Symposium, tribute was paid to two public health heroes who led in the science and advocacy of rotavirus vaccines, and in the promotion of global health.

Dr. Albert Z. Kapikian
May 9, 1930 — February 24, 2014
“Every major rotavirus vaccine in development today has benefited from research done at the NIH by Dr. Kapikian and his trainees and colleagues.”
— Dr. Roger Glass, Fogarty International Center, NIH, USA

Dr. Ciro de Quadros
January 30 1940 — May 28, 2014
“Ciro de Quadros’ light will illuminate the rest of us in the public health field for many, many more years.”
— Mathuram Santosham, Johns Hopkins University, USA
Rotavirus is the leading cause of severe diarrhea in children under five all over the world, and the three-day Symposium took stock of advances in the fight against rotavirus and upcoming opportunities to further the control and prevention of rotavirus.

“We’re beginning a huge global experiment,” said Roger Glass, of the Fogarty International Center in the United States. “We are hoping to change the epidemiology of rotavirus in the world over the next few years by the introduction of attenuated vaccines of different sorts.”

Today two rotavirus vaccines are in use globally, another three are in use nationally, with a fourth on the way, and others are in development. The two rotavirus vaccines (Rotarix and Rotateq) in global use have been administered to over 150 million children in 69 countries. These include 37 low- and middle-income countries, 31 of which have done so with Gavi support; three through PAHO’s revolving fund; and three without outside support.

Rotavirus vaccines have been introduced in countries of the Americas, Europe, and Africa. However, in Asia, only the Philippines has partially introduced rotavirus vaccine, despite the high burden of the disease in the region. Yet, this is poised to change, as earlier this year the Government of India licensed ROTAVAC, a vaccine developed and produced in India.
Dr. Harsh Vardhan, Union Minister of State for Health and Family Welfare, India, emphasized India’s commitment to reducing childhood deaths from rotavirus: “If there is a preventable cause of disease, and somebody dies from it, then it is the failure of the system,” he said.

Speakers highlighted India’s leading role in South Asia in introducing rotavirus vaccine, and its enormous potential to benefit the children in India. “Rotavirus vaccine could prevent 22,000 to 35,000 deaths; 82,000 to 300,000 hospitalizations; and almost 700,000 outpatient visits in India,” said Mathuram Santosham, of Johns Hopkins University in the United States.

Speakers presented data showing post-licensure, real-world impact of rotavirus vaccines in protecting against diarrheal deaths and disease, including against hospital admissions for all-cause diarrhea, and for severe rotavirus gastroenteritis (RVGE). Among the evidence cited:

- In Mexico, rotavirus vaccine is credited with lowering the rotavirus mortality among children under five by 46%;
- In South Africa, here has been a 40-50% reduction in all-cause diarrhea hospitalizations among children, and a 60-70% reduction in rota-associated hospitalizations among vaccinated children since the vaccine was introduced in 2009;
- In Brazil, there were 1,500 fewer deaths in children under five between 2007-2009, and 130,000 fewer under-five hospital admissions for diarrhea following vaccine introduction;
- In Ghana, there was a 50% reduction in rotavirus diarrhea hospitalization following the introduction of rotavirus vaccination;
- In Finland, hospitalizations for rotavirus gastroenteritis in children under two dropped by 88% compared to the pre-vaccination years 2001-2006, and there was a 70% reduction in hospitalizations for acute gastroenteritis due to any cause.

Although many studies have found that vaccine efficacy is higher in high income countries (80 to 90%) compared to low income countries (45 to 60%), because of the high disease burden in poor countries, the impact of the vaccine is much higher in low income countries.

A number of speakers addressed possible approaches to improving the efficacy of existing vaccines, including through altering vaccine schedules and adding a vaccine dose. Speakers also presented alternative vaccine approaches which may provide higher efficacy in low-income countries, including a neonatal vaccine, and inactivated injectable vaccines.

Several studies demonstrated the ability of these vaccines to induce “herd immunity,” with evidence from the United States, El Salvador and South Africa and other countries that vaccination of infants can also protect older children by reducing their exposure to the virus.

A number of speakers addressed the issue of intussusception, and noted that both Rotarix and RotaTeq have been associated with a slight increase in intussusception. However, time and again, the benefits have been demonstrated to far outweigh the risks.
The Symposium also emphasized the need to approach rotavirus vaccination as part of a comprehensive approach to controlling diarrheal disease. “By inclusion of rotavirus vaccine, India has all of the ingredients for diarrhea disease control...we have ORS, we have zinc, we have breastfeeding, you name it. Therefore, there is no reason that we will not accelerate progress,” said Vinod Paul, with the All India Institute of Medical Science.

But the Symposium was not only a presentation of evidence, it was also a celebration of people—the people who have pioneered and persevered in the fight against rotavirus and for the rights of every child to grow up healthy and strong.

In the words of Harsh Vardhan, Union Minister of State for Health and Family Welfare, India, “I have attended so many conferences here in New Delhi, but this is one of those rare ones where there is very high quality participation from almost all parts of the world of highly committed people, so that makes this conference certainly far better and more unique in many senses.”
**I. WELCOME**

Roger Glass, Fogarty International Center, National Institutes of Health, USA

Roger Glass welcomed the participants to the 11th International Rotavirus Symposium. While the early meetings convened fewer than 40 people, today’s welcome more than 650 people from 56 countries. “We really have a lot to celebrate at this meeting,” Glass said. “We’ve come a long way.”

He noted the many milestones that have been passed in the global fight against the deadly diarrheal disease of rotavirus, among them:

- Global recognition of the role of rotavirus as a major cause of childhood death and disease, and surveillance in about 60 countries;

- The development and approval of two globally licensed vaccines (Rotarix from GSK, and RotaTeq from Merck), which are decreasing rotavirus deaths, disease and hospitalizations wherever they are used;

- Three nationally licensed vaccines in China, Vietnam, and India, and new candidate vaccines in the pipeline;

- The use of vaccines in 69 countries;

“It’s particularly exciting for me to be in India for this meeting because India has really taken the lead for rotavirus vaccines and research in Asia,” Glass said. He underscored the leadership of Prime Minister Narendra Modi, who recently declared that the “Government of India will provide rotavirus vaccine to all Indian children.”

Glass emphasized the many ways in which India is providing leadership in the fight against rotavirus. The Department of Biotechnology has supported research on rotavirus for 29 years; the Indian Council of Medical Research established rotavirus surveillance across the country; and Indian industry is making safe, effective low-cost vaccines, including the recently licensed ROTAVAC, developed by Bharat Biotech of India. In addition, a potential reassortant vaccine by Serum Institute has entered an efficacy trial, and there is ongoing research on new vaccines by the biotech firms Shanta, Biological E.

“This is really a landmark opportunity to think about the importance of rotavirus and the impact that this could have in India over the next few years,” Glass said.

Glass concluded with tributes to two global health heroes, each of whom had led the science and advocacy of rotavirus and rotavirus vaccines for decades before their recent deaths. Dr. Al Kapikian at the U.S. National Institutes of Health organized the first four rotavirus symposia; and Dr. Ciro de Quadros, with the Sabin Vaccine Institute, organized the previous six symposia.
Tribute to Dr. Al Kapikian
Excerpts from remarks by Dr. Roger Glass

Dr. Kapikian was my mentor and the mentor of many of us here. Dr. Kapikian was the discoverer of Norwalk virus and hepatitis virus. He developed the first ELISA assays for rotavirus; the first growth of human rotaviruses was in his lab by Richard Wyatt. His lab determined rotavirus serotypes; conducted epidemiological studies of the importance of disease; determined reassortment of rotavirus genes that Harry Greenberg worked on in the lab; genetic uniqueness of neonatal strains that George Flores worked on—which is the reason we have two neonatal vaccines in development; conducted the first rotavirus vaccine trials with Leif Gothefors from Sweden who is here; studied gene function with John Patton who is still in the Kapikian lab; and conducted global burden of disease studies with Duncan Steele and myself.

He also had the first licensed rotavirus vaccine for humans, Rotashield. He developed the UK reassortment vaccine that is being developed here by the Serum Institute of India and Shantha. And he worked on further development of Rotashield and on non-replicating rotavirus vaccines.

So I would conclude that every major rotavirus vaccine in development today has benefited from research done at the NIH by Dr. Kapikian and his trainees and colleagues.

Al Kapikian was also a member of the WHO Board steering committee when the diarrheal disease program was formed, and it was at that Board that he promoted the idea of global vaccination, together with Ruth Bishop, who was the discoverer of rotavirus, and Tom Flewett who gave rotavirus its name.

Al was a family man, with three sons and more grandsons. He was a wonderful husband, and Kathy Kapikian, his wife, is in the audience today. She’s an international artist in her own right, and an absolutely wonderful woman who shared her meals and her home with so many of us over the years.

Al would always end his talks with this slide of building a rainbow, because he said that no effort in rotavirus could be done alone, it required many people. … And he always wanted to give credit to everyone, and I think this meeting is our effort to give credit to all of you who have come so far to join us.

Tribute to Dr. Ciro de Quadros
Excerpts from remarks by D. Mathuram Santosham

Ciro de Quadros was a true public health hero. I’ve known Ciro for many, many years. He was my friend, mentor and guide. I had the great opportunity and good fortune to be the co-chair with him of the ROTA Council.

Ciro was an amazing individual. His sense of humor was amazing. In very difficult situations Ciro would break the tension by just cracking a joke — and then make sure that he got what he wanted.

Ciro started out working on the smallpox eradication program in the 70s. He’s credited with eradication of polio and measles from the Americas. Ciro never took no for an answer. Just to give you an example of the kinds of things Ciro did: during the late ‘70s and ‘80s there were a lot of civil wars in South America. He was actually able to negotiate a truce so children could be vaccinated against polio because he was determined to eradicate polio. That’s the kind of person he was.

In April of this year, he was given the Pan American Health Institute (PAHO) Public Health Hero award, and he gave a stunning speech. And only those of us who knew him, knew that he was dying. He was in his last days. And I had the great privilege of congratulating him, and he and I hugged each other.

I will just end by quoting what Jawaharlal Nehru said when Mahatma Gandhi died.

The light has gone out in our lives. The light has gone out, I said, yet I was wrong, for the light that shone in this country was no ordinary light. The light that has illumined this country for these many years will illumine this country for many more years.

I know that Ciro de Quadros’ light will illuminate the rest of us in the public health field for many, many more years.
K. VijayRaghavan, Secretary, Department of Biotechnology, India

“Vaccine preventable diseases are a huge, huge problem across the world, and India sadly leads in the size of this problem with rotavirus... But India is unique amongst the places where these problems are greatest in that it has also the possibilities of providing solutions—through its technology, its health ministry, its industry. These solutions have implications for the entire world.”

— K. VijayRaghavan, Department of Biotechnology, India

Secretary VijayRaghavan acknowledged the scope of India’s challenge with rotavirus, and described the dynamic science and policy process underpinning India’s recent decision to introduce rotavirus vaccine to the country’s birth cohort of 27 million newborns every year. That process is driven by collaboration across ministries that takes concrete form in the National Technical Advisory Group on Immunization (NTAGI), which advises the Ministry of Health and Family Welfare on all immunization matters.

VijayRaghavan called for “much more live interaction between policy, evidence and science.” This involves research that goes all the way from basic to translational, brings in economics, and works with policy cells inside and outside various ministries to make sure there is an “interactive positive atmosphere.” Not only will such an approach move the science and its impact further, faster, but it is also necessary to avoid polarization on vaccine issues, including with anti-vaccination activists.

Lov Verma, Secretary, Department of Health and Family Welfare, India

“It is a happy coincidence and a joyful coincidence that only a month before this conference was organized, our National Technical Advisory Group on Immunization recommended India include rotavirus vaccine in its national program, and India has accepted the case for rotavirus immunization, along with other vaccines.”

— Lov Verma, Department of Health and Family Welfare, India

Secretary Verma noted that India has outstripped much of the world in lowering its rates of child mortality. Nonetheless, “childhood diarrhea remains a very strong challenge for us,” and children ages six to 24 months, and those who are malnourished are at the highest risk. “In addition to preventing deaths, we need to prevent the undue suffering and economic impacts that diarrheal hospitalization has on the child and the family,” he said.

To meet this challenge, the Indian public health system is promoting “Health as a social Movement.” Regarding the prevention of diarrheal disease, this social movement has many components: promoting rotavirus vaccine to promotion of exclusive breastfeeding and hand washing for prevention of all-cause diarrhea; and promotion oral rehydrations solution and zinc as the mainstay of management during active disease.
V.M. Katoch, Secretary, Indian Council of Medical Research

“This is a very momentous occasion to greet all of you: After more than 40 years of fighting against rotavirus, we have a global effort and today ... we have reached the stage where there are successes on the horizon.”

— V.M. Katoch, Indian Council of Medical Research

“India is now in a stage where there is evidence-based decisions,” Katoch said. He noted India’s surveillance system of more than 30 laboratories has provided evidence of that rotavirus causes 40 percent of severe childhood diarrhea, and is also responsible for adult illness.

With the evidence in hand, the next step was “a massive and successful effort towards awareness generation for childhood diarrhea control with dedicated funding,” and a call for partners, including corporations to get involved in the drive toward better sanitation.

The evidence also motivated India to develop its own vaccine against the disease. “We had a vaccine, the global vaccines, but developing our own vaccine was a long journey,” Katoch said. “It showed that you can think differently, and you can find a solution.”

Harsh Vardhan, Union Minister of State for Health and Family Welfare, India

“If there is a preventable cause of disease, and somebody dies from it, then it is the failure of the system.”

— Harsh Vardhan, Union Minister of State for Health and Family Welfare, India

In his remarks to the Symposium, the Union Minister of Health focused on the issue of equity, noting that despite the many years India has had a universal vaccination program in place, 30 percent of children are still unable to derive the benefit of universal immunization for a multiple of reasons.

“‘But each and every reason is not beyond control,’ Vardhan said. ‘They can all be taken care of.’ He therefore urged the symposium to not only brainstorm regarding scientific issues related to rotavirus vaccine, “But also to have brainstorm about how we can make sure that the vaccine will be available to 100% of children of the whole world.”

Vardhan thanked Indian Prime Minister Narendra Modi for his vision in supporting the introduction of rotavirus vaccine. He noted that in the coming years the government will focus research to develop additional vaccines for vaccine-preventable diseases, the creation of high quality laboratories in medical colleges all over the country, strengthening evidence-based medicine, and Introducing, one-by-one, all of the vaccines that are available.

This work will be buoyed by a social movement for health. “What is needed in this country and all over the world is to make preventive education, preventive strategies, development of positive health attitudes, a big movement.”
Jitendra Singh, Union Minister of State for Science & Technology, India

“This is one of the best of times for all of us in the scientific community to be living and working in India, because you couldn’t have better encouragement and support from the political system, and the Prime Minister himself is very keenly involved in all the scientific endeavors.”

—Jitendra Singh, Union Minister of State for Science & Technology, India

The scientific climate in India is ripe with possibility, and this possibility spans fields from space exploration to biomedicine, according to Jitendra Singh. He highlighted several positive trends for science and public health in India, among them: collaboration and synergy across Ministries; a focus on support for the “common man” and preventive medicine, symbolized by the Indian rotavirus vaccine; cutting-edge scientific capacity in biomedicine; and the ability to bring innovations to scale in a cost-effective manner.

“Providing world-class service in a cost-effective manner is something in which India has distinguished itself,” he said. Singh likened India’s recent launch of satellites from France, Singapore and Japan to its nimbleness in scientific innovation and cost effectiveness — the same nimble-ness now seen in the development of vaccines against rotavirus.

Trevor Mundel, President, Global Health, Bill & Melinda Gates Foundation

“On the vaccine front, there can be no more important partner for us than the manufacturers and the people involved in vaccines in India.”

