THE SCIENTIFIC PROGRAM COMMITTEE WOULD LIKE TO THANK THE FOLLOWING FOR THEIR SUPPORT TOWARD THE ORGANIZATION AND SUCCESS OF THIS MEETING:

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Introduction

For three days in August 2018, 275 scientists, public health officials, policy makers, and government and industry representatives from more than 50 countries convened in Minsk, Belarus, to focus global attention on rotavirus, one of the biggest causes of child mortality worldwide. It is ubiquitous and affects children globally. After a brief incubation period, projectile vomiting and up to a week of acute watery diarrhea can result in rapid dehydration that leads to death.

Although rotavirus vaccines are utilized in 96 countries, 57 percent of all children—including over 70 million infants—still lack access to the lifesaving vaccines. Vaccine financing for lower middle-income countries and countries transitioning away from donor support is a major barrier to access. At the same time, two new rotavirus vaccines from India, ROTAVAC and ROTASIL, are entering the global market, promising to lower vaccine cost. Furthermore, researchers are developing novel approaches to enhance efficacy and coverage.

Opening the Symposium, Amy Finan, chief executive officer of the Sabin Vaccine Institute, posed the question of the day: “How can we reach more children with the vaccines? That’s really why we’re here today: to expand rotavirus impact, improving coverage and equity.”
The Symposium’s host, Natalia Zhukova, deputy minister of health and chief state sanitarian of Belarus, noted that the government of Belarus first recognized the severity of rotavirus in the early 1990s. With new data in hand, Belarus is evaluating whether to introduce rotavirus vaccine into its national immunization schedule. The forum itself, she said, would help in that decision. This, in turn, may set a precedent for more of Europe’s middle-income countries to do the same, none of which have yet introduced the vaccine.

Two opening presentations provided the context for in-depth discussions. Roger Glass, M.D., Ph.D., director of the Fogarty International National Center and associate director of NIH for Global Health, presented a broad overview of the issues. Jacqueline Tate, US Centers for Disease Control (CDC), speaking on behalf of Umesh Parashar, M.D., M.B.B.S., CDC, gave the Fourth Roger Glass Lecture, highlighting the impact of rotavirus vaccines thus far.

The Symposium was hosted by the Sabin Vaccine Institute, CDC, PATH, ROTA Council, the Fogarty International Center at the U.S. National Institutes of Health (NIH), the Government of the Republic of Belarus, and the Bill & Melinda Gates Foundation. For a complete listing of sessions and speakers, with links to presentations, see Addendum I.
Progress and Challenges

Over the past 45 years, “Amazing things have happened,” said Roger Glass, reviewing the history of rotavirus and rotavirus vaccines.

The first milestone was Ruth Bishop’s discovery of rotavirus 45 years ago followed by Timo Vesikari’s demonstration of the basic principles of live oral rotavirus vaccine in 1984. This was followed by the first rotavirus vaccine developed by Al Kapikian in 1998. The first International Rotavirus Symposium was held in 1984, which reached an eight-year hiatus brought about by possible rotavirus vaccine-associated intussusception (IS) in 1999. The Bill & Melinda Gates Foundation supported vaccine development beginning in the early 2000s, preceding the launch of two new rotavirus vaccines in 2006. In 2007, Gavi, the Vaccine Alliance (Gavi) supported rotavirus vaccine introduction in low-income countries, which was followed by the World Health Organization (WHO) recommendation of including rotavirus vaccines into the national immunization program of all countries in 2009.

Since 2006, the introduction and use of the pentavalent RotaTeq (RV5) produced by Merck & Co., Inc. and the human monovalent ROTARIX (RV1) vaccine produced by GlaxoSmithKline Biologicals (GSK) has led to steep declines in rotavirus-associated deaths, disease and hospitalizations. The Global Rotavirus Surveillance Network (GRSN), which has 82 participating countries, reported a 40 percent decrease in the prevalence of rotavirus in countries that introduced the vaccine.

Importantly, there have been dramatic declines in rotavirus deaths. In 1985, of about 4 million annual diarrheal deaths in children under-five worldwide, 800,000 were due to rotavirus. By 2012, there were less than 1 million diarrheal deaths with 250,000 due to rotavirus. These numbers have dropped even further, with 215,000 rotavirus-related child deaths in 2016, according to the WHO.

Tate noted that the benefits of rotavirus vaccines extend further by reducing hospitalizations for severe rotavirus and rotavirus-related seizures. In the United States (US), for example, use of rotavirus vaccines led to declines in both all-cause gastroenteritis hospitalizations and rotavirus hospitalizations, not only for children under-five years of age, but also for children five to 17 years of age and adults 18 to 64 years of age. In addition, several studies have demonstrated a reduced risk of childhood seizures associated with rotavirus vaccination with up to a 24 percent reduction according to one study.

As of August 2018, 96 countries have introduced rotavirus vaccines, including 46 low-income countries supported by Gavi, with an additional 16 Gavi countries planning its introduction.

However, many middle-income countries face financial challenges and have yet to introduce rotavirus vaccines. Although the largest number of unvaccinated children globally reside in middle-income
countries, these countries find themselves both ineligible for foreign aid programs and unable to afford vaccines at full cost, according to Craig Burgess, M.D., senior technical officer, JSI Research and Training Institute Inc.

Inconsistent vaccine efficacy (VE) also contributes to inequities in protection. The current vaccines are less effective in low-income countries with high rotavirus mortality rates than in high-income countries with low rates. A meta-analysis found that in high-income countries, such as the US and Finland, VE against severe rotavirus-related hospitalization ranges from 80 to 100 percent whereas in low-income countries in Africa and South East Asia, VE is just 45 to 70 percent. According to Glass, the combination of a VE of about 50 percent in low-income countries and vaccine coverage rates of about 70 to 80 percent would reduce severe rotavirus disease only by about one-third — leaving roughly 63 percent of severe cases unchanged by vaccination in many countries in Africa and Asia.

According to Glass, while the progress in rotavirus vaccination since 2006 means that approximately 34 million children are vaccinated for rotavirus every year, “it leaves nearly 100 million children who are unvaccinated. We have a long way to go.”

Against this backdrop, the Symposium considered crucial issues, including:

- The most recent calculations of disease burden and vaccine impact
- Increasing impact and equity by expanding coverage, including through two new vaccines that might improve vaccine efficacy in low-income countries
- Advances in rotavirus immunology and virology
- Barriers and enablers of vaccine introduction and impact
Global Burden of Disease and Vaccine Impact

Christopher Troeger, M.P.H., researcher, Institute for Health Metrics and Evaluation (IHME), reported on the burden of rotavirus disease and the impact of rotavirus vaccine as determined by IHME’s Global Burden of Disease (GBD) study in 2017. The GBD is a systematic, scientific effort to quantify the comparative magnitude of health loss from all major diseases, injuries and risk factors, globally, regionally and at country levels by sex and age group. It draws on the expertise of over 1,300 collaborators in 114 countries to analyze data and provide country-specific insights.

Using its in-depth methodology, the 2017 GBD found that diarrhea was the third leading infectious cause of under-five mortality globally, responsible for 533,800 deaths in 2017. Rotavirus is the leading cause of diarrhea mortality both among children under-five and for all ages. In 2017, rotavirus was responsible for 35 percent or 185,390 deaths. Sub-Saharan Africa bears the biggest burden, with more than 125,000 deaths every year, followed by South Asia, where more than 30,000 children under-five die annually from rotavirus.

