A Report from the 12th International Rotavirus Symposium

BILL & MELINDA GATES foundation

CDC Centers for Disease Control and Prevention

NIH Fogarty International Center

Murdoch Childrens Research Institute

The University of Melbourne

PATH

ROTA Council Rotavirus Organization of Technical Allies

SABIN Vaccine Institute

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Introduction

From September 7-9, 2016, 350 experts from 50 countries met in Melbourne, Australia, for the 12th International Rotavirus Symposium to share recent scientific data on rotavirus (RV) epidemiology and immunology, the current status of the licensed RV vaccines, and data on the impact of the introduction of RV vaccines in several countries. The 12th International Rotavirus Symposium was convened by the Sabin Vaccine Institute in collaboration with the Bill and Melinda Gates Foundation, the U.S. Centers for Disease Control and Prevention, the U.S. National Institutes of Health Fogarty International Center, Murdoch Children's Research Institute, the University of Melbourne, PATH and the Rotavirus Organization of Technical Allies (ROTA) Council.

The symposium's host city was particularly appropriate this year, as Melbourne is home to Professor Ruth Bishop, a driving force behind the decades-long search for a safe, effective vaccine against RV. Bishop led the team at The Royal Children's Hospital Melbourne that discovered the virus in 1973 and was the first to demonstrate the development of protective immunity following natural RV infection in newborn infants. For her vast contribution to the field of RV prevention, Bishop was honored at this year's symposium that featured a roundtable discussion on women leaders' role in the scientific advancement of RV.

Participants included representatives from public health agencies and universities around the world, the World Health Organization's (WHO) Global RV Surveillance Network and U.S. Centers for Disease Control and Prevention who, presented findings from surveillance programs established to monitor the global burden of RV infection and measure vaccine impact to inform future policymaking decisions on RV prevention.

The current generation of vaccines against rotavirus, the leading cause of diarrheal disease in children under five years old, was introduced just a decade ago. In the intervening years, 81 countries have implemented RV vaccination, and recent estimates indicate that as a consequence 2.4 million deaths will have been averted between 2007 and 2025 (1), and that RV was responsible for an estimated 215,000 deaths in children under five years of age between 2000 and 2013 (2). Though considerable progress has been made in expanding the uptake of RV vaccine coverage, which has reached 85 to 95 percent in some countries, RV vaccination rates remain low in many parts of the world, particularly in Asia, and rates of new rotavirus vaccine introductions have slowed.

The overarching message at the meeting reinforced that RV vaccines are effective at preventing deaths and hospitalizations due to diarrheal disease and have the greatest impact on children and infants. Several countries have reported a drop in diarrheal disease caused by RV even in unvaccinated segments of the population, likely due to indirect (herd) protection through reduced RV disease and subsequent transmission.

Yet in the face of these successes, the public health community remains concerned that the effectiveness of the vaccine is lower in low- to middle-income countries relative to high-income countries. While it is still unclear why these differences exists, several avenues of research have been put forward, that attribute these differences to variances in the microbiome, in nutritional status, in co-infection with other enteropathogenic viruses or bacteria, or that "hygiene" may be differentially shaping the immune response after vaccination in these different settings.

Keynote: The Roger Glass Lecture: "Can we do better?"

Dr. Gagandeep Kang, Department of Gastrointestinal Sciences at the Christian Medical College (CMC) in Vellore, India, gave this year's Roger Glass Lecture on the subject of differential vaccine effectiveness in high- and low-income settings, titled, "Can we do better? Oral vaccines in the developing world." Dr. Kang provided a comprehensive overview of the performance of oral vaccines in low- and middle-income countries and identified critical factors affecting oral vaccine performance and stressed the need to understand impact of the vaccine in its environmental context – from a child's nutritional state to the natural composition of bacteria living in the digestive system – affects vaccine performance. Kang's research has shown that many factors may impact the immunogenicity of oral RV vaccines, including the vaccine's viral titers the timing of doses, concomitant oral poliovirus vaccine administration, and the host's microbiome. She also indicated that while maternal antibodies affect immune response to oral RV vaccines, withholding breastfeeding at vaccination is insufficient to increase immunogenicity. Lastly, she indicated that vaccine responses are no different in malnourished children, and that zinc may play an important role in the development of an immune response to a vaccine.

Global perspectives of RV vaccination: Introduction and uptake

To combat the burden of RV disease, 81 countries have introduced RV into their national vaccination programs as of May 2016, including more than 50 Gavi-eligible and low- to middle-income countries (LMIC). Gavi is providing significant backing to increase global RV vaccine introductions by substantially subsidizing the purchase of the vaccine in the poorest countries. Seventeen additional Gavi-eligible countries are expected to introduce RV vaccination to their national programs in the next five years.