— Trevor Mundel, Bill & Melinda Gates Foundation

Trevor Mundel highlighted India’s leadership in global health: from fighting polio and eradicating it from India, to the “new kid on the block”, rotavirus, and to the recent licensing of an indigenously produced rotavirus vaccine in India - ROTAVAC vaccine, Bharat Biotech, is an Indian rotavirus vaccine for the infants of India which carries the highest burden of rotavirus associated mortality. The country has been a leader in improving child survival, lowering the national under-five mortality rate by almost 50 percent since 1990.

Vaccines developed and produced in India have played no small part in the global accomplishment of MDG 4 to reduce childhood mortality, and contribute to child survival globally. Indian vaccine manufacturers supply more vaccines to Gavi and children in developing countries than any other. Most recently, the Indian government has decided to add three new vaccines to its Universal Immunization Program for Rotavirus, Rubella, and Inactivated Polio Vaccine; and to add Japanese Encephalitis vaccines for adults.
“It’s not commonly known, but India supplies the majority of vaccines to kids in developing countries,” Mundel said. “These are high quality, cost-effective vaccines.” They include MenAfriVac, Serum Institute of India for preventing meningitis in Africa; Shanchol, Shantha Biotecnics for a highly effective cholera vaccine being stockpiled by WHO; and a pentavalent vaccine by Bio-E.

Mundel noted the large gap in rotavirus vaccine coverage in South Asia, precisely the area where the disease takes its biggest toll. But introduction of ROTAVAC in India is set to change that. And, as in South Africa, where rotavirus vaccines have reduced diarrhea hospitalizations among children by 40-to-50 percent, vaccine introduction in India is going be “a great step forward to eliminating rotavirus as a major cause of mortality in young kids,” he said.

Mundel noted other major opportunities for the global control of diarrheal diseases in the next decade, including through the continued development and use of vaccines and medicines against diarrhea; the scale up of non-sewered sanitation solutions, and access to clean water.

**OPPORTUNITY FOR IMPACT OF ROTA VACCINE GREATEST IN ASIA**

*67% of all rotavirus deaths occur in these 10 countries (2008)*

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Total Global Deaths</th>
<th>Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (21.8%)</td>
<td>21.8%</td>
<td>98,621</td>
</tr>
<tr>
<td>Nigeria (9.1%)</td>
<td>9.1%</td>
<td>41,057</td>
</tr>
<tr>
<td>Pakistan (8.6%)</td>
<td>8.6%</td>
<td>39,144</td>
</tr>
<tr>
<td>DR Congo (7.2%)</td>
<td>7.2%</td>
<td>32,653</td>
</tr>
<tr>
<td>Ethiopia (6.2%)</td>
<td>6.2%</td>
<td>28,218</td>
</tr>
<tr>
<td>Afghanistan (5.6%)</td>
<td>5.6%</td>
<td>24,423</td>
</tr>
<tr>
<td>Uganda (2.3%)</td>
<td>2.3%</td>
<td>10,637</td>
</tr>
<tr>
<td>Indonesia (2.2%)</td>
<td>2.2%</td>
<td>9,970</td>
</tr>
<tr>
<td>Bangladesh (2.2%)</td>
<td>2.2%</td>
<td>9,857</td>
</tr>
<tr>
<td>Angola (1.9%)</td>
<td>1.9%</td>
<td>8,788</td>
</tr>
</tbody>
</table>

% is percent of total global rotavirus deaths

2012 presentation by Jacqueline Tate at the 10th Int’l Rotavirus Symposium
THE SECOND ROGER GLASS LECTURESHP

“The right passion and commitment, the right ideas, the right focus, really does make a difference. So, to those younger people in the audience, I would just urge you to use your abilities to further this agenda.”

—Duncan Steele, Bill & Melinda Gates Foundation

The Roger Glass Lectureship was established two years ago to recognize an individual who has made outstanding contributions in the field of rotavirus research and vaccines. It was therefore aptly named after Dr. Roger Glass, described by Mathuram Santosham as “not only an out-standing scientist, but also a true mentor, who has provided a tremendous amount of scientific energy to the whole rotavirus field.”

Glass himself introduced the recipient of this year’s lectureship, Duncan Steele, of the Bill & Melinda Gates Foundation. It was because of Steele’s “seed work” in Africa — through which he trained nearly all of the scientists now active in the African rotavirus surveillance network, that Gavi later supported the introduction of rotavirus vaccine in 12 African countries, Glass said. Steele has also led rotavirus activity at WHO, worked on the introduction and testing of vaccines at PATH, and now at the Gates Foundation, “He’s continuing a global saga to help move rotavirus vaccines and the rotavirus research forward,” Glass said.

Steele’s lecture provided a sweeping overview of the history of rotavirus research and surveillance, and of vaccine development, introduction and impact, highlighting the seminal contributions of several individuals, including Dr Albert Kapikian, Dr Ciro de Quadros and Dr Roger Glass. He concluded with a look at the challenges ahead for realizing the full public health impact of rotavirus vaccines:

- Biological Challenges of the virus which is ubiquitous and versatile adapting to the changing environment; and the host where the most vulnerable children are most challenged to mount a robust immune response to the vaccine
- Technical Challenges of rotavirus vaccine development, including new candidates which are needed to provide sufficient supplies of affordable and cost-effective, safe vaccines for the world’s children.
- Programmatic Challenges of delivering the vaccines where they are needed most in the “hard-to-reach” infant populations where the stability of the vaccines is crucial and where the administration of these oral vaccines must accommodate programmatic feasibility and poor resources
- Funding Challenges to pay for the vaccines, which includes looking at ways to enhance the production capacity and the supply of the new vaccines, but also needs to examine ways to enhance the performance of the current vaccines to generate greater public health impact
- Safety Challenges of rotavirus vaccines which have been plagued with the rare adverse event of intussusception in 1-2 excess cases per 100,000 children vaccinated.

The challenges, however, are nothing if not a “call to action,” Steele said. “We are a global community. We are working together. There are global collaborations, which are fantastic, but really, individuals – such as Al Kapikian or Ciro de Quadros, and many of you in this audience - do make all the difference.”
INDIAN EXPERIENCE WITH ROTAVIRUS VACCINES

India is the birthplace of 27 million newborns every year, and home to 120 million children under five years of age. Through persistent and determined effort, India has decreased under-five mortality from 114 deaths/1,000 live births in 1990 to 52/1,000 in 2012. Still, childhood diarrhea remains a major cause of child mortality, accounting for 13 percent of all deaths in children under-five children.

Several speakers described the burden of rotavirus disease in India; the country’s surveillance system; rotavirus strain distribution; and the result of the Phase III clinical trial that led to the licensing of India’s first indigenous rotavirus vaccine, ROTAVAC.

Rotavirus Disease Burden in India

Gagandeep Kang, Christian Medical College, India

Rotavirus burden of disease in India

Diarrheal diseases are the second most important cause of child deaths in India, and rotavirus diarrhea is the most important cause of diarrheal deaths, hospitalizations and outpatient visits for children under five years of age in India, reported Gaganddep Kang.

She presented estimates of the current burden of rotavirus disease among children under five in India, and the potential impact of a national immunization program using a rotavirus vaccine of similar efficacy to ROTAVAC. Kang derived the estimates from

Richardson V, Pichardo JH, Solares MQ et al. NEJM; 2010: 362: 358-360

Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.

41% reduction
a combination of community studies of disease incidence and data generated by the Indian Rotavirus Surveillance Network, with UNICEF under-five mortality estimates factored in. The community studies were part of the Global Enterics Multi-Center Study (GEMS 1), funded by the Bill & Melinda Gates Foundation.

The combined data provided an up-to-date understanding of the impact of rotavirus on children in India, indicating that nearly 80,000 children die due to rotavirus every year, and nearly 60,000 of these are children under two years of age.

In addition, there are:

- 872,000 annual hospital admissions
- 3.27 million associated outpatient visits
- 11.37 million episodes of rotavirus gastroenteritis each year

The total direct cost for the above is 10.37 billion Indian rupees each year.

A national immunization program that achieves 75 percent coverage would prevent nearly 27,000 deaths, more than 290,000 rotavirus hospitalizations, and avert more than 2.1 million cases of rotavirus every year.

### ESTIMATED BURDEN OF ROTAVIRUS IN INDIA

- **Risk Events**
  - 1:345 ~78,000 Deaths
  - 1:31 ~872,000 Hospitalizations
  - 1:8 ~3.3 million Outpatient visits
  - 1:2 ~11 Million episodes

*In birth cohort of 27 million*  

J.John, Vaccine, 2014
The Indian National Rotavirus Surveillance Network
Rashmi Arora, Indian Council of Medical Research, India

Approval of India’s first indigenous rotavirus vaccine, developed through a public private partnership, was predicated on the implementation of nationwide surveillance of rotavirus and review of the evidence. Arora reported on the Indian Rotavirus Strain Surveillance Network, set up by the Indian Council of Medical Research in December 2005 to generate timely and geographically representative information on the clinical, epidemiological, and virological features of severe rotavirus disease in Indian children.

A seminal study of the burden of rotavirus disease and its epidemiology was conducted using network data collected from December 2005 to June 2009. The multi-center, hospital-based study enrolled children under five who were admitted for acute diarrhea and who required hospitalization with rehydration for at least six hours. The study demonstrated that the burden of rotavirus disease was much higher than previously estimated: 39.8 percent vs 20.4 percent.

Data has also shown that infection and disease occur early in life, with 13 percent of cases in children under six months of age. Surveillance detected more than a dozen common enteric pathogens between 2007-2010, and found that children with rotavirus diarrhea had more severe disease than those with diarrhea from other causes.

Data analysis also revealed that the proportion of children admitted to hospitals with rotavirus diarrhea increased over the years. Before 2000, the median positivity for rotavirus in children with diarrhea was 26 percent; after 2005 it was 39 percent.

AGE OF CHILDREN ADMITTED FOR GASTROENTERITIS IN INDIA
Sanjay Mehendale noted the importance of having a baseline understanding of rotavirus strain diversity in order to monitor changes that follow introduction of rotavirus vaccine and to help guide decisions about which vaccine to introduce into national immunization programs.

He described the results of the Indian Rotavirus Strain Surveillance Network studies conducted from 2005-2009 (NRSN1), which included 10 sites, and a second study conducted from 2012 to the current day (NRSN2), which included 28 sites as of July 2014. NRSN2 will continue until 2016.

NRSN1 screened 6,954 children, of which 2,778 (40 percent) were found rotavirus positive using ELISA. NRSN2 screened 4,072 children, of which 1,812 (44.5 percent) were rotavirus positive.

In both study samples, G1P[8] was most dominant type nationwide. Its prevalence increased substantially between the two studies, rising from 29.5% of all typed strains in NRSN1 to 61.3% of all typed strains in NRSN2. Other genotypes detected included G2[P]4, G9[P]8, G12[P]6, and G12[P]8. The study also showed that severe dehydration at the time of hospitalization was significantly higher for children infected with G2P[4] than with other major genotypes.
Mehendale noted that, in India, where there is enormous rotavirus strain genetic diversity, it is possible that unusual rotavirus strains may become more prevalent after vaccine implementation, and that given the huge disease burden and future introduction of rotavirus vaccine, a strong platform of strain monitoring will remain important. The National Rotavirus Surveillance Network of the Indian Council of Medical Research will continue to generate national level evidence on rotavirus strain diversity.

### CURRENT VACCINES AND REPORTED STRAIN SPECIFIC EFFECTIVENESS

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>ROTARIX</th>
<th>ROTATEQ</th>
<th>ROTAVAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Monovalent [RV1]</td>
<td>Pentavalent [RV5]</td>
<td>Monovalent [RV1]</td>
</tr>
<tr>
<td>Nature</td>
<td>Attenuated human strain</td>
<td>Human-bovine reassortment</td>
<td>Human-bovine reassortment</td>
</tr>
</tbody>
</table>

### Efficacy of Bharat Biotech’s human monovalent 116E vaccine

**Nita Bhandari,** Society for Applied Studies, India

"**With ROTAVAC, around a fifth of all severe gastroenteritis episodes were prevented in children under two years of age.**"

—Nita Bhandari, Society for Applied Studies, India

Nita Bhandari reported on the results of a Phase III double-blind placebo controlled trial, in which 6,799 infants aged six to seven weeks were randomly assigned to either receive the prospective vaccine, or receive a placebo. Infants in the vaccine group received three doses of an oral human-bovine natural reassortant vaccine (116E) at ages six, 10 and 14 weeks, along with the other standard vaccines received at those times within the National Immunization Schedule. There was a little less than a 0.3 percent dropout rate, and in the end 4,354 infants receiving vaccine were included in the analysis, as were 2,187 placebo recipients.
The study team carefully tracked any serious adverse events, which occurred with the same frequency in both the vaccine and the placebo group. To ensure thorough reporting and immediate response to any medical complications, families were given mobile phones with contact numbers already set up. Study staff followed up weekly with families through home visits or on the phone, and a study team stood ready to manage any illness with physicians available around the clock. All costs were covered by the study team.

Eight cases of intussusception were reported in the vaccine group, however none occurred within 30 days of receiving a vaccine dose, and all were after the third dose.

A clear picture of vaccine efficacy emerged from the trial. Efficacy against severe rotavirus gastroenteritis during the first year of life was 56.3 percent, and in the second year of life was 48.9 percent. Overall efficacy was 55.1 percent.

The vaccine also proved efficacious against less severe rotavirus infections, and reduced hospitalizations in which rehydration therapy was needed. It was moderately immunogenic as measured by serum anti-rotvirus IgA, and appeared to offer broad protection against the most commonly circulating rotavirus genotypes in India.

“Our conclusions are that ROTAVAC is efficacious in the prevention of severe rotavirus gastroenteritis, rotavirus gastroenteritis of any severity, and severe gastroenteritis of any etiology,” Bhandari said.

As a next step, with interministerial oversight, the study team will perform a limited roll out of ROTAVAC through the public health system to get more information on rare side effects such as intussusception.

### Efficacy of ROTAVAC® in Prevention of Gastroenteritis Up to 2 Years of Age

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>n</th>
<th>Vaccine Efficacy % (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe RV GE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Till 2 yrs of age</td>
<td>ROTAVAC® N= 4354</td>
<td>93 (2%)</td>
<td>102 (5%)</td>
</tr>
<tr>
<td>Till 1 yr of age</td>
<td>Placebo N= 2187</td>
<td>57 (1%)</td>
<td>65 (3%)</td>
</tr>
<tr>
<td>Severe RV GE requiring hospitalization* or supervised rehydration therapy$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Till 2 yrs of age</td>
<td>ROTAVAC® N= 4354</td>
<td>92 (2%)</td>
<td>102 (5%)</td>
</tr>
<tr>
<td>Till 1 yr of age</td>
<td>Placebo N= 2187</td>
<td>57 (1%)</td>
<td>65 (3%)</td>
</tr>
<tr>
<td>Very Severe RV GE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Till 2 yrs of age</td>
<td>ROTAVAC® N= 4354</td>
<td>12 (&lt;1%)</td>
<td>14 (&lt;1%)</td>
</tr>
<tr>
<td>Till 1 yr of age</td>
<td>Placebo N= 2187</td>
<td>9 (&lt;1%)</td>
<td>9 (&lt;1%)</td>
</tr>
<tr>
<td>RV GE of any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Till 2 yrs of age</td>
<td>ROTAVAC® N= 4354</td>
<td>406 (9%)</td>
<td>310 (14%)</td>
</tr>
<tr>
<td>Till 1 yr of age</td>
<td>Placebo N= 2187</td>
<td>226 (5%)</td>
<td>172 (8%)</td>
</tr>
</tbody>
</table>

Episodes of severe rotavirus gastroenteritis had a Vesikari score of 11 or greater and presence of rotavirus (Rotacclone positive and VP6 or VP4 and VP7 positive by RT PCR) strains
Episodes of very severe gastroenteritis had a Vesikari score of 15 or greater
*Inpatient admission for at least 6 h in a treatment facility or hospital
$Administration of oral rehydration salts or intravenous fluids
ROTAVAC and Intussusception in India

Gagandeep Kang, on behalf of Jacob John, Christian Medical College, India

Presenting on behalf of Jacob John, with the Christian Medical College, India, Gagandeep Kang detailed the findings from ROTAVAC’s Phase III trial regarding intussusception (IS). In India, the background IS rate is estimated at about 18 per 100,000, but data weaknesses limit the usefulness of this number as a baseline.