Diarrhea mortality is largely preventable and is highly influenced by poor water, sanitation, hygiene infrastructure, childhood undernutrition and existing rotavirus vaccines, which have prevented tens of

![Rotavirus Deaths and Mortality Rates](image)

Courtesy of Chris Troeger, Institute for Health Metrics and Evaluation, University of Washington
thousands of deaths. Indeed, GBD also found that under-five diarrhea mortality has decreased by 70 percent since 1990 and by 44 percent since 2007. It is estimated that in 2016, rotavirus vaccine averted 28,000 deaths among children under-five. Yet, this represents just 15.3 percent of potentially avertable deaths and full use of the vaccine could have prevented 83,200 deaths in 2016 alone.

Likewise, Adam Cohen, M.D., M.P.H., Immunization Vaccines and Biologicals at WHO, reported a 40 percent decline in the overall prevalence of rotavirus from 2008 to 2016 in countries that have introduced the vaccine and participate in the Global Rotavirus Surveillance Network (GRSN).

As both morbidity and mortality caused by rotavirus declines, the Global Pediatric Diarrhea Surveillance (GPDS) network is working to understand the other major causes of pediatric diarrhea. Surveillance of both rotavirus and pediatric diarrhea is critical for the generation of data that can inform on all aspects, from national vaccine policy to priority-setting for the development of vaccines that target other causes of childhood diarrhea, such as *Shigella* and norovirus — both of which have vaccines in development.

Preliminary GPDS results in 2017 show that while the largest percentage of diarrheal disease (more than 25 percent) is attributable to rotavirus, adenovirus, norovirus and *Shigella* are each responsible for over five percent of diarrheal disease, with another 12 pathogens accounting for the remaining fractions.

**Global Pediatric Diarrhea Etiology (2017)**

*Preliminary data*  
*Courtesy of Adam Cohen, World Health Organization*
Increasing Vaccine Impact and Equity: Expanding Coverage

The Symposium discussed several paths to increasing vaccine impact and equity. First by expanding coverage with existing vaccines, including the two new vaccines from India, and secondly by understanding and addressing the reasons behind lower vaccine efficacy in high mortality, low-income settings. Thirdly, the key issues of vaccine cost and supply, and other barriers as well as enablers that influence country decision-making were addressed.

Vaccine Impact: Two New Vaccines to Increase Coverage in Asia and Beyond

Two new vaccines, both developed in India, have been pre-qualified by the WHO for global use in national immunization systems. [Editor’s note: ROTAVAC was pre-qualified in January 2018. ROTASIIIL was prequalification one month after the Symposium, in September 2018.]

Several Symposium participants noted that increasing demand for rotavirus vaccines, coupled with the high cost of current vaccines, made the WHO prequalification of ROTAVAC in January 2018 and the pending prequalification of ROTASIIIL a welcome development. Both vaccines are being used ever more widely in India, being or have been evaluated in African countries, and are less expensive than the two original rotavirus vaccines, ROTARIX and RotaTeq. India’s public health system is using ROTAVAC in nine states, covering about a third of the Indian birth cohort since mid-2016. ROTASIIIL has been used in one state in the nation since 2017. For both vaccines, it is too early to measure post-introduction impact.

ROTAVAC is produced by Bharat Biotech, a 22-year-old Indian company that holds 60 patents and has developed the only WHO prequalified typhoid conjugate vaccine. ROTAVAC’s early development was supported by the NIH and CDC. Indian researchers continued development, resulting in a microdose formulation—a single dose of 0.5 ml, compared to other rotavirus vaccines that are 1.5 to 2.0 ml per dose. The formulation is packaged in a box slightly larger than a cell phone, holding up to 300 doses, which greatly reduces demands on the cold chain, as explained by Bharat Biotech’s Sai Prasad, president of quality operations.

Clinical trials, including a large, three-year Phase III clinical trial, later proved its safety and demonstrated efficacy of about 55 percent. Meanwhile, there is an ongoing 100,000 subject safety study and a birth dose study is underway to assess a possible neonatal vaccine schedule. ROTAVAC is also being evaluated in Vietnam and has been introduced in Palestine with the support of the Rostropovich Vishnevskaya Foundation as well as a 150,000-dose donation by Bharat Biotech.
Since its launch in India in 2016, Bharat has produced nearly 50 million doses of this live, oral vaccine. “We do have a manufacturing capacity of about 200 million doses,” Prasad said, “but again, it doesn’t transfer overnight. We just need advanced notice of about three to four months to make it happen.”

ROTASIIL, another promising vaccine now available globally, was developed by the Serum Institute, which is perhaps best known for the meningococcal conjugate vaccine, MenAfriVac. ROTASIIL is a live, attenuated pentavalent vaccine developed from five human-bovine reassortant strains received from the NIH.

To help mitigate cold chain-related challenges, ROTASIIL was developed to be thermostable and can be stored at 37 degrees Celsius for 250 days, as reported by Serum Institute’s Sajjad Desai, M.D. Phase III clinical trials in India demonstrated vaccine efficacy of 60.5 percent against very severe rotavirus diarrheal disease and 36 percent against severe rotavirus diarrheal disease. Since launching the vaccine in the state of Jharkhand, India in April 2018, more than 1 million doses have been distributed. Meanwhile, two large Phase IV clinical studies are planned.

**Vaccine Impact in Africa**

Within Africa, the picture is slightly different, as reported by Karen Kotloff, M.D., on behalf of the Vaccine Impact on Diarrhea in Africa (VIDA) study. Since rotavirus vaccine introduction, the incidence of mild and severe diarrheal disease is decreasing and causative agents are shifting. As rotavirus recedes, the relative contribution of other pathogens is rising, e.g. Cryptosporidium, Campylobacter and *Shigella*.

The VIDA study showed that infants sickened by rotavirus and other diarrheal diseases have stunted growth compared to infants who were not, and that the odds of dying are 8.5 times higher in affected babies than in healthy babies for 60 days after an episode. In almost every area where it has been introduced in Africa, rotavirus vaccines have reduced the incidence of diarrhea. New studies show that Malawi experienced a 31 percent decline in diarrheal mortality post-vaccine introduction and that the vaccine was 34 percent effective against all-cause diarrheal mortality.

Furthermore, Sammy Khagayi, Kenya Medical Research Institute, reported that the monovalent rotavirus vaccine, introduced in July 2014, was shown to have a vaccine effectiveness of 58 percent for children.

**In essence, what we have seen or what we found in Kenya is that the monovalent rotavirus vaccine offers significant protection against this rotavirus-associated hospitalization.**

—SAMMY KHAGAYI
Kenya Medical Research Institute
who received at least one dose. The only exception to these positive outcomes appears to be in The Gambia. For reasons that are not yet understood, the vaccine has had very little impact there and the incidence of diarrhea actually increased, Kotloff explained.