The ROTAVAC Phase III clinical trial was designed to access efficacy and not intussusception risk. However, it operated based on an abundance of caution, and was designed to “capture every last case of intussusception,” Kang said. Using strict criteria, medical personnel followed up 1,361 “suspected” cases of IS. Even relatively common occurrences such as blood in the stool served as triggers to determine whether the culprit was IS.

Of these, 1,300+ cases, only 11 proved to be IS, and none of those occurred within the short window of risk associated with vaccination. None of the children who had IS required surgery.

The team compared the IS findings among trial participants, to other children brought to the hospital at the same time. Among this general population, 61 children came because of IS. Whereas trial participants suspected of IS were brought to the hospital for follow up within 10 hours, children from the general population typically arrived 48 hours after the onset of symptoms, and half required surgery.

Asian Experience with Current Vaccines

ROTARIX

Bernd Benninghoff, GlaxoSmithKline Biologicals

“We have been gathering data from Mexico, Brazil and Panama, and the rates of death associated with acute gastroenteritis are certainly substantially reduced, so that is a fantastic finding.”

—Bernd Benninghoff, GlaxoSmithKline

Benninghoff reported on GlaxoSmithKline’s (GSK) ten years of experience with Rotarix, a two-dose vaccine based on a single strain (G1P8) of a human rotavirus. Beginning with large-scale clinical trials that involved over 100,000 infants in both developed and less developed countries, the vaccine was shown to be highly effective. Trial efficacy rates ranged from 92% in Japan to 81% in Latin America and 49% in Malawi.

Since its first commercial introduction in Mexico in 2004, 100 million babies have received the two-dose vaccination, leading to a reduction in severe rotavirus disease, hospitalizations and deaths. In Mexico, the vaccine is credited with lowering the annual death rate from rotavirus among children under five by 46%. To date (September 3, 2014), 54 countries have introduced Rotarix into their national immunization program, with similar results.
The vaccine has proven to be broadly effective against a range of disease strains, including G2P4. In Belgium, it had an efficacy of almost 95% against G1P[8]; 85% against G2P[4], and 90% against G4P[8].

Benninghoff also underscored the safety of the new rotavirus vaccines. In the United States, for example, there has been no detectable increase in the number of hospital discharges for intussusception among infants since the re-introduction of rotavirus vaccines in 2006. However, a meta-analysis of risk data across Mexico, Brazil, Australia, and the U.S. did suggest a slightly increased risk in the first seven days following vaccination.

“This small temporal increase in risk for IS should be put in perspective with the well documented substantial benefits of RV vaccination,” Benninghoff said.

He stressed the importance of early protection against rotavirus, especially in many less developed countries where children from 2 to 24 months of age shoulder the major burden of disease. Younger infants can have greater difficulty in correcting the fluid imbalance caused by rotavirus diarrhea, putting them at greater risk from the disease. In Africa, where the incidence of rotavirus is higher during the first year of life, timely vaccination is especially critical to reduce the burden of disease.
Michelle Goveia, Merck & Co., Inc.

Michelle Goveia updated the conference on the use of RotaTeq® worldwide and new findings on the correlation between the immunogenicity of RotaTeq and its efficacy. RotaTeq is a human-bovine reassortant vaccine that protects against the G1, G2, G3, and G4 strains of virus, as well as any G serotype that contain P1A[8]. The first of three doses is given at six to 12 weeks of age, with subsequent doses at least four weeks apart, and the final dose is given at no later than 32 weeks of age. It is an oral-liquid, ready-to-use vaccine.

Since it was first licensed simultaneously in the United States and Nicaragua in 2006, and received global pre-qualification by the World Health Organization in 2010, RotaTeq has been licensed in more than 110 countries, with nearly 120 million doses distributed worldwide (as of June 2014). Large and robust pre- and post-licensure studies have demonstrated its safety and effectiveness, in both high- and low-income countries.

Data from Nicaragua during several years following vaccine introduction (2007-2010) demonstrated impact of RotaTeq. Data from five cities with vaccine coverage of at least 70% for 3 doses has shown that the vaccine provides 76% protection against severe rotavirus across all ages, and provides 85% protection in children less than one year old. In a more recent study, researchers collected data from household visits to families with children under two years of age. The visits took place in a city that had achieved 82% vaccine coverage for at least one dose.

Prior to vaccine introduction, rotavirus had affected young children with a frequency of 11.5 episode per 100 child-years. Post-vaccine introduction this was reduced to 4.2 episodes per 100 child-year.

To better understand immune responses to the vaccine, Merck analyzed pooled clinical trial data to evaluate the association between immunogenicity and efficacy. This included analysis of individual subjects in high-income countries and aggregated population-level data pooled from four efficacy trials (including low income countries).

The individual data showed that after the third dose, higher levels of G1 serum neutralization antibody (SNA) titers were associated with lower odds of contracting any rotavirus gastroenteritis. The population-level data showed higher efficacy associated with both higher SNA and anti-RV IgA titers.

Goveia noted that future studies are needed to support the use of Postdose 3 G1 SNA titers as a correlate of protection for RotaTeq.

Merck and its partners are conducting several studies to further understand and improve the use of RotaTeq globally. These include: evaluation of the implementation of RotaTeq in Burkina Faso; post-marketing safety evaluations in Japan; Phase III safety and efficacy trial in China; burden of disease study in China; and a study of safety and immunogenicity among HIV+ infants. In addition, a Vaccine Vial Monitor (VVM) Compatible Formulation with Longer Shelf Life is anticipated to be available.
Jessica Fleming addressed the question of whether the timing of rotavirus immunization can improve efficacy in high-mortality countries. It’s an important question because the countries with the highest child mortality from rotavirus also have the lowest vaccine efficacy with existing rotavirus vaccines.

For example, in the high mortality countries of India, Bangladesh, Kenya, Malawi and Ghana the existing commercial rotavirus vaccines have an efficacy of on 43%-to-64%, compared to low mortality countries in the Americas and Europe where efficacy ranges from 85% to 100%.

Several of the hypothesis that have been suggested to explain this phenomenon are complex, and would be very costly and difficult to address, Fleming said. These include issues such as children’s nutritional status; gut morphology; and the presence of comorbidities.

However, scientists have also suggested that efficacy might be improved by adjusting the timing and schedule for rotavirus vaccinations.

Fleming reviewed evidence in several high mortality countries that considers the impact of the number of rotavirus doses and their timing. Immune response may be sensitive to vaccine timing for several reasons. Firstly, even slight delays (measured in weeks) in the age of first vaccination may enable infant immune systems to respond more robustly. In addition, the younger the infant, the higher the likelihood that maternal antibodies will interfere with the infant’s immune response.

Fleming reported that:

- In Vietnam, longer intervals between the standard two doses of Rotarix (two months vs. a one month interval) led to higher seroconversion in infants (indicating a stronger immune response);
- In the Philippines there was overall higher seroconversion with doses given at older ages;
- In Karachi, Pakistan, adding a third dose of Rotarix did not significantly increase immunogenicity among infants, and seroconversion tended to be highest in infants with the lowest maternal DNA titers;
- In Bangladesh, a third dose of Rotarix given at nine months of age led to higher sero-conversion, and that if given during a routine nine-month doctor visit could maximize public health benefit while minimizing delivery cost.
- A comparison between Vietnam and the Philippines showed overall higher seroconversion in the former, likely because infants in Vietnam were slightly older when they received the vaccine (8, 13, and 17 weeks vs. 6, 10, and 15 weeks in the Philippines);
Two natural rotavirus infections confer virtually 100% protection against moderate and severe rotavirus disease caused by any strain of the virus. Scientists have sought to duplicate this protection with a rotavirus vaccine. However, scientists still do not understand exactly what immune mechanisms protect against rotavirus—knowledge that could help guide the development of even better vaccines and treatment strategies.

**Importance of IgA Protection of Rotavirus Infection**

**Margaret Conner**, Baylor College of Medicine, Texas, USA

After being infected by or vaccinated against rotavirus, the levels of certain disease-fighting antibodies increase. In particular, IgG increases in the serum, and IgA increases in the serum and the intestine. Scientists have used levels of serum IgA as an indicator of vaccine take, although it is not a good predictor of protection against future infection. Margaret Conner, with the Baylor College of Medicine in Texas, and colleagues designed a set of experiments to ascertain whether IgA is required for protection, and if so, whether it is serum IgA or intestinal IgA. To do so, they used genetically modified mice that lacked critical components of the immune system associated with IgA and intestinal immunity.

### RV VACCINE EFFICACY LOWER IN COUNTRIES WITH HIGH RV MORTALITY

<table>
<thead>
<tr>
<th>WHO mortality rate</th>
<th>RV vaccine efficacy</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>43–64%</td>
<td>Bangladesh, Ghana, India, Kenya, Malawi, Mali</td>
</tr>
<tr>
<td>Intermediate</td>
<td>64–72%</td>
<td>Vietnam, South Africa</td>
</tr>
<tr>
<td>Low</td>
<td>85–100%</td>
<td>Americas, Europe, Western Pacific</td>
</tr>
</tbody>
</table>
Mice are a good model for human rotavirus, because they exhibit the same course of infection and the same basic immune response as people.

Conner found that mice lacking the ability to produce IgA in the intestine were not protected from reinfection, demonstrating that intestinal IgA plays a critical role in establishing immunity against rotavirus.

“This was actually the first direct evidence that IgA is essential for protective immunity against any enteropathogen,” Conner said.

Conversely, the researchers found that systemic antibody response that produce serum IgA were not sufficient to clear intestinal rotavirus. Still left unclear, however, are the signaling pathways required to induce rotavirus-specific IgA protective immunity. While ruling out some possible pathways, work is ongoing to determine the specific mechanisms at work.

**On the trail of a potential vaccine target**

**James Crowe**, Vanderbilt University, USA

James Crowe took a different tack, focusing on the antibody response to the rotavirus protein VP6. Rotavirus is a three layered particle, and VP6 comprises the middle layer. It is therefore protected from most antibodies that can typically recognize only the proteins on the virus’ outer surface, VP4 and VP7, and these are the proteins that have mostly been considered the target of the immune system’s neutralizing antibodies. In fact, however, natural infection with rotavirus produces antibodies to VP4, VP7 and VP6, and the highest titer of human antibodies is to VP6, Crowe said.

He showed that there is a specific clone of human antibody, called RV6-26, that is able to enter cells infected with rotavirus when it is expressed as an IgA, which is typical of mucosal antibodies. During a certain stage in infection, when the virus particle has been reduced to two layers, RV6-26 is able to bind to a critical site on VP6.

Crowe and his team used advanced molecular techniques to analyze the detailed three-dimensional anatomical structure of both VP6 and RV6-26, and see just how they fit together. He found that RV6-26 blocks a pore in VP6, preventing the extrusion of viral RNA needed to create new virus particles.

“We think this class of human antibodies similar to RV6-26 is very common, and use a physical blockade to block the channel. They probably are attracted and achieve this through electrostatic interference that staples the particle together so that it can’t breathe. The particle has to open up just a little bit to let the RNA out... and it appears that these antibodies prevent that,” Crowe said.

While other antibodies bind to VP6, none bind in quite the same way to successfully block the pore and thus halt virus transcription.
Crowe pointed out implications for vaccine design, noting that because of the complexities of VP6, and the fact that there is more than one way to bind to VP6 on a virus particle, the entire viral particle itself would likely need to be included in a vaccine, rather than just the protein.

**ELECTROSTATIC ANALYSIS OF BINDING INTERACTION**

When rotavirus invades host cells, there is a battle between the viruses and the cells. The cell deploys a series of antiviral measures to control the infection. At the same time, the virus takes counter-measures to be able to replicate in the cell. Susana Lopez investigated just how rotavirus is able to overcome the host cells’ defenses.

She reported on several detailed molecular events that explain how rotavirus infection is able to severely inhibit protein synthesis by the host cell, and commandeer the cell’s operation to synthesize its own proteins. In the first step, a rotavirus protein called NSP3 prevents translation of the cell’s messenger RNA, which forms a template for protein synthesis.

**Rotavirus Strategies to take over the host cell response**

**Susana Lopez, National Autonomous University of Mexico, Mexico**

“We are learning a lot about cellular biology, but we are also learning about the weak points of the virus so that we can design antivirals that exploit those weak points of the virus’ replication.”

—Susana Lopez, National Autonomous University of Mexico
synthesis. The virus also blocks the transport of mRNAs between the cell nucleus and cytoplasm.

“The cell protein synthesis is almost completely shut down, and the cell is now committed to make only viral proteins,” Lopez said. The virus compromises several other components of the cell’s translation machinery as well.

**Why rotavirus tends to stick to its animal hosts and what it means for vaccines**

**Harry Greenberg**, Stanford University, USA

Rotavirus is a highly host-range restricted virus, meaning that the human rotavirus very specifically infects humans, and does not easily infect any other animal species. Likewise, monkey rotaviruses are unable to infect mice. For example, in a mouse, a non-mouse rotavirus will grow about 10,000-fold less well than a mouse rotavirus, explained Harry Greenberg.

Scientists have used this feature of rotavirus to their advantage, developing highly attenuated and effective vaccines that combine non-human rotavirus with human rotavirus. Examples include both Rotashield (a monkey-human recombinant) and RotaTeq (a cow-human recombinant).

Greenberg reported new insights into the genetic basis of host-range restriction. Using a mouse model, his team found that the rotavirus protein NSP1 is necessary for promoting efficient growth of rotavirus in the mouse intestine. An NSP1 protein derived from a cross between mouse and monkey rotaviruses substantially restricted replication. In contrast, the role of the rotavirus protein VP4 was strain specific in promoting infection, and varied from minor to substantial with some mixed-species VP4s greatly restricting repletion in the mouse intestine.

Further studies indicated that species-specific rotavirus in their natural host are able to replicate efficiently because NSP1 inhibits the function of interferon, a protein that would normally cause nearby cells to ramp up their anti-viral defenses.

“Rotavirus has figured out how to inhibit interferon signaling, not only in cells that are infected but at least in some strains in cells that are not infected,” Greenberg explained. During both the induction and amplification phase of disease, rotavirus presumably makes a secreted product that can block interferon activity at a distance, and Greenberg’s lab is currently working to identify that product.

In sum, Greenberg concluded that the findings help explain why recombinant vaccines based on strains that typically infect different species are highly attenuated when used in children.
POST-LICENSENCE IMPACT AND SAFETY OF ROTAVIRUS VACCINATION

Speakers presented data showing post-licensure, real-world impact of rotavirus vaccines in protecting against diarrheal deaths and disease, including against hospital admissions for all-cause diarrhea, and for severe rotavirus gastroenteritis (RVGE). The studies, conducted in both more- and less-developed countries, provide insights into vaccine efficacy and safety across a range of settings, enabling real-world results to be compared to each other and to the original clinical trial results.

Rotavirus Vaccine Experience in Early-Adapter African Countries

Rotavirus is the major cause of severe, acute gastroenteritis in African children. Clinical trials of Rotarix and RotaTeq showed only modest efficacy in Africa and Asia, especially in comparison to high-income countries. But even with lower efficacy, rotavirus vaccines have an enormous impact in reducing the high burden of disease.

So far, some 12 African countries have introduced rotavirus vaccines into the routine childhood immunization programs. But studies in the early adopter African nations of Ghana, Rwanda, South Africa and Botswana indicate both early success and the need for more evidence, including on specific developments, such as vaccine break-through disease in Ghana.

Vaccine Impact in South Africa

Michelle Groome, University of the Witwatersrand, South Africa

“Vaccine effectiveness appeared to be sustained through the second year of life with similar protection amongst HIV exposed and unexposed children.”
—Michelle Groome, University of the Witwatersrand, South Africa

Just over one million babies are born in South Africa every year, and in 2009, diarrhea was responsible for 18% of deaths in children under five years of age. The Government of South Africa introduced Rotarix into its national immunization program in August 2009.

In the first reported evaluation in Africa of the field effectiveness of rotavirus vaccination in a setting with high prevalence of HIV infection, researchers found that the monovalent human rotavirus vaccine had a two-dose effectiveness of 57% and a one-dose effectiveness of 40% for children aged 18 weeks to 23 months. Protection was similar in age groups 18 weeks–11 months and 12–23 months.

Michelle Groome reported on the case-control study, conducted at seven hospitals in South Africa from April 2010-October 2012. Cases were children age-eligible to receive the vaccine, who were hospitalized for laboratory-confirmed acute rotavirus diarrhea; children with non-rotavirus diarrhea served as the study controls.
Some 30% of children in the study area are born to HIV-infected mothers, and efforts to prevent mother-to-child transmission have successfully lowered the rate of HIV infection among new-borns. Only 45 of the 540 rotavirus cases enrolled in the study were HIV positive, therefore, there was not enough data to assess vaccine effectiveness in HIV-infected children, however, vaccine effectiveness appeared similar amongst HIV exposed and unexposed children.

All-cause diarrhoeal hospitalisations among children <5 years in Soweto, South Africa decreased after introduction of the rotavirus vaccine.

Vaccine Impact in Ghana

**George Armah**, Noguchi Memorial Institute, Ghana

“We provided evidence of more than 50% reduction in rotavirus diarrhea hospitalization following the introduction of rotavirus vaccination.”

—George Armah, Noguchi Memorial Institute, Ghana

The Government of Ghana introduced Rotarix in the national immunization schedule in April 2012. Since introduction, vaccine coverage has been very high, reaching more than 90% of eligible children with at least one dose of vaccine.

George Armah led a case-control study using active surveillance in seven hospitals, located across Ghana’s three major ecological zones. The study enrolled age-eligible children who entered the hospitals with severe diarrhea. Of 608 children enrolled, 97.5% had been
vaccinated for diarrhea; more than twice as many were rotavirus negative (414) than rotavirus positive (203).

Preliminary results of the study—which will continue until 300 rotavirus positive children are enrolled—indicate a more than 50 percent reduction in diarrhea hospitalizations in children less than 60 months of age after the first year of vaccine introduction during the rotavirus season.

One exception to this overall downward trend arose in the northern Ghana’s Navrongo district, where children ages 12-23 months experienced a spike in rotavirus, despite high vaccination rates. Investigation revealed that the dominant genotypes were G10 and G12 strains, which had not previously been seen in Ghana. Armah noted that his team plans to further investigate the outbreak and whether the trend continues next year.

Overall, however, the study showed that the youngest children benefited most: with a 71% reduction in hospitalization rate for babies under 1 year of age; a 16% reduction among 12-25 month olds; and a 45% reduction in children over 24 months. Overall vaccine effectiveness during the first year of vaccine introduction was 65%.

“We’ve seen a substantial decline in hospitalization for all-cause diarrhea among children under five years in Ghana,” Armah said.

Armah said that the study provides good evidence to support the use of rotavirus vaccines in the routine EPI program in Ghana and more widely Africa.

**MOST CASES WERE RECRUITED FROM NAVRONGO**

![Pie charts showing recruitment percentages from different locations.](chart)
Vaccine Impact in Rwanda

Maurice Gatera, speaking on behalf of Fidele Ngabo, Rwanda Ministry of Health

Rwanda is a small country, whose 10.5 million citizens have a life expectancy of just 55 years. Infant mortality stands at 50/1,000 births, while under five mortality is 76/1,000 births. In 2011, 21% of under-five deaths were due to diarrhea.

In May 2012, Rwanda became the first African country to introduce the pentavalent rotavirus vaccine RotaTeq into its national immunization program. Today, three-dose vaccine coverage is a high 96%.

Presenting on behalf of Fidele Ngabo, Maurice Gatera reported the results of a study assessing vaccine impact to date on all-cause diarrhea hospital admissions for children under five years of age. The study compared the results of active surveillance for rotavirus diarrhea in eight sentinel hospitals for almost two years pre- and post-vaccine introduction. It also incorporated data compiled by the Health Management Information System on diarrhea hospitalizations from 27 district hospitals between January 2009 and December 2013.

The study found that:

• Rotavirus hospital admissions decreased in all age groups post-vaccine introduction, with the greatest decrease occurring among children 3-17 months of age;

• The proportion of total hospital admissions due to diarrhea decreased from ~20% pre-vaccine introduction to 13% post-vaccine introduction;

• Annual peak in diarrheal hospitalizations, which corresponds to a peak in rotavirus disease, was substantially blunted in 2013 compared to the 2009-2011 baseline.

Malawi

Naor Bar-Zeev, University of Liverpool, United Kingdom

“We have good early indication of population level impact in Malawi... and strong and robust evidence of vaccine effectiveness.”

—Naor Bar-Zeev, University of Liverpool, UK

Malawi has a population of 16 million people and a rapidly declining but still high under five mortality rate of about 71 children per 1,000 live births. Malnutrition is a severe problem, and 49 percent of children in Malawi are stunted. Prior to rotavirus vaccine introduction, about one-third of child deaths in the country were due to diarrhea.

A clinical trial of Rotarix in Malawi showed an efficacy of just 40 percent, lower than in other settings. “Nevertheless, given the history and given the trial efficacy, and then the subsequent WHO recommendation [to introduce rotavirus vaccine], the vaccine was introduced in October 2012,” said Naor Bar-Zeev.
Bar-Zeev reported the results of a case-control study assessing the impact of Rotarix in Blantyre, a city of 1 million residents. After widespread introduction, vaccination rates improved, with a corresponding lowering of hospital emissions for severe diarrhea.

“If we were just to compare the 2014 data where we really had good vaccine coverage with the pre-vaccine period, you’d see an overall reduction in rotavirus incidence of 43 percent, a statistically significant result,” Bar-Zeev said. The infant rotavirus detection rate was 50.3% pre-vaccine, compared with 39.6% and 30.8% in successive years following vaccine introduction.

The study also tracked rotavirus genotypes, and found the biggest post-vaccination change on G1, with a much more variable impact on G2. “The important point to be made here is the need for ongoing surveillance, particularly around the G2 question.”
Vaccine Impact in Botswana

Margaret Mokomane, Botswana National Health Laboratory, Botswana

Botswana, a country of two million people, introduced monovalent rotavirus vaccine (Rotarix) in July 2012, providing one of the first opportunities to assess the effectiveness of rotavirus vaccination under routine conditions in Africa. Botswana is not a Gavi-eligible country, therefore, the government purchased the vaccine without outside support.

Margaret Mokomane reported on an ongoing case-control evaluation of vaccine effectiveness. Beginning in June 2013, researchers enrolled age-eligible children with severe diarrhea in four hospitals across Botswana. Considering only those children with confirmed vaccine records, the study enrolled 123 children who tested positive for rotavirus and 232 case-negative controls.

It found vaccine effectiveness of 59% for children who received two doses of Rotarix, and 45% for children who received only one dose. While the country has an HIV prevalence of almost 17%, the researchers found no significant difference between cases and controls regarding HIV exposure.

“In conclusion, we feel that RV1 vaccination is associated with a lower risk of severe rotavirus diarrhea in Botswana,” Mokomane said. “We also think this is comparable to trials in neighboring countries in Africa.”

### ROTAVIRUS VACCINE EFFECTIVENESS IN BOTSWANA

<table>
<thead>
<tr>
<th>Vaccine dose</th>
<th>No (%) rotavirus positive cases (n=123)</th>
<th>No (%) test negative controls (n=232)</th>
<th>% vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 dose</td>
<td>45 (37%)</td>
<td>58 (25%)</td>
<td>—</td>
</tr>
<tr>
<td>1 dose</td>
<td>23 (19%)</td>
<td>43 (19%)</td>
<td>45% (-15-74)</td>
</tr>
<tr>
<td>2 doses</td>
<td>55 (45%)</td>
<td>131 (56%)</td>
<td>59% (22-78)</td>
</tr>
<tr>
<td>&gt;= 1 dose</td>
<td>78 (63%)</td>
<td>174 (75%)</td>
<td>54% (19-75)</td>
</tr>
</tbody>
</table>
Rotavirus introduction and effectiveness in Latin America and Caribbean

Lucia Helena de Oliveira, Pan American Health Organization

When rotavirus vaccine were first licensed in 2006, six countries in the Americas were the first in the world to introduce it. Today, there are hospitals conducting sentinel surveillance in 16 countries in Latin America and the Caribbean, with 95 sentinel sites, reported de Oliveira. The sites systematically report their data to the Pan-American Health Organization, and this surveillance system has enabled researchers to track both the disease and vaccine effectiveness.

Based on this surveillance data, de Oliveira reviewed the experience of Latin America and the Caribbean with rotavirus vaccine introduction and impact.

Previous studies in individual countries have previously highlighted the effectiveness of rotavirus vaccination in Latin America and the Caribbean. For example:

- Brazil had 1,500 fewer deaths in children under five between 2007-2009, and 130,000 fewer under-five hospital admissions for diarrhea following vaccine introduction;

- In Panama, following vaccine introduction in 2006, diarrhea-related hospitalizations decreased by 22% in 2007 and 37% in 2008;

- In El Salvador, bouts of diarrhea decreased 48% and 35% in the rotavirus season in 2008 and 2009, respectively, compared with the average pre-introduction rate in 2005 and 2006.

Vaccine introduction also significantly reduced child deaths due to diarrhea in Bolivia, Honduras, Venezuela and Nicaragua.

A study published in 2011, in which de Oliveira was a co-author, showed that among middle-income Latin American countries with published data (Mexico, Brazil, El Salvador and Panama), rotavirus vaccines had contributed to a 22%-41% reduction in gastroenteritis-associated deaths; and 59%-81% reduction in rotavirus hospitalizations among children younger than five.

Studies have also compared rotavirus hospitalizations and deaths averted through rotavirus vaccine to the number of intussusception-related deaths caused by the vaccines. In Mexico, for example, use of rotavirus vaccines prevented 660 deaths, while causing two deaths related to intussusception. In Brazil, rotavirus vaccines prevented 640 deaths, while causing three IS-related deaths.

de Oliveira is the first author of a new systematic review of literature and meta-analysis of studies in children under five who had been hospitalized with laboratory-confirmed rotavirus diarrhea in Latin America and Caribbean. It ultimately included eight case-control studies that involved 27,713 children. It showed that the two licensed vaccines, Rotarix and RotaTeq, consistently protected against diarrhea-related hospitalizations in the region.
“We can say that rotavirus vaccines provide good protection against rotavirus disease in children less than 12 months, when the disease is much more severe and fatal in developing countries,” de Oliveira said.

Furthermore, even one dose conferred significant protection. “This is so important because in some settings it is very difficult to reach children less than 12 months in order to complete the vaccine schedule,” she said.

However, there was a decline in effectiveness in children older than one year of age, an observation that calls for monitoring of disease among older children, while in general improving surveillance and monitoring genotype distribution.

**DOCUMENTED BENEFITS VS. RISK OF ROTAVIRUS VACCINATION UNDER ROUTINE USE**

<table>
<thead>
<tr>
<th></th>
<th>RV hospitalizations (deaths) prevented</th>
<th>Intussusceptions (deaths) caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>12,000 (660)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>Brazil</td>
<td>70,000 (640)</td>
<td>55 (3)</td>
</tr>
</tbody>
</table>

Patel, NEJM 2011;364(24);2283-2292

**Rotavirus Experience in High Income Countries**

**Four-year safety and effectiveness in Northern Europe**

Timo Vesikari, University of Tampere, Finland

“In my hospital, it doesn’t take a sophisticated epidemiologist to see that there is an effect,” Vesikari said. “The hospitalizations go down, and, now, rotavirus constitutes just about 13 percent of all gastroenteritis seen.”

—Timo Vesikari, University of Tampere, Finland

Finland is one of only five countries in Europe that has a national immunization program for rotavirus, and is the only country that uses RotaTeq exclusively. With a population of just 5.5 million and 60,000 babies born every year, Finland introduced universal rotavirus vaccination in September 2009. Babies receive the three doses of pentavalent human-bovine vaccine at ages two, three and five months, and vaccine coverage nationally stands at over 95 percent. Thus far, Finland has vaccinated 300,000 infants with RotaTeq. Because of that, “Finland might be the best case in the world to study the total effects and full story of RotaTeq vaccine,” Vesikari said.
He reported on a four-year prospective study covering hospital admissions from 2009 to 2013. Findings pointed both to very high vaccine effectiveness and large reductions in rotavirus and all-cause diarrhea among young children:

- Vaccine effectiveness was 95.8% for fully vaccinated children and 93.9 percent for children who had received at least one dose.
- Hospitalizations for rotavirus gastroenteritis in children under two dropped by 88% compared to the pre-vaccination years 2001-2006.
- There was a 70% reduction in hospitalizations for acute gastroenteritis due to any cause.

On the other hand, there was no observed herd effect—no reduction in rotavirus hospitalizations of children who were too old to be vaccinated.

Regarding strain diversity, the study found no evidence the vaccine was exerting selective pressure on circulating wild-type rotavirus strains. However, it did detect the emergence of a vaccine-derived double reassortant rotavirus strain (vdG1P[8]) are an important cause of post-vaccination diarrhea and may ultimately make up a sizable proportion of rotavirus gastroenteritis in the future when vaccine has largely eliminated wild-type rotavirus gastroenteritis.

The researchers also found prolonged intestinal infections caused by vaccine-derived reassortant G1 viruses in some children, which were detected through viral shedding.

Regarding intussusception, “exactly one case has been reported as causally related to RotaTeq vaccination” within seven days after the first dose, making the benefit-risk ratio strongly positive.

In conclusion, Vesikari noted that “Finland has the highest real-life effectiveness of RotaTeq vaccine, probably because of the optimal vaccine schedule, and low level of maternal antibody that allows uptake.” Finland has also seen the highest impact on hospitalization, probably due to the country’s 95% vaccine coverage rate.
Health benefits of rotavirus vaccination in developed countries: United States

Umesh Parashar, Centers for Disease Control and Prevention, USA

“Rotavirus positive diarrhea admissions and emergency room visits has almost disappeared in some seasons, and overall there’s been a 70% to 80% reduction. It is a very marked, rapid and visible impact of the vaccine.”

—Umesh Parashar, Centers for Disease Control and Prevention, USA

RotaTeq was recommended for use in the United States in February 2006; Rotarix in June 2008. Since RotaTeq was first introduced into the national immunization program in 2006, rotavirus vaccine coverage has gradually improved, from 44 percent in 2009 to 73 percent in 2013.

Parashar reported that numerous studies have measured the effectiveness of RotaTeq. The results show that “a full three-dose series of RotaTeq has a very high effectiveness, anywhere from 85 percent to 92 percent. And this is not very dissimilar from the 90 to 95 percent efficacy seen in clinical trials. It reassures us that the vaccine is working well in routine programmatic use.”

Although there is less data available for Rotarix, Parashar reported that the effectiveness of the two vaccines is fairly similar in routine use.

Passive disease reporting from a network of 67 laboratories that report weekly on the number of positive test results for rotavirus have shown a 70% to 90% reduction of cases in years since vaccine introduction.