However, across much of the continent, rotavirus vaccines are saving lives. Approximately 75 percent of countries (34 countries) in the African region use rotavirus vaccine, the highest proportion of any WHO region. In just the past two years, five additional African countries have introduced the vaccines: Lesotho, Cote D’Ivoire, Uganda, the Democratic Republic of Congo and Benin. Introduction is expected in Nigeria, the country with the highest rotavirus mortality rate (55,000 deaths annually), in 2019.

The Opportunity and Challenge of Europe’s Middle-Income Countries

Danni Daniels, WHO Regional Office for Europe, reported on rotavirus for the European region. Nearly one-third of its 53 countries have introduced rotavirus vaccine nationwide.

When viewed through the lens of income categories, a different picture emerges. Nearly 40 percent of the region’s 32 high-income countries have introduced the vaccines, including universal vaccination in Austria, Belgium, Finland, the United Kingdom and more recently, Germany. However, none of the region’s middle-income countries, for whom donor support is unavailable, have done so.

Among them, Belarus is actively considering rotavirus vaccine introduction. The country experiences about 20,000 cases of rotavirus annually, with the number of cases increasing by about ten percent a year, according to Irina Glinskaya, deputy chief medical officer, State Institution “Republican Center for Hygiene, Epidemiology and Public Health.” Approximately 90 percent of cases are in children under six years of age, and 22 percent are in children under one year. The government is currently deciding which vaccines to introduce to minimize disease risks in the country. Along with rotavirus, vaccines for pneumococcus, varicella, meningitis and human papilloma virus (HPV) are under consideration.

Meanwhile, five of the region’s seven lower-income countries eligible for donor support have introduced the ROTARIX vaccine: Armenia, the Republic of Moldova, Georgia, Uzbekistan and Tajikistan. All of these countries also participate in the region’s Global Rotavirus Surveillance Network (GRSN) along with Azerbaijan and Ukraine. GRSN monitors sentinel surveillance of hospitalized cases of acute diarrhea among children less than five years of age, obtaining clinical epidemiological and laboratory data as well as genotype information on a subset of specimens.

Tajikistan’s Anvar Nazurudinov, M.P.H., deputy director, State Institution “Republican Center of Immunoprophylaxis,” reported that the percentage of rotavirus-related hospitalizations in children under-five years went from 42 percent before introduction to 28 percent after vaccine introduction. Similarly,
in Uzbekistan, there was a 50 percent decrease in the proportion of rotavirus infection in children hospitalized with diarrhea, from 26 to 11 percent, as reported by Renat Latipov, M.D., Ph.D., Research Institute of Virology, Uzbekistan.

GRSN data has provided powerful evidence for national vaccine introduction decision making. Both Armenia and the Republic of Moldova, for example, relied on this data in deciding to introduce rotavirus vaccines. The data enabled rotavirus disease burden estimates and later demonstrated the impact of vaccine introduction.

A third regional surveillance network, EuroRotaNet, tracks rotavirus strain diversity data, both pre- and post-vaccination, in 14 European countries. Following more than ten years of surveillance, 70,000 rotavirus strain samples have been collected and 65,000 of those have been genotyped.

Post-vaccine introduction has seen a continuous decline in the proportion of the G1P[8] genotype (the strain used in ROTARIX), and the surveillance system has detected no evidence that vaccination programs are driving the emergence of rotavirus vaccine escape mutants. Rather, “The vaccine works like natural infections,” protecting children at a young age from severe disease, reported Miren Iturriza-Gomara, M.Sc., Ph.D., University of Liverpool.

![Genotype Distribution Pre- and Post-Rotavirus Vaccine Introduction, 2013–2017]( Courtesy of Anvar Nazurdinov, State institution Republican Center of Immunoprophylaxis, Tajikistan)
Expanding Vaccine Impact and Equity in High-Mortality Settings

Scientists around the world—and many attending the Symposium—are working to deepen an understanding of how to increase the efficacy of rotavirus vaccines and lower their cost. This research extends from new approaches to vaccine development to basic science and field research assessing factors potentially related to vaccine efficacy.

All rotavirus vaccines currently in use are orally administered live vaccines. Although they significantly lower the burden of rotavirus disease, they have lower efficacy in low-income, high mortality countries, begging the question of whether another approach would be more effective. Pursuit of more efficacious vaccines across low-income settings has helped fuel the development of new vaccine approaches.

New Vaccine Approaches

The vaccine pipeline is diverse, including an attenuated live oral birth dose (neonatal) and parenteral vaccines that are non-replicating and injectable. Carl Kirkwood, Ph.D., senior program officer, Bill & Melinda Gates Foundation, noted that any new vaccines need to match the performance of RotaTeq and ROTARIX. If successful, they would offer domestic manufacturing options, add to the supplier base, promote competition and possibly better efficacy than current vaccines.

A Neonatal Vaccine: Julie Bines, M.D., Murdoch Children’s Research Institute (MCRI), reported on a randomized, double-blind, Phase III clinical trial of the human neonatal rotavirus vaccine, RV3-BB. The trial was conducted in Indonesia, where 31.4 percent of infant deaths were due to diarrhea, and up to 61 percent of diarrhea cases among children under-five were caused by rotavirus.

RV3-BB is designed to target rotavirus from birth. It was developed from an asymptomatic strain of rotavirus first isolated from healthy newborns in obstetric hospitals in Australia in 1975. As RV3-BB was derived from the neonatal rotavirus strain G3P[6], it has potential to target the P[6] rotavirus protein that circulates widely in Africa and parts of Asia, suggesting that RV3-BB may work well in those regions.

As Bines explained, in many low-income countries where existing rotavirus vaccines have more limited efficacy, the first episode of rotavirus also occurs earlier in life than in higher income countries. Additionally, as more women in low-income countries give birth in hospitals, a birth dose offers the opportunity to increase vaccine coverage. A birth dose may also lessen safety concerns regarding the risk of IS, a condition which creates a serious bowel blockage and occurs naturally in infants, with a peak around six to 12 months of age. Providing the first dose of a rotavirus vaccine at a time when naturally occurring IS is very rare has a potential safety advantage.
The Indonesian clinical trial used RV3-BB manufactured by the Indonesian pharmaceutical company Bio Farma. In this trial, 550 babies received the placebo, 549 received a three-dose neonatal schedule beginning within the first five days of life and 550 received a three-dose infant-schedule beginning at eight weeks. After 18 months, the neonatal vaccine schedule yielded 75 percent efficacy and the infant vaccine schedule yielded 51 percent efficacy.

Safety results were also strong, with the incidence of adverse events similar across all three groups and no episodes of IS within the 21-day risk period after any dose of vaccine or placebo. The results add to Phase I and II trial results that demonstrated safety, immunogenicity and protection against a variety of rotavirus strains. A study is ongoing in Malawi to assess the optimal dose of vaccine to produce an immune response in an African population.

**The Promise of Non-Replicating Rotavirus Vaccines (NRRVs):** Although the reasons for lower rotavirus vaccine efficacy in low-income countries are not fully understood, parenteral vaccines could bypass several suspected causes related to oral vaccines.

As noted by Michelle Groome, Ph.D., M.S., D.C.H., University of the Witwatersrand, injected vaccines avoid any possible interference by either rotavirus antibodies in breast milk or transplacentally acquired maternal rotavirus antibodies. They also avoid potential interference related to the co-administration of oral polio vaccine. Furthermore, as injectable vaccines bypass the need for replication in the gut, they may prove safer than oral vaccines, whose replication is suspected to be at the root of the rare case of rotavirus vaccine-associated IS. A further benefit is the likely lower cost of manufacturing parenteral vaccines.