Seven hospitals across the country participate in the New Vaccine Surveillance Network, which enrolls children who are admitted with severe diarrhea. In the two years prior to vaccine introduction, the network reported about 200 cases of acute gastroenteritis a year, about half of which were caused by rotavirus, making it the most important cause of severe diarrhea in children.

“In the post-vaccine years, rotavirus positive diarrhea admissions and emergency room visits has almost disappeared in some seasons, and overall there’s been a 70% to 80% reduction. It is a very marked, rapid and visible impact of the vaccine,” Parashar said.

Analysis has shown high vaccine effectiveness against a range of circulating strains. But some post-vaccine changes in strain circulation could “simply represent natural variation,” he explained.

Data has also demonstrated “herd immunity,” in which vaccination of young infants indirectly protects older children and adults by reducing transmission. “While we’ve prevented about 56,000 hospitalizations in vaccine-eligible young children, an additional 10,000 hospitalizations were averted in these older age groups (up to 64 years of age), where we never even knew rotavirus was a severe problem,” Parashar said.
Health benefits vs Intussusception risk of rotavirus vaccination in Australia

Julie Bines, Murdoch Children’s Research Institute, Australia

“The risk-benefit of rotavirus vaccination in the Australian context is judged to be highly favorable by Australian policy makers, healthcare providers and by parents, and the uptake of rotavirus vaccines remains very high in Australia.”
—Julie Bines, Murdoch Children’s Research Institute, Australia

Mothers across Australia give birth to about 300,000 babies each year, and there is a background intussusception (IS) rate of about 80 per 100,000 babies before the first birthday.

The Australian National Immunisation Program delivers all included vaccines free of charge, and included RotaTeq and Rotarix starting in July 2007. After inclusion, about half of Australian states chose to introduce Rotarix, and half chose RotaTeq. Vaccine coverage quickly reached a rate of 85% for two or three doses by 12 months of age. Bines reported that initial post-vaccine surveillance pointed to a very low level of IS risk for both vaccines, prompting a broader study that covered 2007 to 2010. The study was commissioned by the Australian regulator, the Therapeutic Goods Administration. It reviewed a nationwide database on
hospitalizations for codes related to IS in infants, and supplemented this data with a case-control study conducted in four pediatric hospitals.

The study detected 306 cases of IS over the three years. It identified a small but significant increase in the risk of IS—of about six per 100,000 babies immunized. The greatest increase in risk was in the first week after receiving either of the vaccines.

“Without the vaccination program, we had about 144 cases of intussusception. Following the vaccination introduction, 158,” Bines said.

Bines also reported on the benefit assessment, as an important part of the risk assessment. Since vaccine introduction, there has been a 71 percent or greater reduction in rotavirus admissions, averting about 7,000 to 8,000 admissions.

“We’ve been able to find a post-marketing surveillance scheme that is sensitive enough to predict such a very small degree of risk associated with the introduction of a new vaccine,” Bines said. “We feel this provides great confidence to the public that post-marketing surveillance systems are able to detect very rare events like intussusception.”

### EFFECT OF A ROTAVIRUS VACCINATION PROGRAM ON ROTAVIRUS ATTRIBUTABLE GASTROENTERITIS AND IS IN AUSTRALIA

<table>
<thead>
<tr>
<th>Annual Hospitalisations in children &lt; 5 years of age</th>
<th>Without vaccination program</th>
<th>With vaccination program</th>
<th>Number of events averted or caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus-attributable gastroenteritis #</td>
<td>11073</td>
<td>4545</td>
<td>- 6528</td>
</tr>
<tr>
<td>Vaccine-attributable intussusception *</td>
<td>144</td>
<td>158</td>
<td>+14</td>
</tr>
</tbody>
</table>
INTUSSUSCEPTION: WEIGHING BENEFIT AND RISK

Intussusception (IS) is a condition in which the bowel telescopes in upon itself presenting a potentially life-threatening condition. Globally, the background rate of IS in infants is 74 cases per 100,000 infants under one year of age. But this rate varies by region, and many countries lack any data on background rates.

The concern about rotavirus vaccines and IS goes back to experience with the world’s first rotavirus vaccine, RotaShield, which was introduced in 1998 in the United States. After 1.8 million doses of vaccine had been administered, 15 associated cases of IS were detected, or one excess case for every 10,000 vaccines, leading to the vaccine’s withdrawal. At the time of withdrawal, there was limited data about the background rates of IS or about the benefits of rotavirus vaccine.

Following the RotaShield experience, the scientific community decided that future rotavirus vaccine trials would need to be large enough to detect a risk of 1 IS for every 10,000 vaccine recipients. This led to some of the largest and most expensive clinical trials ever conducted. These trials found no increased risk of IS with vaccination.

Gagandeep Kang of Christian Medical College in India said, “What these studies showed us, as we now know in hindsight, is that if you’re looking for small risks, even these large clinical studies are not big enough.” The role of detecting such very small risks has therefore fallen to post-vaccine introduction surveillance, which can include hundreds of thousands of children who receive rotavirus vaccines.

To date, most post-marketing studies have taken place in high- and middle-income countries (US, Australia, Brazil, Mexico), and have shown a very low-level of risk in some settings, mainly during the first week after the first dose.

“The studies that have been done in these four countries estimate there is approximately one-to-five excess cases of IS per 100,000 vaccinated infants,” said Jacqueline Tate, with the U.S. CDC.

The World Health Organization’s Global Advisory Committee on Vaccine Safety and national regulatory agencies reviewed this data and unanimously reaffirmed the recommendation for use of rotavirus vaccine, concluding that the proven benefits of vaccination far outweigh the very low-level risk of IS.

Tate noted that additional data is needed from developing country settings where the benefit-risk balance may be affected by factors such as age at immunization and access to health care of infants that do develop IS. Furthermore, robust data is needed to appropriately guide vaccine policy. Indeed, WHO’s Global Advisory Committee on Vaccine Safety and other expert groups have recommended a standardized approach to monitoring IS at the population level in conjunction with the introduction and roll-out of rotavirus vaccines.

Tate presented a study design called “self-controlled case-series studies” than can evaluate IS risk when it may be difficult to recruit patients for standard case-control studies, and when the background rate of IS is unknown, and which is the often case in countries that have weak surveillance system.

Jacqueline Tate of the Centers for Disease Control & Prevention in USA explained how it works: the period of time immediately after vaccination is classified as the risk period. Any time outside that risk period is the control period. “You want to see if there are excess cases occurring in your risk period compared to your control period;” she explained. If so, it suggests that there is an association with vaccination.

Tate reported that a case-series study in Mexico succeeded in detecting a risk of one-to-two excess cases per 100,000 vaccinated children.

“It appears that based on the data that’s available...the case-series approach may be the most efficient mechanism to quantify the risk associated with rotavirus vaccines,” Tate concluded.
INTUSSUSCEPTION “NATURALLY OCCURING” OR BASELINE

- Etiology not well defined
- Uncommon: 74 cases per 100,000 infants
  - Incidence varies by region and age
- Peak incidence coincides with age at vaccination

BENEFITS VS. RISKS OF VACCINATION

Estimated Possible Risk: 1–5 Excess Intussusception Cases Per 100,000 Vaccinated Infants

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea Hospitalizations (Deaths) Prevented</th>
<th>Intussusception Cases (Deaths) Caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>11,600 (663)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>Brazil</td>
<td>69,600 (640)</td>
<td>55 (3)</td>
</tr>
<tr>
<td>Australia</td>
<td>7,000 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>US</td>
<td>53,000 (16)</td>
<td>48 (0)</td>
</tr>
</tbody>
</table>

RISK OF INTUSSUSCEPTION

<table>
<thead>
<tr>
<th>Dose</th>
<th>Risk window (days)</th>
<th>Cases</th>
<th>Incidence ratio (95% confidence interval)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>1-7</td>
<td>4 (1.2%)</td>
<td>1.2 (0.4 to 3.7)</td>
<td>1.4 (0.4 to 5.0)</td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>1-7</td>
<td>24 (8.7%)</td>
<td>5.9 (3.4 to 10.5)</td>
<td>6.3 (2.8 to 14.4)</td>
</tr>
</tbody>
</table>

1 to 2 excess cases of IS per 100,000 children vaccinated

*Case-series adjusted for age in 14 day interval; denominators used for risk-window percents include unvaccinated and cases >21 days; Case-series model only includes post-exposure intussusception events; total child-months of follow-up = 62.5 within 1-7 days and 2004 child-months for the cases outside the 1-21 day risk window

Patel et al, NEJM, 2011
NEW VACCINES

Update from the Serum Institute Of India, Ltd

Prasad Kulkarni, Serum Institute of India Limited, India

Kulkarni reported on development and testing of an oral pentavalent bovine-human reassortant rotavirus vaccine developed by the Serum Institute of India in collaboration with the U.S. National Institute of Allergy and Infectious Diseases. It includes the rotavirus antigens G1, G2, G3, G4 and G9. It is made in a dry powder form and is stable for up to three years at 2 to 8°C, and at 25°C, for two years at 37°C, and for six months at 40°C.

The Serum Institute of India has already completed testing through Phase IIb, revealing that the vaccine candidate had a seroconversion rate of 56% following the first dose and 60% following the second, and no safety concerns. The company is now in the midst of two Phase III clinical trials, one in India and the other in Niger.

The Indian trial began in May 2014. It has enrolled 1,000 infants, and will ultimately enroll 7,500. Half of the infants will be vaccinated at six, ten and 14 weeks of age, concurrent with other standard vaccinations. All infants will have weekly home visits, and follow up will continue until the infants reach two years of age.

Once 122 cases of severe rotavirus gastroenteritis are detected, the researchers will conduct an interim analysis. “We hope that we will get those cases by Q3 or Q4 of next year and then we will apply for licensure and pre-qualification,” Kulkarni said.

Other studies are planned to demonstrate consistency in manufacture of the vaccine, and to demonstrate non-interference with other routine vaccinations.

Update from Shantha Biotechnics, India

Mandeep Singh Dhingra, Shantha Biotechnics Limited/Sanofi Pasteur, India

“If I just try to put things into perspective, WHO mortality data basically tells us that a child dies every 70 seconds from rotavirus. That is a huge burden.”

—Mandeep Singh Dhingra, Shantha, India

Dhingra provided an update on the company’s bovine-human reassortant vaccine, which is based on the strains licensed from the U.S. National Institutes of Health. Shantha’s formulation is a fully liquid tetravalent vaccine, containing the VP7 serotypes G1, G2, G3 and G4.

After successfully completing a Phase I safety study in healthy adult volunteers, and a Phase II study in infants that demonstrated that the vaccine elicits a significant immune response as per dose and appears safe, Shantha has received approval to conduct a Phase III study of its Bovine-Human Reassortant...
Tetravalent Vaccine (BRV-TV). In the planned study, 1,182 infants will be randomized into two groups, one receiving the new vaccine candidate, and the other receiving RotaTeq vaccine. Both groups concomitantly also receive the oral polio vaccine and DTwP-HepB-Hib Pentavalent vaccine. The study is being conducted at 12 sites in India which are pediatric or public health departments attached to medical schools.

“We are trying to demonstrate the non-inferiority of our vaccine versus the licensed Rotavirus vaccine, RotaTeq, in terms of serum IgA sero-response rates,” Dhingra said. The study will also seek to demonstrate non-interference with other standard childhood vaccines in India, including diphtheria, tetanus, pertussis, hepatitis B, HIB and polio.

**ROTAVIRUS BURDEN**

**A Definite Need For Rotavirus Vaccines**

- Estimated 78,500 deaths, 872,000 hospitalizations, over 3.2 million outpatient visits and 11.37 million diarrhea episodes due to rotavirus in children <5

- The globally common G1P[8], G2P[4], and G9P[8] rotavirus strains were also the most frequently detected strains in numerous studies in India in both inpatients and outpatients<5 years of age

- Estimated 453,000 (420,000 – 494,000) RVGE associated deaths occurred worldwide in 2008
  - 5% of all child deaths
  - Cause-Specific mortality rate of 86 per 100,000 population aged < 5 years

1. John J. Vaccine 2014;32:A5-A9  
2. Tate JE Vaccine 2014;32S:vii-xii  
3. WHO Weekly Epidemiological Record 2013;88(5):49-64

---

**Innovation to develop heat-stable a rotavirus vaccine**

**Davinder Gill, MSD Wellcome Trust Hilleman Laboratories**

Hilleman Laboratories is a research and development non-profit joint venture between Wellcome Trust and Merck, the developer of RotaTeq. Gill discussed its work to adapt RotaTeq to be a heatstable rotavirus vaccine that can be delivered easily and affordably in low-income counties. Now licensed in more than 110 countries around the world, RotaTeq is already proven to be a safe and highly effective vaccine. However, its use is dependent on cold chain storage that drives up costs and restricts access.
Working with the RotaTeq vaccine formulation, Hilleman Laboratories has developed a dry powder form of the vaccine that is stable at the high temperatures common in many tropical low-income countries.

“We are looking at a shelf life of this vaccine of up to almost three years at 37°C, and approximately 16 months at 45°C,” Gill said. This would make the vaccine practical for a country like India, where the time from delivery by the manufacturer to use of the vaccine in the field is approximately 11 months, as it passes through a five-tier storage and distribution system.

Furthermore, the vaccine is packaged simply using a two-chambered device: one has the diluent and the other the powder. When the seal separating the two chambers is broken, the diluent is released to mix with the powder. The devices have a footprint of 6 cc, allowing 150,000 doses to be packed in one cubic meter. This is a “dramatic optimization,” compared to current vaccines that have an individual footprint of compared to 50 cc to 140 cc, Gill reported.

The new formulation is set to enter Phase I clinical trials next year, and, given the extensive testing and clinical approval of the parent vaccine, RotaTeq, “Our goal very much is to seek registration based on the Phase II data,” Gill said, “In that respect we can actually move through the clinical development of this vaccine very quickly.”

Neonatal vaccine advances

Margie Danchin, Murdoch Children’s Research Institute, Australia

“A birth dose strategy with the vaccine is associated with a strong vaccine take and provides the earliest opportunity for protection against rotavirus disease from birth.”

—Margie Danchin, Murdoch Children’s Research Institute, Australia

Margie Danchin reported the results of a Phase II clinical trial of a novel neonatal rotavirus vaccine, RV3-BB, which aims to protect infants from birth. It is based on a human neonatal strain, G3P[6], which was isolated from healthy newborns in obstetric hospitals in Melbourne in 1975.

A neonatal vaccine strategy takes advantage of the fact that neonatal rotavirus strains replicate well in the newborn’s gut, even in the presence of maternal antibody and breast feeding. Danchin explained that the strains are asymptomatic and associated with protection against rotavirus disease early in infancy. A birth dose strategy would also be associated with a lower risk of intussusception, given that the natural risk of IS is very low during the neonatal period.

Previously, a Phase I trial of RV3-BB had found a vaccine take of 89 percent, and detected no safety issues.

Danchin revealed the results of a recently completed Phase IIA trial conducted in New Zealand. Ninety-six children were randomized into one of three arms: 32 neonates received the first of three doses between 1 and 5 days of age; 32 infants received the first dose at 8 weeks of age, and 32 infants received a placebo.
The trial found no significant difference in the number or severity of adverse events among the three groups. Vaccine take between the infant and placebo groups was similarly high, at 90 percent for the neonatal schedule, and 93 percent for the infant schedule.

“Clearly the Phase I and IIa trials of the RV3-BB vaccine using a birth dose or an infant dose strategy provide proof of principle that this vaccine is well-tolerated and immunogenic,” Danchin said. She reported that a Phase IIB efficacy trial against severe rotavirus disease is currently underway in Indonesia.

![Cumulative Vaccine Take - ITT](CUMULATIVE_VACCINE_TAKE-_ITT.png)

**Progress with a killed vaccine**

Stan Cryz, PATH, USA

“*The conclusion from the Phase I trial is that the vaccine is safe and well-tolerated, and it elicits a robust immune neutralizing antibody response.*”

—Stan Cryz, USA

Stan Cryz reported on another novel rotavirus vaccine. As opposed to the currently licensed oral live virus vaccines, Cryz is working on an inactivated, injectable vaccine. It makes use of a portion of rotavirus protein VP8, which is then fused to the tetanus toxin P2 CD4 epitope.

Cryz outlined the benefits of an inactivated, injectable vaccine over currently licensed oral live rotavirus vaccines. They are expected to be less expensive and could have higher efficacy in low-income countries than do oral live vaccines by avoiding factors that
impair immune response, particularly other interfering microbes in the infant digestive tract. The VP8 subunit candidate could be available at less than $1 per dose, and possibly less than $0.25 per dose, Cryz said.

Cryz reported the results of the first human trial of the P2-VP8, which began enrolling its first participants in December 2012. The Phase I, double-blind, randomized placebo-controlled study examined the impact of three different doses of the experimental vaccine in healthy adult volunteers.

The response was effective against several P[8] strains, modest in response to P[4] strains, and meager to P[6] strains, leading the investigators to conclude that a trivalent P[4], P[6], P[8] vaccine will be required to provide a broad protective response against the P serotypes most commonly seen in the field. Such a trivalent vaccine is now undergoing toxicity studies.

Meanwhile, Cryz has launched a Phase I/II clinical trial in South African toddlers and infants to examine its safety and immunogenicity, as well as to surmise possible field efficacy by analyzing the impact of the P2-VP8 vaccine on replication of the Rotarix vaccine strain in vaccinated participants.

**Baoming Jiang**, Centers for Disease Control & Prevention, United States

“*Basically we demonstrated that the three doses of this inactivated rotavirus vaccine induce comparable IgG and IgA responses.*”

—Baoming Jiang, CDC USA

Baoming Jiang took a different approach to an inactivated rotavirus vaccine (IRV). In contrast to P2-VP8 vaccine, which uses just one rotavirus protein, the CDC-9 vaccine uses an entire inactivated virus. Indeed, Baoming cautioned against a vaccine reliant on only the VP8 antigen, given that its high mutation rate could lead to a loss in vaccine efficacy.

Baoming highlighted the potential role and importance of a whole-virus inactivated vaccine. He noted that it could overcome some of the limitations of live oral vaccines, including avoiding the risk of intussusception associated with live oral vaccines.

The CDC-9 rotavirus strain should provide cross-protection against a range of rotavirus strains, by virtue of presenting numerous protein targets for the human immune response. Furthermore, Baoming stressed that it is a simple and inexpensive approach.

Initial animal studies have now shown that the CDC9 vaccine produces a strong immune response whether it is injected in the skin or in the muscle. In addition, the vaccine was found to produce both an IgG and an IgA immune response. Previously, scientists had thought that only a live oral vaccine could produce a significant IgA immune response.

“We innoculate in three does, and then we challenge the animal with rotavirus. Basically we demonstrated that the three doses of IRV induce comparable IgG and IgA responses,” Baoming said.
Thus far, the CDC’s IRV program has completed pre-clinical studies of CDC-9 that show proof of concept for serum antibody in macaques; proof of concept by intramuscular immunization in mice, guinea pigs and piglets; and proof of concept by skin immunization in mice and piglets.

The CDC has established several partnerships to drive the work forward, including with vaccine manufacturers, biotechnology companies and NGOs, with the goal of moving the vaccine into human clinical trials within the next two years.

**RISK FACTORS FOR LOWER PERFORMANCE OF LIVE ORAL ROTAVIRUS VACCINE**

Factors that lower viral titer
- Breast milk
- Maternal antibodies
- Stomach acid
- Prior exposure

Factors that impair immune response
- Malnutrition - Zn, Vit A
- Interfering microbes - viruses and bacteria
- Other infections - HIV, malaria, TBC

Others: Novel & diverse strains
Host genetic diversity
NEW INSIGHTS IN STRAIN DIVERSITY

Distribution and reassortment among human and animal rotaviruses revealed by comparative genome analyses

Jelle Matthijnssens, University of Leuven, Belgium

Matthijnssens shared insights regarding the distribution and reassortments among rotaviruses infecting human and animal populations, as revealed by comparative genome analyses. Along similar lines, Patton revealed a critical genetic barrier to reassortment between human and animal rotaviruses.

Matthijnssens noted that the amount of genetic data available to understand rotavirus is rapidly growing. The number of completely sequenced human rotavirus strains in GenBank more than doubled from 2012 to 2014, from 400 to over 800. There is also a growing number of completely sequenced rotavirus strains infecting a variety of animals including cattle, pigs, horses and cats, and the one thousandth rotavirus genome will soon be sequenced.

Matthijnssens has used this data to develop an overarching genotype classification system including all 11 gene segments, allowing the identification of species specific genotype constellations.

SEQUENCE-BASED CLASSIFICATION FOR 11 GENE SEGMENTS

<table>
<thead>
<tr>
<th>GENE PRODUCT</th>
<th>PERCENTAGE IDENTITY</th>
<th># GENOTYPES</th>
<th>GENOTYPE DESIGNATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP7</td>
<td>80%</td>
<td>27 G</td>
<td>Glycosylated</td>
</tr>
<tr>
<td>VP4</td>
<td>80%</td>
<td>37 P</td>
<td>Protease Sensitive</td>
</tr>
<tr>
<td>VP6</td>
<td>85%</td>
<td>20 I</td>
<td>Inner capsid protein</td>
</tr>
<tr>
<td>VP1</td>
<td>83%</td>
<td>11 R</td>
<td>RNA-dependent RNA-polymerase</td>
</tr>
<tr>
<td>VP2</td>
<td>84%</td>
<td>11 C</td>
<td>Core protein</td>
</tr>
<tr>
<td>VP3</td>
<td>81%</td>
<td>10 M</td>
<td>Methyltransferase</td>
</tr>
<tr>
<td>NSP1</td>
<td>79%</td>
<td>22 A</td>
<td>Interferon Antagonist</td>
</tr>
<tr>
<td>NSP2</td>
<td>85%</td>
<td>11 N</td>
<td>NTPase</td>
</tr>
<tr>
<td>NSP3</td>
<td>85%</td>
<td>14 T</td>
<td>Translation Enhancer</td>
</tr>
<tr>
<td>NSP4</td>
<td>85%</td>
<td>18 E</td>
<td>Enterotoxin</td>
</tr>
<tr>
<td>NSP5</td>
<td>91%</td>
<td>13 H</td>
<td>pPhosphoprotein</td>
</tr>
</tbody>
</table>

Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx
Analysis of this data has revealed that the vast majority of important human disease-causing rotavirus strains belong to two main genetic constellations, with a small number of strains possessing a third, more minor constellation. The two main human constellations are referred to as either Wa-like (type 1 constellation) or DS-1-like (type 2 constellation), whereas the minor constellation is referred to as AU-1-like (type 3 constellation).

Cattle (and other two-toed ungulates), pigs, horses, cats, and dogs each have their own set(s) of typical genotype constellations, with minor overlap among constellations. These typical genotype constellations are well conserved. However, interspecies transmissions do occur, but they usually represent dead-end infections. However, reassortments can occur when strains belonging to different host species are able to coinfect the same host, and this can give rise to new strains that can cause disease and circulate among humans.

Mathijnssens reviewed several examples of rotavirus interspecies transmission and reassortment events:

- Surprisingly various animal derived gene segments were identified in circulating human G2P[4] strains in Belgium. Several of these reassortant strains were detected over several consecutive rotavirus seasons, suggesting they are fit enough to transmit and circulate in the human population;

- An unusual bovine-like rotavirus strain was detected in a child with gastroenteritis in Belgium during the rotavirus season 2013-2014. Analyses revealed unique VP7 and VP4 gene segments, potentially representing novel G and P-genotypes;

- Possible interspecies transmission of bat rotaviruses to humans and horses.

Reflecting on these findings, Mathijnssens pointed out that, “With decreased circulation of typical rotavirus strains in populations with a high vaccination coverage, unusual animal rotaviruses may have increased opportunities to infect humans, which necessitates continued surveillance.”

John Patton, National Institute of Allergy and Infectious Disease, NIH, USA

Patton reported on research into the genetic barriers to reassortment between human and animal rotavirus strains, noting that an understanding of those barriers could also allow scientists to predict what new strains could appear and gain a foothold rather than rapidly die out.

Genetic sleuthing led Patton to focus on the role of the NSP1 gene in rotavirus. NSP1 proteins inhibit interferon, which is a key response of the innate immune system. Activated by the arrival of a virus in a cell, interferon triggers subsequent immune reactions to disarm or destroy the virus. “NSP 1 is really the magic play from the virus’s point of view for getting control of the innate immune system of the host,” Patton said.
Comparing gene sequences of NSP1 variants and their amino acid counterparts, Patton found that NSP1 proteins in humans (and pigs) function differently than NSP1 proteins found in all other animal rotaviruses.

In humans and pigs, NSP1 blocks the production of interferon by disabling the protein NF-κB. In all other animals, NSP1 blocks the production of interferon by degrading its protein transcription factors, called IRF (interferon regulatory factors). Both NF-κB and IRF must reach the cell nucleus in order to trigger interferon, so blocking just one of them does the job of disabling this key immune response.

Comparing the NSP1 molecules in humans and pig rotaviruses to rotavirus strains that infect other animals discloses that “These NSP1 molecules have different functions and they have probably co-evolved to work best in a certain cell type of a certain species.” Furthermore, the genetic differences determine “a really big difference at a protein function level,” mitigating against the possibility of reassortment between human and most animal rotaviruses.

PHYLOGENETIC RELATIONSHIP AMONG ALL KNOWN NSP1 PROTEINS

NSP1 genotypes

A1, A2, A8: human, porcine
A3-A16: other animals
Do Vaccination Programs Change Strain Distribution?

Jon Gentsch, Centers for Disease Control & Prevention, USA

“The vaccine effectiveness against a variety of strains is comparable. That is reassuring in that there is substantial cross-protection against all of these strains,”

—Jon Gentsch, USA

Rotavirus strain surveillance in the vaccine era is ultimately meant to answer several questions, including whether vaccination pressures allow the emergence of vaccine escape mutants or animal strains in human populations; and whether the vaccines provide good cross protection that extends to rare serotypes.

To address these questions, Gentsch first compared global data on pre-vaccine strain diversity from 1996 to 2007, to post-vaccination strain diversity, from 2007 to 2012. The data show that “Strains have not really changed dramatically in general,” Gentsch said, with the same five or six strains continuing to predominate. At the same time, there is significant regional variation; regionally common strains tend to emerge, such as P[6] in Africa; and a variety of rare strains occur (there are now a total of 85 known human rotavirus strains).

He pointed to strain information compiled by the New Vaccine Surveillance Network in the United States. Its seven sites conduct population-based surveillance, provide annual estimates of vaccine effectiveness and hospitalization trends, and examine serotype-specific protection. The data show the emergence of new strains after vaccine introduction, but with no loss of vaccine efficacy.

Meanwhile, in Belgium, widespread vaccination has been associated with an increased proportion for hospitalized cases of rotavirus due to the strain G2P[4].

Viewed globally, the changes in strain prevalence between pre-and post-vaccination eras “are difficult to distinguish from natural variation,” leading to the need for ongoing surveillance to monitor vaccine effectiveness and to “really understand whether the vaccine is going to have an impact on strains over the longer term,” Gentsch concluded.
Miren Iturriza Gomara, EuroRotaNet, University of Liverpool, UK

"While natural infection and rotavirus immunization provides a good degree of cross-protection against disease upon reinfection... cross-protection may not be equally lasting or efficacious against all genotypes."

—Miren Iturriza Gomara, UK

Gomara reported on the results of EuroRotaNet, a surveillance network established to gather comprehensive information of the rotavirus types co-circulating in Europe, pre- and post-vaccine introduction. Between 2006 and 2013, 16 European countries contributed more than 52,000 characterized samples.

Of these, 93 percent contained a single rotavirus strain, yielding a total of 48 different genotypes. However, only six of these had a prevalence of >1 percent of the total, and these six are considered the common or epidemiologically significant strains circulating in Europe.

Overall, the data could provide only limited visibility into trends arising post vaccination, as European countries have been slow to introduce rotavirus vaccine, Gomara said. Austria and Bel-gium introduced a vaccine in 2006, so all of their data is post-vaccine introduction. Finland introduced universal vaccination in 2009; Germany and the United Kingdom did so in 2013. So while it is an ever-changing landscape, most of the samples represent pre-vaccination strains.

The United Kingdom is one of the only countries with pre- and post-vaccination surveillance data. It shows that G1P[8] has...
remained dominant for the last seven or eight years, including during the short time since the vaccination program began. “However, I would also like to highlight that 20 percent are wild-type G1P[8], and 50 percent, which is a very large proportion, appear to be vaccine-derived strains,” Gomara said.

In Belgium and Austria, the first two countries to introduce universal vaccination for rotavirus in Europe, G2P[4] seems to predominate. This has not seen in Finland or the UK to date. The age-distribution of disease is similar for all strains except G2P[4], which has a heightened impact on people 66 years of age and older.

The data suggest that rotavirus vaccine introduction has not resulted in the emergence of vaccine breakthrough strains or in the selection of unusual rotavirus strains. While noting that surveillance and analysis is ongoing, and the data is in many ways preliminary, Gomara concluded that overall, shifts in the relative prevalence of rotavirus genotypes and the temporal distribution of rotavirus infections varies significantly between seasons and countries, and occurs naturally in the absence of vaccine pressure.