The most advanced parenteral candidate is the recombinant subunit vaccine P2-VP8. Initially developed by the NIH and then further advanced by the Seattle-based organization PATH, P2-VP8 has undergone its most rigorous test yet, as reported by Groome. A trivalent formulation of the vaccine was tested in a double-blind, randomized placebo-controlled, descending-age, dose escalation study between March 2016 and January 2018.
The study found strong tolerability, good safety and high immunogenicity in adults, toddlers and infants. Three doses proved more effective than two and protection with the trivalent vaccine was stronger than that provided by the original monovalent version. Following this, researchers plan to explore prime-boost regimens that combine the oral rotavirus vaccines and the P2-VP8 vaccine.

In addition to the P2-VP8 vaccine update, participants heard a report on a VP6 subunit rotavirus vaccine and the rationale for using an inactivated whole rotavirus as a vaccine (IRV). Baoming Jiang, CDC, noted that IRV formulations are highly heat stable and potent in vitro and have shown strong proof of concept in animals, proving highly immunogenic and protecting piglets against rotavirus. Clinical development of IRVs are in progress at several centers, including the Serum Institute in India and Chongqing Zhifei Biological Products Company in China.

**Basic Research: Immunology and Virology of Rotavirus**

Delivering the Ruth Bishop Lecture, Ulrich Desselberger, M.D., University of Cambridge, reviewed basic research, including past and recent insights into viral structure and the function of various structural and non-structural proteins. In addition insights regarding its replication in enteroids, rotavirus RNA assortment and packaging, rotavirus pathogenesis, human neutralizing antibodies and novel rotavirus vaccine candidates in development were discussed.

Other presenters highlighted the potential of innovative new tools to deepen the scientific understanding of rotavirus. Mary Estes, Ph.D., Baylor College of Medicine, explained how scientists are using intestinal stem cells obtained from biopsy specimens from bariatric surgery patients to develop human intestinal enteroid (HIE) cultures. These cultures can be coaxed to mature into different epithelial cell types normally found in several parts of the intestine and are easily infected by human rotavirus.

Estes noted a range of important public health questions that can be explored using these cell cultures, including the study of innate immune responses to rotavirus, genetic differences in histo-blood group antigen expression and susceptibility to vaccine viruses as well as various rotavirus strains. In addition, “We think we can use them to study vaccine interference, coinfections with pathogens, and in the future to test probiotics,” she said. The researchers also co-infected the cultures with rotavirus and live polio and found that not only does co-infection inhibit rotavirus replication, but it actually increases polio replication.

Harry Greenberg, M.D., associate dean for research, Stanford University School of Medicine, is also using HIE cultures in his search for a correlate of protection, which could be identified through a simple blood test to determine whether a new vaccine is likely to work, thereby lowering the cost of clinical trials in vaccine development. Using HIE cultures, Greenberg identified numerous human anti-VP8 antibodies that neutralize rotavirus, confirming such neutralizing activity within a human cell culture for the first time. This perhaps brings the holy grail of a correlate of protection one step closer.
Delving into Factors Impacting Efficacy

Researchers are also going through the results of clinical trials and setting up novel experiments to search for clues that may explain lower efficacy in high mortality settings. Among the studies presented were those that addressed nutritional status, host genome factors and differences in the gut microbiome.

**Nutritional Status in Kenya:** In his analysis of vaccine effectiveness (VE) in Kenya, Sammy Khagayi, Kenya Medical Research Institute, found evidence of significant VE among well-nourished children, but none for those who were stunted and underweight. When his team looked at children with normal weight, VE was a significant 78 percent. However, for children who were either moderately or severely malnourished in terms of underweight, the vaccine had no significant impact. Similarly, in children of normal height for age, VE was 73 percent, while in children who were either moderately or severely stunted, VE was not statistically significant.

“We thought that this may explain, in part, the lower efficacy in low- and middle-income settings compared to high-income settings,” Khagayi said.

**Secretor Status:** Histo-blood group antigens (HBGAs) are expressed not only on the surface of red blood cells, but also on cells lining the gut. The presence of specific HBGAs on the gut mucosa, detectable in saliva, appear necessary for rotavirus to bind to and thus, infect intestinal cells. Therefore, some scientists hypothesize that HBGA antigens play a role in vaccine take. One classification of HBGAs is based on the genes that determine secretor status. Researchers investigated whether a person’s secretor status impacts vaccine take (indicating successful vaccination) and came up with conflicting results.

George Armah, Ph.D., senior research fellow, Noguchi Memorial Institute for Medical Research, University of Ghana, found that among 166 Ghanaian children who had been vaccinated as infants with RV1, secretors were 3.2 times more likely to experience strong vaccine take than non-secretors. Following vaccination, about 41 percent of secretors seroconverted compared with 13 percent of non-secretors. He concluded that the likelihood of vaccine take and efficacy for any particular rotavirus vaccine may differ across regions based on differences in HBGA distributions across populations.

Benjamin Lee, University of Vermont, presented on the effect of secretor status and susceptibility to infection with Rotarix vaccine.
Meanwhile, a study by Benjamin Lee, M.D., University of Vermont, examined vaccine take in 174 vaccinated children and found that neither of the two indicators of vaccine take appeared to be significantly influenced by secretor status. “At least for this population, we believe that secretor status is unlikely to mediate reductions in vaccine uptake, although it does appear to have an effect on rotavirus IgA immunogenicity,” Lee concluded.

**Microbiome Impacts:** Vanessa Harris, M.D., Amsterdam Medical Center, shared research that indicates certain types of bacteria found in the gut, known as Bacteroidetes (such as Prevotella), correlate with low vaccine response, while other bacteria, known as gamma proteobacteria (which include *E. coli*, *Salmonella*, *Shigella* and *Campylobacter*), correlate with high vaccine response.

However, none of these studies strongly indicated causation rather than simple correlation. Therefore, Harris and her team carried out a proof of principle study in 63 healthy adult males in the Netherlands. They used antibiotics to modulate the microbiome prior to rotavirus vaccination. One volunteer group was treated with Vancomycin, a narrow-spectrum antibiotic that depletes gram-positive bacteria but produces a bloom in proteobacteria (the bacteria previously associated with stronger vaccine take). A second group of men received broad spectrum antibiotics that obliterated their microbiome and a third group received no antibiotics.

Researchers found that although antibiotics did not alter absolute anti-RV immunoglobulin A (IgA) titers, the group that received Vancomycin experienced a boost in rotavirus vaccine immunogenicity seven days after vaccination. While acknowledging the study’s limitations, Harris concluded, “This proof of principle showed that modulation of the microbiome is capable of altering rotavirus vaccine immunogenicity... This is an important finding that we can build upon.”

Other studies, including one on potential vaccine interference from breast milk antibodies, found no clear relationship to vaccine take. Thus, while tantalizing hints continue to emerge, the main reasons for the discrepancies in VE remain elusive. In the meantime, scientists and policy makers are pursuing other paths to improve country adoption of rotavirus vaccines.

Although the implementation of rotavirus vaccines across the globe has led to dramatic reductions in rotavirus mortality, rotavirus remains one of the most important etiologies of lethal diarrhea in infants in low- and middle-income countries. That’s likely because the vaccines are just underperforming in settings where rotavirus mortality is higher.

—Vanessa Harris, M.D.
Amsterdam Medical Center
Barriers and Enablers of Vaccine Introduction and Impact

The barriers examined were cost-effectiveness, understanding of vaccine safety, vaccine hesitancy and perceptions of rotavirus disease severity within a country. In addition to improving vaccine efficacy and lowering vaccine cost, other enablers include strategies to strengthen data capture, improve system coordination and planning, raise community awareness and strengthen country ownership.

Cost-Effectiveness, Supply and Price

Based on a new analysis, Frédéric Debellut, health economist, PATH, reported that over the next 10 years, rotavirus vaccination would avert 582,000 deaths. However, for countries not currently utilizing rotavirus vaccines, an understanding of their cost-effectiveness is often paramount.

A number of presentations reviewed recent cost-effectiveness studies. These included a study of cost-effectiveness in Gavi countries as well as perspectives from several countries at different levels of economic development.

Cost-Effectiveness in Gavi Countries: Debellut reviewed the cost-effectiveness data for low-income countries eligible for Gavi support. He noted that rotavirus vaccine is highly cost-effective for Gavi countries overall and in each Gavi-eligible country.

One analysis examined rotavirus vaccination in 73 Gavi countries. It projected the costs and benefits of vaccination across 10 birth cohorts, from 2018 to 2027, compared to no vaccine. It assumed a constant price for the vaccine over the ten years, using the Gavi price per dose of US$2.02 for ROTARIX, US$3.20 for RotaTeq and US$1.00 for ROTAVAC.

It found that rotavirus vaccination remains cost-effective in Gavi countries, with an average cost per DALY averted of US$247, or 0.15 times the GDP per
capita. Economic benefits include some US$771.7 million in health care cost savings to country governments and US$1.1 billion in health care cost savings to society.

Additionally, over the ten years assessed, routine nation-wide rotavirus vaccination in all Gavi countries would avert around 165.5 million cases, consisting of 82.7 million outpatient visits, 8.2 million hospitalizations, 14.7 million DALYs and 582,000 deaths from rotavirus in children. The greatest number of deaths averted would be in Africa (361,305 deaths or 62.1 percent of the total), followed by Southeast Asia (132,409 deaths or 22.8 percent of the total).

**Cost-Effectiveness in Different Country Contexts:** Countries wrestling with whether to introduce rotavirus vaccine need a solid understanding of its cost-effectiveness, whatever their level of economic development.

Three speakers presented the results of cost-effectiveness studies in three different economic contexts. Justice Nonvignon, Ph.D., University of Ghana, reported on a cost-effectiveness study of rotavirus in Ghana, whose economy has been growing rapidly and is preparing to transition away from Gavi support.

Munkh-Erdene Luvsan, MBA, M.P.H., Ph.D., Mongolian National University of Medical Sciences, reported on rotavirus vaccination in Mongolia, which recently transitioned from Gavi support. John Farrow, M.Sc., Ph.D. candidate, London School of Hygiene & Tropical Medicine, reported on a cost-effectiveness study of 21 non-Gavi-eligible middle-income countries in Europe.

In all cases, the speakers indicated that cost-effectiveness depended heavily on the vaccine procurement price and most assessments assumed a price of either about US$6.00 to 6.50 for middle-income countries or the Gavi price of approximately US$2.00 per dose. However, these prices may be lower than what middle-income countries actually pay in today’s market. All three studies reported a high level of cost-effectiveness, with substantial returns to government and society over a multi-year period. Notably, lower price assumptions yielded cost-savings on a large scale.

**UNICEF Perspective of Reducing Vaccine Price:** The United Nations International Children’s Emergency Fund (UNICEF) supplied vaccines worth more than US$1.3 billion in 2017, amounting to about 2.4 billion doses, representing almost 35 percent of children vaccinated globally, and managing about 2,500 vaccine shipments a year. “So, it’s a really huge task,” said Gideon Chelule, contracts manager, UNICEF.

According to Chelule, the key to lower prices is to match supply with demand. Chelule acknowledged the current widespread mismatches between rotavirus vaccine demand and supply, exacerbated by the fact that one RV1 manufacturer monopolizes almost 90 percent of the market. Chelule had several suggestions for correcting the imbalance between supply and demand. He urged governments to look at all products equally, rather than setting a firm preference for one in particular. Being able to source different products from different producers, including the lower cost newly prequalified India vaccines, would “mitigate others’ lead time delays and product failures,” he said.
Furthermore, countries need to make longer-term commitments for vaccine purchases, backed by multi-year forecasting and budgeting. The power of long-term, high-volume agreements was evident in the pricing obtained by Gavi, where an initial price of US$7.00 per dose eventually came down to US$2.00 per dose.

However, middle-income countries acting independently do not have the necessary volume demand. Therefore, “We need to move some of these middle-income countries to fully procure through either UNICEF or other mechanisms, such as regional procurements,” he said.

Some countries are moving in that direction. Montenegro, an upper-middle-income country, is trying to establish multi-year joint procurement for southeastern European countries and establish a Regional Immunization Technical Advisory Group (RITAG), according to Senad Begic, M.D., Ph.D., deputy director, Institute for Public Health of Montenegro. Countries higher up the income ladder can also benefit from such arrangements. For example, Estonia and Latvia began a joint procurement for rotavirus vaccine in 2016, according to Natalia Kerbo, Health Board, Republic of Estonia.

**Achieving Financial Stability in National Immunization Programming:** Meanwhile, Georgia provided an example of how to achieve financial sustainability in vaccine programming. Vladimer Getia, National Center for Disease Control and Public Health, explained the country’s legislative framework supporting immunization. It provides a centralized purchasing mechanism that utilizes UNICEF, which is also backed by a national tender process if UNICEF is unable to meet the country’s demand. The tender process uses an electronic unified procurement system.

The national immunization program has a special budget, and it plans new vaccine introductions four years in advance. Between 2012 and 2018, its immunization budget increased five times and the national health budget increased three times, supporting a universal health program. Georgia has also overcome challenges to financial sustainability posed by the need to use foreign currency, a requirement of vaccine companies. However, fluctuations in foreign currency exchange rates can undercut the government’s purchasing power. To balance out this risk, Georgia pre-purchases vaccines one year in advance.

However, cost-effectiveness and vaccine price are not the only concerns countries must consider as they decide on vaccine introductions, and a number of presentations explored the range of enablers and barriers to new vaccine introduction and impact.

**New Studies Assess Safety Concerns**

Jacqueline Tate, CDC, reviewed the history and current assessment of rotavirus vaccine association with IS, a potentially dangerous blockage of the bowel. It is a naturally occurring disorder in infants, with background rates that vary by region, for example, less than 10 per 100,000 infants in Bangladesh and more than 300 per 100,000 infants in Vietnam.
However, after the world’s first rotavirus vaccine, Rotashield, was introduced in the US, it was found to cause one excess case of IS for every 10,000 vaccinated children. This forced rotavirus vaccine introduction and development to shift gears. Rotashield was withdrawn from the US market less than a year after its introduction, as safety concerns overshadowed consideration of the benefits.