### PARTICIPATING COUNTRIES AND NUMBER OF ROTAVIRUS STRAINS
(Includes data September to August in each of the season between 2006 to 2013)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>179</td>
<td>3</td>
<td>107</td>
<td>289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>NA</td>
<td>610</td>
<td>413</td>
<td>381</td>
<td>527</td>
<td>281</td>
<td>350</td>
<td>185</td>
<td>2,747</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>338</td>
<td>328</td>
<td>361</td>
<td>549</td>
<td>677</td>
<td>562</td>
<td>153</td>
<td></td>
<td>2,968</td>
</tr>
<tr>
<td>Denmark</td>
<td>185</td>
<td>277</td>
<td>260</td>
<td>318</td>
<td>224</td>
<td>168</td>
<td>86</td>
<td>16</td>
<td>1,534</td>
</tr>
<tr>
<td>Finland</td>
<td>140</td>
<td>265</td>
<td>224</td>
<td>52</td>
<td>98</td>
<td>51</td>
<td>30</td>
<td>6</td>
<td>866</td>
</tr>
<tr>
<td>France</td>
<td>577</td>
<td>767</td>
<td>810</td>
<td>906</td>
<td>840</td>
<td>806</td>
<td>757</td>
<td>3</td>
<td>5,466</td>
</tr>
<tr>
<td>Germany</td>
<td>39</td>
<td>964</td>
<td>752</td>
<td>736</td>
<td>368</td>
<td>462</td>
<td>269</td>
<td></td>
<td>3,590</td>
</tr>
<tr>
<td>Greece</td>
<td>NA</td>
<td>NA</td>
<td>591</td>
<td>423</td>
<td>364</td>
<td>462</td>
<td>229</td>
<td></td>
<td>2,069</td>
</tr>
<tr>
<td>Hungary</td>
<td>388</td>
<td>586</td>
<td>436</td>
<td>386</td>
<td>314</td>
<td>475</td>
<td>66</td>
<td>164</td>
<td>2,815</td>
</tr>
<tr>
<td>Italy</td>
<td>333</td>
<td>1,290</td>
<td>753</td>
<td>1,379</td>
<td>1,121</td>
<td>1,304</td>
<td>1,108</td>
<td>113</td>
<td>7,401</td>
</tr>
<tr>
<td>Lithuania</td>
<td>1</td>
<td>585</td>
<td>456</td>
<td>528</td>
<td>432</td>
<td>594</td>
<td>395</td>
<td>1</td>
<td>2,992</td>
</tr>
<tr>
<td>Slovenia</td>
<td>353</td>
<td>631</td>
<td>468</td>
<td>434</td>
<td>473</td>
<td>493</td>
<td>280</td>
<td>20</td>
<td>3,152</td>
</tr>
<tr>
<td>Spain</td>
<td>544</td>
<td>662</td>
<td>537</td>
<td>613</td>
<td>824</td>
<td>1,479</td>
<td>509</td>
<td>41</td>
<td>5,209</td>
</tr>
<tr>
<td>Sweden</td>
<td>32</td>
<td>578</td>
<td>115</td>
<td>109</td>
<td>111</td>
<td>150</td>
<td>169</td>
<td>2</td>
<td>1,266</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>16</td>
<td>138</td>
<td>859</td>
<td>560</td>
<td>378</td>
<td>254</td>
<td>313</td>
<td>110</td>
<td>2,628</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>845</td>
<td>910</td>
<td>975</td>
<td>876</td>
<td>681</td>
<td>664</td>
<td>1,039</td>
<td>61</td>
<td>6,051</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,791</strong></td>
<td><strong>8,591</strong></td>
<td><strong>8,010</strong></td>
<td><strong>8,250</strong></td>
<td><strong>7,611</strong></td>
<td><strong>8,208</strong></td>
<td><strong>5,860</strong></td>
<td><strong>722</strong></td>
<td><strong>51,043</strong></td>
</tr>
</tbody>
</table>
A wide-ranging session on rotavirus policy covered several topics: WHO recommendations regarding existing vaccines; whether restrictions on the age of vaccination are beneficial; WHO vaccine safety assessment regarding intussusception; and the potential value of withholding breastfeeding at the time of vaccination to increase vaccine efficacy. Additionally, the symposium heard from the head of India’s Department of Biotechnology on factors affecting policy making, nationally and globally.

**National and Global Policy Making**

Vijay Raghavan, Department of Biotechnology, India

“It is important to propose the audacious for the public good.”

—Vijay Raghavan, India

“The many ways in which we address science policy and its implementation in society are dated, dated not because they are wrong, but dated because the world is dramatically changing.” So began Raghavan, as he introduced a wide ranging talk on the speed of communications and its impact on public health.

Raghavan noted India’s own “rather dramatic change in the speed in which India has taken decisions about immunization.” In particular, last July (2014) Prime Minister Narendra Modi announced the introduction of four new vaccines into the national immunization program, including the indigenously produced rotavirus vaccine, ROTAVAC. “India will now provide vaccines against 13 life-threatening diseases for 27 million children annually, the largest birth cohort of the world.”

While describing the organizational policy-making structure that facilitated this latest development, Raghavan repeatedly called attention to the fundamental “need to grasp that the ways in which we communicate need to change hugely,” given that the previously linear growth of communication and science has become an exponential change in the way ideas propagate, sometimes leading to the rapid propagation of irrational ideas.

Raghavan noted that, “We as a scientific community are still caught in a stepwise linear mode of communication and of getting evidence on board.” Many scientists have addressed this misalignment by “jumping in to what they call the analysis of ‘big data,’” with the mistaken belief that by collecting all of the information possible they can predict the trends of science and disease.

Raghavan argued that multiple aspects of understanding and solving problems must be brought together from the outset: connecting policy, evidence, and molecular biology in a dynamic manner through collaboration within small cells of people who have both a breadth and depth of knowledge.

Policy making in today’s world is a matter of a step-by-step ratcheting up of the science and of public opinion. “We need to understand the biology. We need to get the evidence... rational steps are being taken very carefully.
at each stage. Right?” But that is not enough. “While doing this, we tend to forget that it is important to propose the audacious for the public good,” he said. Failing to do so means “constantly responding to what happens rather than putting forth ideas about what needs to be done on a longer term.”

As an example of an audacious idea, Raghavan pointed to the role of the European Molecular Biology Laboratory, which had an extraordinary impact on molecular biology by amplifying the spread of basic research in a post-war situation.

“Could we not do this with Africa—in the broadest aspects linking biology with public good?” he asked. “Bringing in vaccines ... for public good can actually communicate to people at large in a currently very cynical context that scientists can drive public good in big ways,” he said.

Raghavan concluded, saying, “The foundation of many of the structures we have are vital...and we need to ratchet up every successful decision, but we also need to think audaciously, think big and think for the future because the world is dramatically changing and we need to communicate in such a changing world.”

**WHO Rotavirus Policy**

**Age of Vaccination**

**Narendra Arora, The Inclen Trust, India**

Narendra Arora provided an update on WHO rotavirus vaccine policy from the WHO Strategic Advisory Group of Experts (SAGE). WHO’s formal positions on rotavirus vaccines are available in statements published in 2007, 2009, and 2013. Its recommends including rotavirus vaccines in all national immunization programs and to do so as a priority in countries with high rotavirus fatality rates, such as in south and south-eastern Asia and sub-Saharan Africa.

WHO also makes more specific recommendations about how to rotavirus vaccines, and in 2012, the SAGE meeting reviewed evidence about the potential of rotavirus vaccine to further reduce mortality by having a more flexible immunization schedule.

Up until that point, WHO had recommended that rotavirus vaccine be initiated before 15 weeks and concluded by 32 weeks of age, being delivered along with the childhood diphtheria-tetanus-pertussis (DTP-1) vaccine. The recommendation was intended to both reach children at the earliest possible age in order to prevent serious or even fatal occurrences of rotavirus gastroenteritis, and to complete the course of vaccination before children reached the age at which they were naturally more susceptible to intussusception.

But there were several problems with this approach. Arora noted that early immunization can be challenging in developing countries, and that the timing and scheduling of doses are often not maintained. “In several low and middle income countries, including India, only about 60 percent of
children receive the first does of DTP by 15 weeks of age, and only 50 percent receive the third dose by 32 weeks of age, and therefore you can see a large proportion are missing out on this vaccine,” he said.

The SAGE committee therefore weighed the benefits and risks of removing the age restriction. Analysis revealed that removing the age restriction, and allowing infants to begin their vaccination schedule later during their first year, would save an additional 47,000 lives, even while taking into account a potential 300 deaths caused by vaccine-related intussusception.

WHO therefore modified its recommendation regarding age of vaccination. Although still favoring early immunization, it stated that allowing infants to receive rotavirus vaccine together with DTP regardless of the recommended time of DTP vaccination could save many more lives.

### Optimizing Immunization Schedules

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Median (5&lt;sup&gt;th&lt;/sup&gt; and 95&lt;sup&gt;th&lt;/sup&gt; percentiles)</th>
<th>Rotavirus Deaths Averted</th>
<th>Associated Intussusception Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricted</td>
<td></td>
<td>155,800 (83,300 to 217,700)</td>
<td>253 (76 to 689)</td>
</tr>
<tr>
<td>No age restriction</td>
<td></td>
<td>203,000 (102,000 to 281,500)</td>
<td>547 (237 to 1160)*</td>
</tr>
<tr>
<td>No age restriction (vs. age restriction)</td>
<td>47,200 additional rotavirus deaths averted (18,700 to 63,000)</td>
<td>294 additional IS deaths associated (161 to 471)</td>
<td></td>
</tr>
</tbody>
</table>

Trade-offs exist when considering various schedule options. Model estimates include large uncertainties.
Safety of Rotavirus Vaccines

Melinda Wharton, WHO’s Global Advisory Committee on Vaccine Safety (GACVS)

“Based on all the work the committee has done over the last ten years, it continues to strongly support the continued use of both vaccines. Although the risk of IS has been found in several populations, the benefits of prevention of severe rotavirus gastroenteritis greatly exceed the risk of the vaccines.”
—Melinda Wharton, Global Advisory Committee on Vaccine Safety

Melinda Wharton reported on GACVS’ ongoing and extensive reviews of the safety of rotavirus vaccines. GACVS was established in 1999 by WHO’s Department of Immunization, Vaccines and Biologicals established GACVS to provide independent, expert scientific advice to WHO on vaccine safety issues of global or regional concern.

GACVS has addressed rotavirus vaccine safety issues in 11 of its 18 meetings held since 2005. It has reviewed both pre-licensure studies and post-licensure studies on the risk of vaccine-related intussusception.

Rigorous review of post-licensure data from Australia suggested a small excess risk of IS; preliminary findings from a study in Mexico found a four-to-five fold increase in IS following the first dose of Rotarix; and data from Australia and the U.S. provided increased risk of IS associated with both Rotarix and RotaTeq.

In the U.S., a small cluster of six cases was identified following the administration of 200,000 doses of vaccine. With RotaTeq, no such cluster was found, however eight IS cases were identified for the 1.3 million doses administered.

Wharton reported that GACVS concluded that the findings show a small risk of IS following administration of both Rotarix and RotaTeq, especially during the first seven days following the first dose. But they also found that, “Overall, the benefits of vaccination for prevention of severe rotavirus gastroenteritis treaty exceed the risk of this adverse event.”

GACVS has also reviewed safety data for ROTAVAC, India’s newly licensed vaccine. In a Phase III study of 4,532 vaccinees and 2267 placebo recipients there was no imbalance between the groups with respect to intussusception or other adverse events or death. There were 11 confirmed cases of IS, with none temporally associated with vaccination.

India is planning a post-licensure study of at least 45,000 vaccinated infants. As noted both Arora and Wharton emphasized WHO’s focus on post-marketing surveillance, and the importance of additional data to assess the risk of IS and to identify any other rare adverse events that might occur. In addition, ongoing work in several countries will present a safety profile in regions where data about the background rate of IS are limited or absent.
Breastfeeding and Vaccine Efficacy

Asad Ali, Aga Khan University, Pakistan

“Our findings suggest that substantially improved clinical protection is not likely with the strategy of withholding breast feeding around the time of vaccination. Therefore, we suggest that breast feeding can continue around the time of rotavirus vaccination.”

—Asad Ali, Pakistan

A persistent question regarding rotavirus vaccines is why the two commercially approved vaccines have substantially lower efficacy among children in low-income countries. One potential explanation is that the force of infection of rotavirus is higher in lower-income countries, causing mothers to have higher antibody titers that they transmit to their babies through breast milk, and that these higher titers inhibit replication of the live virus in the oral vaccines, interfering with vaccine take.

Asad Ali reported on a Phase IV trial that tested this hypothesis. It compared the immunogenicity of Rotarix in infants who were not breastfed for one hour before through one hour after vaccination, to that in infants who were breastfed at the time of vaccination. Immunogenicity was gauged base on seroconversion (anti-rotavirus IgA antibodies of at least 20 U/mL). Overall, 353 infants completed the study; 181 had breastfeeding withheld, and 172 had immediate breast-feeding.

Ali said that the result came as a surprise. After two doses, the seroconversion rate was higher in infants who were breastfed (29 percent), than those who were not (16.6 percent). After three doses, seroconversion was 37.8 percent in the breastfeeding arm, and 28.2 percent in the withholding arm of the trial.

“Our findings suggest that substantially improved clinical protection is not likely with the strategy of withholding breast feeding around the time of vaccination. Therefore, we suggest that breast feeding can continue around the time of rotavirus vaccination,” Ali concluded.

Ali suggested several possible explanations for the surprise finding that breast feeding appears to increase vaccine efficacy rather than decrease it: 1) that it is a chance finding that could be disproven by further research (although several other previous studies have made similar findings); 2) that breast milk provides additional buffering against gastric acid at the time of vaccine administration; or 3) That there is something immunogenic in breast milk.
CLOSING SESSION

The closing session placed the global effort to control rotavirus disease and death within the broader context of a comprehensive strategy to overcome childhood pneumonia and diarrheal disease. Speakers outlined the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD); provided an in-depth look at implementation of that plan, particularly in India; and updated the symposium on Gavi activities.

Global Perspectives on GAPPD (the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea)

Carsten Mantel, World Health Organization, Global Action Plan for Pneumonia and Diarrhea (GAPPD), Switzerland

Robert Black, Johns Hopkins Bloomberg School of Public Health, USA

“We do have effective interventions to control and reduce morbidity and mortality of diarrhea and pneumonia. It’s just a matter of better coordinating the strategies.”

—Carsten Mantel, World Health Organization, GAPPD, Switzerland

Mantel discussed GAPPD’s integrated approaches for the prevention and control of pneumonia and diarrhea, while Robert Black reported on mortality trends and projections for rotavirus.

Every year an estimated 6.9 million children die before their fifth birthday, five million in their first year of life. Pneumonia and diarrhea are still the two major causes of child death in the world due to infectious disease, Black said. Together they account for 25 percent of global under-five mortality, and 75 percent of these deaths are in children under two years of age. Furthermore, the higher a country’s child mortality rate, the larger the proportion of deaths due to pneumonia and diarrhea, Black reported.

The global community united behind the Millennium Development Goals, and Goal Four aimed to reduce under-five mortality by two-thirds between 1990 and 2015. As this date approaches, global discussion has turned to the post-2015 targets, framed as the Sustainable Development Goals (SDGs), Mantel said.

Based on the draft SDGs, countries would commit to reducing under-five mortality to 25/1000 live births or less by 2030. This is similar to the previous commitment made under another global compact, the Promise Renewed for Child Survival, which aims to reduce under-five mortality to 20/1000 live births or less in all countries by 2035.

“These targets basically say the world should converge to have low child morality and to be equitable — to not leave countries behind,” Black said.

The Global Action Plan for Pneumonia and Diarrhea (GAPPD) developed by WHO and UNICEF, recognizes not only that reducing mortality from pneumonia and diarrhea a key to global progress on child survival, but also that these two conditions share much in common from a public health perspective. Most importantly, they share many control measures in common.
The GAPPD publication, “Ending preventable child deaths from pneumonia and diarrhea by 2025,” lays out a strategy to reach that goal. It recognizes that no single intervention can solve the problem.

Common interventions and treatment strategies for pneumonia and diarrhea include the promotion of breastfeeding and hand washing, zinc supplementation, adequate nutrition, and vaccines. In addition to these, the prevention and treatment of pneumonia requires oxygen therapy, and the treatment of diarrhea involves Oral Rehydration Therapy (ORS) and Vitamin A.

Learning from past experience, the GAPPD strategy takes into account the need to strengthen implementation of existing interventions; the persistent need for coordination within ministries and agencies, and among partners; the need for joint advocacy for maternal, child and adolescent health; and the understanding that changing behaviors takes time.

GAPPD provides a general framework for countries and partners to coordinate the scaling up interventions to protect, prevent and treat pneumonia and diarrhea. A number of countries are implementing the GAPPD strategy on a district level, and Mantel provided examples from Bangladesh, India, and Zambia.

- In Bangladesh, district level health services are being integrated for one-stop immunization; treatment; nutrition; water; and sanitation;
- In Zambia, the national launch of rotavirus vaccine is coinciding with focussed efforts to ensure the availability of essential medicines; improve water, sanitation and hygiene; and involve the private health sector, including sugar companies that run health clinics;
- In India, 56 priority districts in four states are preparing detailed plans to implement the strategy.

GAPPD has set its own goals for reducing preventable causes of child death. It aims to:

- Reduce mortality from pneumonia to less than 3/1000 live births by 2025
- Reduce mortality from diarrhea to less than 1/1000 live births by 2025, and
- Virtually eliminate deaths from these diseases by 2035

Black analyzed the possible contribution of rotavirus vaccine to achieving the GAPPD mortality reduction target for diarrhea deaths.