It was another seven years before ROTARIX (RV1) and RotaTeq (RV5) were approved for global use following extensive clinical trials. The trials showed no increased risk within 31 days of either dose of two doses of ROTARIX and no increased risk within 42 days of any dose of RotaTeq.

Since then, other evidence regarding IS has been collected. In Africa, where the case-fatality rates of naturally occurring IS are the highest in the world (10 percent), studies in seven countries have shown no increased risk of IS following rotavirus vaccination. In Germany, the number of IS cases have declined after rotavirus vaccine introduction, “falling from an average of 44 cases per year to 38,” reported Judith Koch, M.D., Robert Koch Institute.

On the other hand, a few post-licensure studies have shown a very low-level of risk in several high- and middle-income countries. They have detected one to six excess cases per 100,000 children vaccinated with both ROTARIX and RotaTeq, as reported by Gagandeep Kang, M.D., Ph.D., Christian Medical College.

Still, the benefits of vaccination, including decreases in diarrhea deaths and hospitalizations, far outweigh the possible short-term risk of IS. Extensive post-licensure studies in the US, Mexico, England, Brazil, Africa, Singapore and Australia have led the WHO’s Global Advisory Committee on Vaccine Safety and national regulatory agencies as well as advisory committees in many countries to unanimously reaffirm the recommendation for use of rotavirus vaccine.

New vaccines are also being scrutinized for any possible IS risk. Kang reported that the ROTAVAC clinical trial detected no increased risk among vaccinated infants. However, the trial was not large enough to detect a small risk, and post-licensure studies are continuing to monitor for IS associated with either ROTAVAC or ROTASIL.
The Problem of Perception

As the burden of disease in middle-income countries does not result in many deaths, convincing policy makers to purchase the rotavirus vaccine may require new approaches to advocacy, as noted by Samir Saha, Ph.D., Child Health Research Foundation, Dhaka Shishu Hospital.

This was the case in Bangladesh. In the Dhaka Shishu Hospital, the country’s largest pediatric hospital, 54 percent of acute gastroenteritis admissions are due to rotavirus, and diarrhea is the third leading cause of all admissions. However, Saha explained that policy makers have hesitated to make rotavirus a priority, since deaths from rotavirus are rare and patients typically leave the hospital within 48 hours, while other diseases, including pneumonia and meningitis, take a larger toll.

However, when Saha’s team researched the larger impact of rotavirus on the health system, they quickly noted the fierce competition for beds in public hospitals (three beds were available for every 10,000 people compared to 31 per 10,000 in the US). Therefore, patients are frequently sent home without being seen, increasing their vulnerability to death and disability. “This is a huge burden on the health system,” Saha said. In 2017, the hospital turned away 6,000 admissible cases in just one year.

Saha’s group calculated that rotavirus vaccination would prevent nearly half of the 1,500 rotavirus patients seeking care at the hospital. This would have the knock-on effect of preventing deaths and disabilities from non-rotavirus cases, such as patients with birth asphyxia, severe pneumonia and other conditions that were being turned away due to a lack of beds.

Researchers and public health advocates have used these insights in a new advocacy strategy to convince policy makers to adopt the rotavirus vaccine. Especially in situations where there are few rotavirus deaths, it is important to focus the attention of policy makers to what vaccination would mean for the overall health system, enabling it to avert deaths and disease due to many causes.

However, while policy makers may be hesitant about vaccines, they are not the only ones. Vaccine hesitancy is also a problem among the public in many countries. Such is the case in the small country of Montenegro. Data shows that for the past five years, rotavirus has been one of the top three causes of gastrointestinal disease, with incidence increasing, as reported by Senad Begic, M.D., Ph.D., deputy director, Institute for Public Health of Montenegro.

Barriers to rotavirus vaccine introduction are common in Montenegro. Among these are vaccine hesitancy, lack of advocacy, limited surveillance data, limited capacities, limited private laboratory sector and low public awareness. Furthermore, 44 percent of the population incorrectly believes that vaccines are directly connected with autism.
Montenegro has many opportunities to address vaccine hesitancy. The country’s small size, its use of electronic medical records, political commitment to vaccines and public health, all work in its favor. On the other hand, the country is working to provide data on the burden of rotavirus. It is also conducting continuous medical education “to get our pediatricians in line with the newest trends in medicine and newest knowledge. We have to let our people know, our citizens and lay public, that the vaccines are the most important thing that human society has ever produced,” Bedic concluded.

Overcoming Social Inequities to Expand Vaccine Coverage

Social inequities, such as gender, geographic location and socioeconomic status, can affect vaccine distribution. While vaccine delivery requires governance, leadership, financing and human resources, it also requires building trust with the community and understanding who the vulnerable populations are within that community, noted Craig Burgess, JSI Research and Training Institute Inc. Unvaccinated populations in low-income settings often live in fragile contexts (i.e. displaced from conflict or natural disasters), urban slums or remote rural areas.

To respond to social barriers to vaccine uptake, the WHO has instituted the Reach Every District (RED) Strategy, which aims to reach 80 percent immunization in all districts and 90 percent coverage nationally for WHO member states. The five components of this strategy include: re-establishing outreach services, supportive supervision, linking services with communities, monitoring and use of data for action and planning and management of resources. According to Burgess, much of this strategy relies of creating community dialogues to build trust and utilizing community members to help with outreach and surveillance.

This strategy also encourages communities to investigate missed opportunities for vaccine delivery. Many people in vulnerable communities come in contact with the health care system only in emergency situations, as noted by Burgess. Therefore, countries should train healthcare workers to take advantage of these interactions, and screen for and provide vaccinations in the emergency room or urgent care settings.

Another intervention created by the WHO European Region is the Tailoring Immunization Programs (TIP), which train health care providers, public health officials and policy makers in tailoring services to expand vaccine coverage. This approach identifies unvaccinated populations within countries, diagnoses barriers and motivators for vaccination and recommends strategies to sustain vaccination coverage. According to Sanjin Musa M.D., Ph.D., Public Health Institute Federation of Bosnia and Herzegovina, it can also be used to address vaccine hesitancy.
Innovative Strategies to Improve Impact

Global coverage of the rotavirus vaccine is estimated at 28 percent. According to Lora Shimp, Immunization Center Technical Director, RAVIN, John Snow Inc., vaccination for rotavirus falls well behind coverage of other vaccine-treatable diseases. There are a number of reasons for low coverage, and economic barriers often feature prominently. Fortunately, innovative strategies for the production and delivery of rotavirus vaccines can help lower costs and increase vaccine use as well as impact.

When making decisions as to which vaccine type to buy, considerations need go beyond vaccine price, said Daniel Payne, Ph.D., M.S.P.H., CDC. He noted that each of the four vaccines now on the market differs in terms of requirements for cold chain, storage space and training for health care providers.

Ongoing innovations in manufacturing, packaging and delivering of vaccines is constantly improving. Advances include the reduction of cold chain footprint, design of more easily self-administered vaccines and the creation of less wasteful packaging at lower costs. According to Darin Zehrung, Program Leader Devices and Tools, PATH, conducting a cost-benefit analysis of different delivery devices can yield important cost-saving mechanisms for vaccine producers, many of which occur early in the production process.

Some novel containers for rotavirus vaccines include: polymer tube/preformed technology and Blow-fill-seal (BFS) technology, which produces liquid-filled containers that are formed, filled and sealed in a continuous, automated system. According to Zehrung’s cost benefit analysis these containers will provide manufacturers with both lower production and delivery costs.

Some vaccines under development are being designed to use transdermal microarray patches, which could deliver a single-dose or a delayed-dose of a vaccine through a person’s skin. Another upcoming technology is integrated reconstitution, which improves the ease and safety of delivering mixed vaccines by physically integrating two chambers, one with the dry product and the other with the diluent. However, according to Zehrung, these technologies are a decade or more away.

Solutions to economic barriers can be complex and long-term. The good news is that while price fluctuations among the four rotavirus vaccines remain, Payne notes that each type is equally effective, as is a mixed-dose course of rotavirus vaccines. Therefore, if countries use more than one type of rotavirus vaccine concurrently, or decide to change vaccine type altogether due to supply availability or costs, the population remains protected.

Improving In-Country Vaccine Delivery

In terms of vaccine delivery, Shimp notes that the global health community often thinks only in terms of distribution from the manufacturer to the country, but not about on-going delivery in-country by health
care workers. Country-level decision makers who distribute vaccines must be involved in deciding the best product and the most feasible delivery solutions.

This country level engagement will increase rotavirus vaccine coverage, and ensure it is part of a package of integrated diarrhea prevention and control strategies. Individuals and systems can be engaged to improve in vaccine delivery through more accurate data collection, training of health care workers and communicating clearly with parents and caregivers. Training for health care workers needs to include education regarding the importance of timing for vaccine doses, especially in regard to rotavirus. Additionally, parents and caregivers need clear guidelines on vaccine schedules with written appointments and vaccine cards to help them track their children’s immunizations.

Bringing Together Production and Delivery

Country level engagement is not only important at the vaccine delivery stage, but also at the production stage. In an effort to promote change in a product development paradigm that is often far removed from the countries and people who will use new vaccines, the WHO designed a Total Systems Effectiveness (TSE) Pilot. Its goal is to enable country demand to inform vaccine development.

According to Birgitte Giersing, Ph.D., technical officer, Initiative for Vaccine Research, WHO, TSE aims to identify the value of products and their attributes from a country program perspective, to guide investment in research and development, and inform priority setting for national immunization programs, global policy decisions and market shaping. A pilot study using rotavirus vaccine is ongoing, and the WHO has proposed a three-year scope of work to take TSE beyond the pilot stage beginning in 2019.

Vaccine manufacturers, investors and global health practitioners can utilize innovations in vaccine production and delivery to ensure that the end product meets the needs of the end user, and to ultimately increase global immunization coverage for rotavirus.

If we do our job well, we’ll be doing two things in parallel. We’ll be helping countries to strengthen and improve their ability to make good decisions about which vaccines should be introduced. But we’ll also be gathering a picture of which type of attributes are going to be most favorable in terms of vaccines.

—BIRGITTE GIERSING, PH.D.
Initiative for Vaccine Research, WHO
Conclusion

Concluding the Symposium, Mathuram Santosham, M.D., M.P.H., chair, ROTA Council, Johns Hopkins Bloomberg School of Public Health, recognized the role of the late Ciro de Quadros, M.D., M.P.H., as a “moving force” in the field of rotavirus and childhood vaccines. Ciro de Quadros acted as Sabin’s former executive vice president and director of Vaccine Advocacy and Education.

While highlighting the context of the Symposium -- the progress and the remaining work represented by the nearly 200,000 children’s lives lost to rotavirus every year -- Santosham recognized the enormous work being done by the rotavirus community, “presentations by young people, cutting-edge research, people from Africa, from Asia, the work that you are all doing just blew me away,” he said.

Most of that work is focused on expanding coverage and equity, in part through improving vaccine efficacy. However, Santosham had a word of caution. In their pursuit of higher vaccine efficacy, he urged researchers to ensure that the solutions they propose do not impede vaccine coverage. While interventions may make scientific sense, they must also work at a programmatic level.

Santosham also urged Symposium participants to think in terms of a comprehensive strategy to combat childhood diarrheal disease, “because our goal is ultimately to reduce deaths.” This means using the opportunity presented by vaccination to also provide parents with oral rehydration salt (ORS) packets, zinc, breastfeeding education and other interventions. Similarly, many of the strategies to prevent diarrhea deaths also apply to the prevention of pneumonia. “So, let’s think about this holistically,” he said.

Such thinking is essential to reach Sustainable Development Goal 3.2 of ending preventable deaths of newborns and children under-five years of age by 2030, and the WHO Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) goal of reducing under-five diarrhea deaths to less than 1 in 1,000 by 2025.

“We have made tremendous progress in addressing rotavirus morbidity and mortality. But more work is needed to reach all children with safe, effective, cost-effective rotavirus vaccines—especially the children who need them most.”
Addendum I: Best Posters

More than 125 scientific posters were accepted for display at the symposium. For the first time ever, the Scientific Program Committee awarded prizes for the best posters. The following poster authors were recognized for their outstanding work:

Sudhir Babji, India, for his poster: Neonatal Rotavirus Infection And Impact on Rotavirus Vaccine Immune Response


Sung-sil Moon, United States, for her poster: Co-administration of Inactivated Rotavirus and Poliovirus Vaccines by Dissolving Microneedle Patch

Molly Steele, United States, for her poster: Predicting the Epidemiological Impact of Changes to Current Rotavirus Vaccine Coverage in the United States

Michelle Groome, South Africa, for her poster: Post-marketing Intussusception Monitoring after Introduction of Oral Rotavirus Vaccine in South Africa

Mohammad Al—Mamun, United States, for his poster: Heterogeneity in Rotavirus Infection Risk Among Children: A Data-Driven Individual-Based Modeling Study

Maria Hemming-Harlo, Finland, for her poster: Rotavirus Vaccination and Autoimmune Diseases

Talia Pindyck, United States, for her poster: Are unique age restrictions affecting rotavirus vaccination coverage in African infants?
Addendum II: Agenda

Opening Session

WELCOME AND INTRODUCTION
Amy Finan

OPENING REMARKS
Natalia Zhukova

INTRODUCTION OF ROGER GLASS LECTURE
Gagandeep Kang

FOURTH ROGER GLASS LECTURE
Umesh Parashar

Session I: Global Burden of Rotavirus Disease

GLOBAL BURDEN OF DISEASE STUDY AMONG CHILDREN UNDER 5 YEARS
Christopher Troeger

GLOBAL PEDIATRIC DIARRHEA SURVEILLANCE NETWORK DEMONSTRATES WHAT PATHOGENS ARE ASSOCIATED WITH ACUTE DIARRHEA IN CHILDREN
Adam Cohen

ETIOLOGY OF DIARRHEAL DISEASE AFTER ROTAVIRUS VACCINE INTRODUCTION
Karen Kotloff

THE COST EFFECTIVENESS OF RV VACCINATION IN GAVI COUNTRIES
Frederic Debellut

Session II: Global Impact & Safety of Rotavirus Vaccines

EFFECTIVENESS OF A MONOVALENT VACCINE ON ROTAVIRUS-ASSOCIATED DIARRHEAL DISEASE HOSPITALIZATION IN KENYAN CHILDREN
Sammy Khagayi