In 2013, an estimated 578,000 children worldwide died from diarrhea. To achieve the GAPPD target, this number would have to be reduced by 83 percent, or to no more than 100,000 global childhood deaths from all-cause diarrhea by 2025.

Of the 578,000 diarrhea deaths, an estimated 231,200 deaths were due to rotavirus. Black calculated that if one assumes rotavirus vaccine efficacy in high mortality settings of 60 percent, and 80 percent vaccine coverage in all countries, rotavirus vaccines would reduce the number of rotavirus deaths by 110,976. While a large reduction, this would still represent only 19 percent of the total reduction needed of deaths due to all-cause diarrhea.

“We absolutely must use the rotavirus vaccine but we must also make full use of other interventions such as ORS and zinc, and nutrition, breast feeding, water and sanitation... to achieve the mortality reduction that we want.”

—Robert Black, USA
Indian Perspectives on GAPPD

“We are keeping equity in the center-stage of the planning process.”
—Rakesh Kumar, India

Rakesh Kumar, Ministry of Health & Family Welfare, India

Vinod Paul, All India Institute of Medical Science

Rakesh Kumar, Joint Secretary of the Ministry of Health and Family Welfare laid clear the nature of the challenge India faces in combating childhood mortality from diarrhea and pneumonia. It is an issue of internal disparities.

While India has made important strides in reducing under five mortality, “The problem is that the progress is not uniform,” Kumar said.

The national rate of reduction was about 8.7 percent between 2009 and 2012, but the mortality rate in two states have increased, and today more than half of child deaths are concentrated in four high burden states - Uttar Pradesh, Bihar, Madhya Pradesh, and Rajashtan.

Given this situation, “We have rally sharpened our focus by identification of 184 high-priority districts across all 29 States,” Kumar reported. Within these districts, the focus is on girls, rural and urban poor, tribal and minority groups, and hard to reach areas. The goal is to scale-up all high impact interventions. “We are keeping equity in the center-stage of the planning process,” Kumar said.

The government is applying GADDP’s integrated approach to protect, prevent and treat both pneumonia and diarrhea, matching investments in scaling up interventions with the disease burden. “We lose about 1.4 million under-five children every year,” Kumar said. Some 52 percent are neonatal deaths, 23 percent are pneumonia, and 13 percent are diarrhea deaths. “It’s more than 80 percent of our under-five mortality because of these three causes,” he said.
“By inclusion of rotavirus vaccine, India has all of the ingredients for diarrhea disease control…we have ORS, we have zinc, we have breastfeeding, you name it. Therefore, there is no reason that we will not accelerate progress.”
—Vinod Paul, India

Vinod Paul, from the All India Institute of Medical Sciences, stressed the importance of scaling up the use of ORS and zinc. "We are sitting at ORS coverage of 43 percent, when Bangladesh is more than 70 percent, and in that country the contribution of diarrhea to child mortality is something like 1 percent. For us it is 13 percent," he said.

Recognizing the need to scale up use of ORS and other interventions, the government of India launched an Extended Intensified Diarrhea Control Fortnight from July 28 to August 8 2014.

Kumar described the activities: the government distributed ORS; established ORS-Zinc “Corners” in villages for intensive awareness generation; and held hand-washing demonstrations in schools. During the second on week, health facilities intensified their medical management of undernourished children.

Fortnight activities reached about 20 million children; one million were treated with zinc and ORS, and millions more were treated for malnourishment or were monitored for growth.

Paul praised the fortnight as a unique effort. “Most people perhaps saw zinc tablets for the first time, including doctors, even those in the public health system.”

Kumar and Paul emphasized the government’s approach of “making health a social movement,” an approach that applies equally to combatting diarrhea and pneumonia.

With 480 days to go—a last mile sprint to achieve MDG 4—Kumar said that India is focused on sustaining the efforts to reduce neonatal mortality, and accelerate immunization coverage and the introduction of new vaccines. This includes rotavirus vaccines, which the government recently approved, and which will be introduced in a phased manner in the universal immunization program.

SHARPENING FOCUS ON HIGH PRIORITY DISTRICTS

184 High Priority Districts (HPDs) across 29 States

Focus on:
- Girl Child
- Rural and Urban Poor
- Tribal & Minority groups
- Hard to Reach Areas
Gavi, The Vaccine Alliance, was set up in 2000, with primary funding from the Bill & Melinda Gates Foundation, and with the participation of other key donors, UNICEF, WHO, the World Bank, the vaccine industry, and civil society. Through Gavi, 73 low-income countries can apply for new and underused childhood vaccines. Gavi invests donor money in bulk vaccine purchases of vaccines, to deliver to countries at the lowest possible price.

Jon Pearman reported on Gavi’s genesis, growth and impact. Through its massive reach, GA-VI encourages competition by manufacturers and ultimately lowers vaccine price. For example, the price of the Hib vaccine — the first vaccine supported by Gavi — has come down from US$3.49 per dose in 2001 to US$2.04 in 2013.

Gavi invests 80 percent of its funds for procuring vaccines, 20 percent in countries’ health systems and program operations. Its provides vaccines for Measles, rubella, HPV, Meningitis A, Pneumococcal, Rotavirus, Pentavalent, Hib, Yellow fever, and Hepatitis B. As the number of vaccines in its program has increased, so, too has its funding needs. Cash outflows have grown from US$160 million per year on average between 2001 and 2005, to US$1.2 billion currently, and a projected US$1.8 billion from 2016 to 2020.
Gavi launched its rotavirus vaccine program in 2002, dedicating US$30 million to the Rotavirus Accelerated Development and Introduction Project (ADIP). Its goal was to support research and build the evidence base regarding rotavirus and rotavirus vaccines, in order to support improved recommendations and policy making. Merck and GSK were key partners in this effort. “They both more than matched the ADIP amount to carry out the Phase IV studio that lead to the WHO SAGE recommendation,” Pearman said.

From Gavi’s first licensure and introduction of rotavirus vaccine in Nicaragua from 2004-2006 to the first Gavi-funded introduction in sub-Saharan Africa in the Sudan in 2011, today 39 Gavi-eligible countries have approved rotavirus vaccines, and 32 have introduced them into their vaccination systems.
INTERACTIVE SESSION: ADVANCING CHANGE THROUGH EVIDENCE AND ADVOCACY

“We need to learn how to communicate in a simple and effective way.”
—Mathuram Santosham, Johns Hopkins University, USA

This interactive session led by the ROTA Council covered the basics of advocacy, posing dozens of multiple-choice questions to conference participants, who punched their answers into handheld consoles—and mostly got them right. The mission of the ROTA Council is to expedite the introduction of rotavirus vaccines as part of a comprehensive effort to control diarrheal disease through the use of scientific evidence and strategic communications.

Joining Naveen Thacker, Deep Children Hospital and Research Center, India, in leading the session, were ROTA Council members Mathuram Santosham, USA; Duncan Steele, USA; Lulu Bravo, Philippines; Julie Bines, Australia; and Tony Nelson, Hong Kong.

Thacker began with the basics: a definition of advocacy, advocates, and the tools of advocacy. “Advocacy is the act of supporting a cause, idea or policy and convincing the right people of its importance and the need to act on it.” While advocates can be anyone who actively supports the cause, discussion focussed on the role of scientists.

“You are experts, you know the policy, you know the subjects, the most compelling messengers are you,” Thacker said. “You have a special role to play, but be careful. Your job...
is to be credible and unbiased. If you look biased, nobody will believe you.”

Another problem that has come up in advocacy is the tendency of scientists to talk to policy-makers in the same way that they talk to each other, i.e., arguing detailed points rather than articulating and sticking to a clear main message.

“The scientific community was the biggest impediment to the introduction of Oral Rehydration Solutions (ORS) into countries, because it got involved in the minutia of the correct sodium content,” Santosham said. “We now know it was not the optimal ORS, but it would have saved millions of lives and we were delaying the process by confusing the decision makers.”

Effective advocacy requires the right audience, message, appropriate communication channels and materials and accurate information. The message itself must address the problem, the solution, a call to action, and convey the benefits of action.

“Most of us in this room are not great communicators, so let us get help on how to communicate,” Santosham said. He urged scientists to share their publications; to put forward positive messages to the press; and to realize that anti-vaccine people will attack no matter what, and that in most cases, responding only provides legitimacy to the attacker.

The take home messages for rotavirus vaccine advocacy:

1) Rotavirus vaccines not only prevent deaths but also hospitalizations and healthcare costs.

2) Rotavirus vaccines are safe.

3) Rotavirus vaccines are cost-effective and a wise investment.

4) Rotavirus vaccines are key to a comprehensive approach to diarrheal disease and are important to prioritize now.

5) Rotavirus vaccines have great potential for India.

Resources for advocacy: rotacouncil.org/toolkit and PATH’s rotavirus.org
CLOSING COMMENTS

Highlights of the 11th International Rotavirus Symposium

“There is absolutely no doubt that we have robust data to conclude that the available rotavirus vaccines have significantly reduced the disease burden... This not only prevents rotavirus diarrhea, it prevents all-cause diarrhea, which has a big implication for child survival programs.”

—M.K. Bhan, India

M.K. Bhan summarized the main points that had been raised and discussed throughout the three-day Symposium, and the extensive evidence base demonstrating the impact of vaccines against rotavirus, the leading cause of severe diarrhea in children under five all over the world.

He noted that two RV vaccines (Rotarix and Rotateq) have been administered to over 150 million children in 69 countries. Both vaccines have dramatically reduced disease and hospitalization wherever they are used, and eight Latin American countries have documented significant reductions in mortality. In addition, there is now robust data to conclude that the available rotavirus vaccines have significantly reduced the disease burden from all-cause diarrhea. Multiple economic analyses have documented the cost-effectiveness of RV vaccines at the current prices.

ROTAVAC, the new vaccine developed in India, demonstrated 56% efficacy in the first year and 55% efficacy up to 2 years of age against severe rotavirus. There were no safety concerns detected in the ROTAVAC trial, although the study was not powered to detect rare side effects. Based on this data, the vaccine has now been licensed in India, and the country has taken the lead in South Asia in implementing rotavirus vaccines, which will benefit all of its children.

In conclusion, Bahn declared: “The delegates strongly endorse the implementation of rotavirus vaccines in the UIP of all countries, especially in South Asia where the disease burden is high.”
C.K. Mishra, Additional Secretary, Department of Health & Family Welfare, India

“The government of India has outlined a mission of providing accessible, affordable and quality healthcare to all of its citizens, ... and we've taken a pledge that we will try and take every step that needs to be taken to ensure that if a death can be prevented, it shall be prevented.”

—C.K. Mishra, India

Additional Secretary Mishra praised the Symposium, saying, "Even though I'm not an expert, as a policy implementer and planner, symposiums like this give us a chance to understand things better...and frame a policy which is appropriate for the population.”

He summarized the Indian government's approach to rotavirus immunization and child health more broadly, noting that:

- Rotavirus is the leading cause of diarrhea deaths in the country, and accounts for about 1/5 of global childhood mortality from rotavirus. It causes 80,000 deaths every year. From a public health perspective, the number of cases of children suffering from diarrhea—almost 2.5 million a year—is a huge concern.

- India is committed to meeting MDG4 and reducing under-5 mortality by two-thirds. It has already set up a newborn care network across the country, and its current focus on preventing deaths due to pneumonia and diarrhea will further propel achievement toward this goal.

- The government of India will implement a phased introduction of rotavirus vaccine this year, hoping to reach 10 million children.

- Rotavirus immunization will build on the polio campaign, which has achieved seemingly insurmountable things, and built a network of disease surveillance across the country.

- The issue of the price of rotavirus vaccine is very relevant, not only for policy makers, but also for the pharmaceutical industry at large, as lower prices would make immunization more accessible. However, regardless of price, the government of India is “committed to providing this vaccine free of cost in our universal program.”

- As India rolls out the rotavirus vaccine, it will be looking to strengthen its entire childhood immunization program, which currently reaches on 75 percent of children. Rotavirus is one of four new vaccines that the government has decided to introduce.

In concluding, Mishra thanked the organizers of the conference, saying, “We do hope and expect that more and more partners will join us in this endeavor. What we need is your technical support. What we need is your guidance. What we need is the latest that is happening else-where in the world. The commitment and resolve is already here with us.”
SPEAKERS

Asad Ali
Aga Khan University
India

George Armah
Noguchi Memorial Institute
Ghana

Rashmi Arora
Indian Council of Medical Research
India

Narendra K Arora
The Inclen Trust
India

Naor Bar-Zeev
University of Liverpool
UK

Bernd Benninghoff
GlaxoSmithKline
Belgium

MK Bhan
India

Nita Bhandari
Society for Applied Studies
India

Julie Bines
Murdoch Childrens Research Institute
Australia

Robert Black
Johns Hopkins University
USA

Lulu Bravo
University of the Philippines
Philippines

Thomas Cherian
World Health Organization
Switzerland

Margaret Conner
Baylor College of Medicine
USA

James Crowe
Vanderbuilt University
USA

Stanley Cryz
PATH
USA

Nigel Cunliffe
University of Liverpool
UK

Margie Danchin
Murdoch Childrens Research Institute
Australia

Lucia de Oliviera
Pan American Health Organization
USA

Rajeev Dhere
Serum Institute of India, Ltd.
India

Mandeep Dhingra
Shantha Biotechnics
India

Jessica Fleming
PATH
USA

Jon Gentsch
Centers for Disease Control & Prevention
USA

Davinder Gill
Hilleman Labs
India

David Goldfarb
McMaster University
Canada

Michelle Goveia
Merck
India

Harry Greenberg
Sanford University
USA

Michelle Groome
University of the Witwatersrand
South Africa

Miren Iturriza Gomara
University of Liverpool
UK

Baoming Jiang
Centers for Disease Control & Prevention
USA

Jacob John
Christian Medical College, Vellore
India
<table>
<thead>
<tr>
<th>SPEAKERS cont.</th>
</tr>
</thead>
</table>
| **Gagandeep Kang**  
Christian Medical College, Vellore  
India | **Vinod Paul**  
AIIMS  
India |
| **VM Katoch**  
Indian Council of Medical Research  
India | **Jon Pearman**  
Gavi Alliance  
Switzerland |
| **Prasad Kulkarni**  
Serum Institute of India, Ltd.  
India | **Hari Pujar**  
Merck & Co.  
India |
| **Rakesh Kumar**  
Department of Health & Family Welfare  
India | **K Vijay Raghavan**  
Department of Biotechnology  
India |
| **Susana Lopez**  
National Autonomous University of Mexico  
Mexico | **Mathuram Santosham**  
Johns Hopkins University  
USA |
| **Carsten Mantel**  
World Health Organization  
Switzerland | **Hon. Jitendra Singh**  
Department of Science & Technology  
India |
| **Jelle Mathijnssens**  
University of Leuven  
Belgium | **Duncan Steele**  
Bill & Melinda Gates Foundation  
USA |
| **Sanjay Mehendale**  
National Institute of Epidemiology  
India | **Jacqueline Tate**  
Centers for Disease Control & Prevention  
USA |
| **CK Mishra**  
Department of Health & Family Welfare  
India | **Naveen Thacker**  
Child Health Foundation  
India |
| **Margaret Mokomane**  
National Health Lab  
Botswana | **Hon. Harsh Vardhan**  
Ministry of Health & Family Welfare  
India |
| **Trevor Mundel**  
Bill & Melinda Gates Foundation  
USA | **Lov Verma**  
Department of Health & Family Welfare  
India |
| **Anthony Nelson**  
Prince of Wales Hospital  
Hong Kong | **Timo Vesikari**  
University of Tampere  
Finland |
| **Fidele Ngabo**  
Ministry of Health  
Rwanda | **Melinda Wharton**  
Centers for Disease Control & Prevention  
USA |
| **Umesh Parashar**  
Centers for Disease Control & Prevention  
USA | **John Patton**  
NIAD  
USA |