EFFECTIVENESS OF MONOVALENT ROTAVIRUS VACCINE IN THE PHILIPPINES
Anna Lopez

ANNUAL VARIATION IN DIRECT AND INDIRECT EFFECTS AND TOTAL IMPACT OF ROTAVIRUS VACCINATION AMONG CHILDREN IN THE US
Julia Baker

INTUSSUSCEPTION SURVEILLANCE IN INDIA
Gagandeep Kang

ROTAVIRUS VACCINES AND INTUSSUSCEPTION. WHAT IS THE LATEST DATA?
Jacqueline Tate

Session III: Burden of Rotavirus Disease and Impact in the European Region

REGIONAL UPDATE
Danni Daniels

EUROROTANET UPDATE
Miren Iturriza-Gomara

COUNTRY SPOTLIGHT: TAJIKISTAN
Anvar Nazurdinov

COUNTRY SPOTLIGHT: GERMANY
Judith Koch

POSTER: EARLY RESULTS ON IMPACT OF ROTAVIRUS VACCINE IN UZBEKISTAN
Renat Latipov
Session IV: Barriers and Enablers to Rotavirus Vaccine Introduction

BELARUS
Irina Glinskaya

ESTONIA
Natalia Kerbo

MONTENEGRO
Senad Begic

Strict Age Limits for Rotavirus Vaccination: Experience from Norway
Terese Bekkevold

Session V: Advances in Rotavirus Immunology & Virology

NEW INSIGHTS REGARDING HUMORAL IMMUNITY TO HUMAN ROTAVIRUSES
Harry Greenberg

SUSCEPTIBILITY TO ROTAVIRUS INFECTIONS
Mary Estes

ROTAVIRUS VACCINES AND THE MICROBIOME
Vanessa Harris

POSTER: NON-SECRETOR HISTO-BLOOD GROUP ANTIGEN PHENOTYPE DOES NOT IMPAIR SUSCEPTIBILITY TO INFECTION WITH ROTARIX VACCINE AMONG INFANTS IN BANGLADESH
Benjamin Lee

Session VI: Current Rotavirus Vaccines in Routine Immunization

ROTATEQ (PENTAVALENT HUMAN-BOVINE (WC3) ROTAVIRUS VACCINE) — AN UPDATE
Ritapurna Das

THE BENEFITS OF ROTAVIRUS VACCINATION WITH HUMAN ROTAVIRUS VACCINE; LESSONS LEARNED FROM IMPACT DATA 2006–2017
Bernd Benninghoff

ROTAVAC — PRODUCT DEVELOPMENT AND PROGRAMMATIC IMPLEMENTATION
Sai Prasad

UPDATES ON ROTASILL DEVELOPMENT
Sajjad Desai

Session VII: Innovative Vaccine Approaches for Rotavirus

PHASE 2 IMMUNE RESPONSES OF A SUBUNIT ROTAVIRUS VACCINE
Michelle Groome

RV3-BB VACCINE PROTECTS AGAINST SEVERE, VERY SEVERE AND ALL-SEVERITY ROTAVIRUS DISEASE FROM BIRTH
Julie Bines

AN ORAL, LIVE ATTENUATED, PENTAVALENT (G1–G4 AND P1[8]), HEAT-STABLE ROTAVIRUS VACCINE (HSRV) PRESENTED IN A SINGLE CONTAINER/CLOSURE DELIVERY DEVICE
Davinder Gill

DEVELOPMENT OF A VP6 SUBUNIT ROTAVIRUS VACCINE
Vesna Blazevic

RECENT ADVANCES IN INACTIVATED ROTAVIRUS VACCINE DEVELOPMENT
Baoming Jiang

DEVELOPMENT OF THE RV3-BB VACCINE AT BIOFARMA
Erman Tritama
Session VIII: Ruth Bishop Lecture

INTRODUCTION OF RUTH BISHOP LECTURE
Julie Bines

RUTH BISHOP KEYNOTE LECTURE
Ulrich Desselberger

Session IX: Poster Highlights

HOUSEHOLD TRANSMISSION OF ROTAVIRUS IN MALAWIAN CHILDREN WITH ACUTE GASTROENTERITIS IS ASSOCIATED WITH DISEASE SEVERITY
Aisleen Bennett

NEONATAL ROTAVIRUS INFECTION AND IMPACT ON ROTAVIRUS VACCINE IMMUNE RESPONSE
Sudhir Babji

ROTAVIRUS VACCINE TAKE IN INFANTS PREDICTED BY SECRETOR STATUS
George Armah

MODULATION OF NEONATAL ROTAVIRUS INFECTION BY HUMAN MILD OLIGOSACCHARIDES, MILK MICROBIOME AND INFANT GUT MICROBIOME
Sasirekha Ramani

Session X: Innovative Strategies to Increase Impact

TOTAL SYSTEMS EFFECTIVENESS (TSE) PILOT: DEVELOPING THE COUNTRY USE CASE USING ROTAVIRUS VACCINES AS A CASE STUDY
Birgitte Giersing

NOVEL PRIMARY CONTAINERS/DELIVERY DEVICES
Darin Zehrung

USER EMPOWERMENT INITIATIVES TO ADDRESS COVERAGE GAPS
Lora Shimp

ALTERNATIVE IMMUNIZATION SCHEDULES / RISK BENEFIT
Carl Kirkwood

Session XI: Vaccine Economics & Financing

COST-EFFECTIVENESS AND BENEFIT-RISK OF ROTAVIRUS VACCINATION IN MIDDLE INCOME COUNTRIES IN THE EUROPEAN REGION
John Farrow

THE COST-EFFECTIVENESS OF RV VACCINATION IN GHANA
Justice Nonvignon

THE COST-EFFECTIVENESS OF RV VACCINATION IN MONGOLIA
Luvsan Munkh-Erdene

ACHIEVEMENTS OF FINANCIAL SUSTAINABILITY OF THE IMMUNIZATION PROGRAM IN COUNTRIES THAT ARE LEAVING GAVI SUPPORT
Vladimir Getia

HOW TO "BOOST" INTRODUCTION OF VACCINES INTO ROUTINE IMMUNIZATION PROGRAMS: IMPLICATIONS OF PROCUREMENT APPROACHES ON PROGRAM COSTS
Gideon Chelule

Session XII: Remaining Programmatic Challenges for the Implementation of Rotavirus Vaccines

INTERCHANGEABILITY OF RVV PRODUCTS
Daniel Payne

MAKING SURE ROTA VIRUS VACCINES ACTUALLY GET DELIVERED TO THOSE WHO NEED THEM MOST
Craig Burgess

ADDRESSING VACCINE HESITANCY AND REACHING VULNERABLE POPULATIONS: LESSONS FROM THE TAILORING IMMUNIZATION PROGRAMS APPROACH
Sanjin Musa

ROTAVIRUS VACCINE IMPACT BEYOND PREVENTING DIARRHEA
Samir Saha

CLOSING MESSAGE
Mathuram Santosham