Two RV vaccines are currently in wide use: RotaTeq® (RV5), a live, oral, pentavalent vaccine produced by Merck and Co., and Rotarix® (RV1), a live, oral, monovalent vaccine produce by GlaxoSmithKline. A third oral RV vaccine, ROTAVAC®, was licensed by Bharat Biotech in 2014; however, to date, ROTAVAC® has only been implemented regionally within India.

RV vaccination has been demonstrated to induce herd protection in countries around the world. In regions where RV vaccines have been introduced, significant decreases in all-cause gastroenteritis and RV hospitalizations have been seen in both vaccinated and unvaccinated groups. This trend was seen following implementation of either RV1 or RV5.

Global RV vaccine uptake has been slower than expected, with the 73 original Gavi-supported countries failing to reach 2001 to 2015 targets. According to Dr. Carsten Mantel of the WHO, a number of issues have impeded uptake: concerns about in-country program readiness and cold-chain capacity, to program sustainability and financing beyond Gavi support, to questions about vaccine supply and safety, and the priority of RV vaccine in the setting of declining all-cause diarrhea mortality and competing vaccine introductions, such as the inactivated polio vaccine. Many countries, particularly those nearing Gavi graduation, are facing difficult cost-benefit decisions on whether to implement RV vaccination versus other important public health interventions.

It was expressed that many decision makers may not be aware that RV is the leading cause of diarrhea and results in a significant number of hospitalizations imposing an economic burden on the health system and on families in direct medical costs and lost wages.

RV disease burden and vaccine impact: Data and data gaps

The WHO-coordinated Global RV Surveillance Network (GRSN) generates and monitors RV disease trends globally (3). Dr. Adam L. Cohen of the WHO presented GRSN's latest RV burden data from each WHO region (Table 1). The Western Pacific and Americas regions recorded the highest and lowest median regional percent RV positivity, respectively. According to Cohen, the data GRSN gathered is currently being used for modeling studies at the CDC and Johns Hopkins, and for monitoring vaccine impact by Gavi.

Cohen identified key remaining gaps GRSN is working to fill, especially the need to focus disease burden and vaccine impact data collection in regions with the most severe data gaps, notably Asia. There is also a need to assess long-term impact of vaccine introduction. Cohen noted that as RV surveillance is, in many ways, diarrheal disease surveillance, the RV framework can also be used to monitor other enteric vaccine-preventable diseases, including enterotoxigenic *Escherichia coli*, Shigella, norovirus and cholera, as well as non-vaccine interventions.

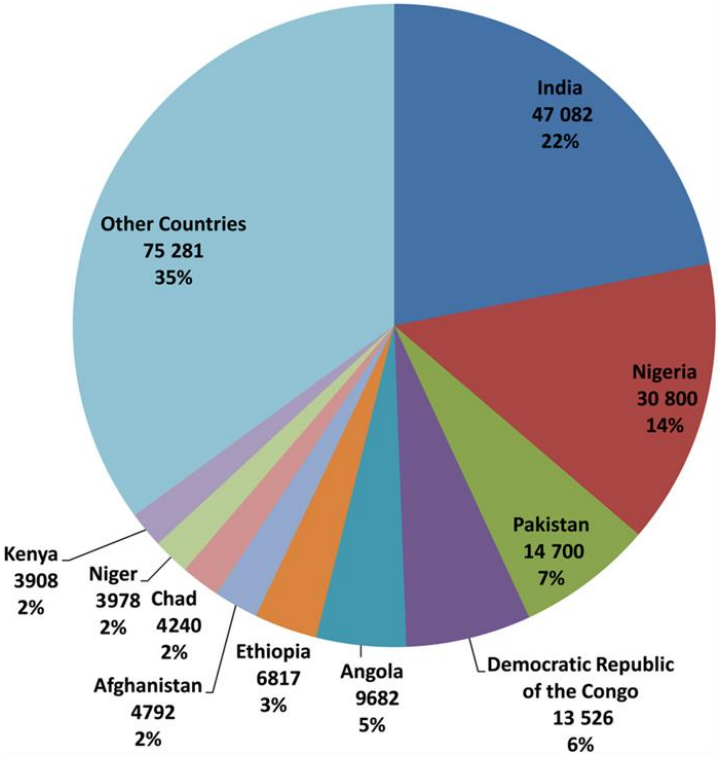
Dr. Duncan Steele of the Bill and Melinda Gates Foundation provided data for global RV mortality in children under five years old in 2013, currently estimated at 215,000 deaths (Figure 1) (2). India, Nigeria and Pakistan had the highest number of under-five RV deaths in 2013, with India contributing 22 percent of the global total.

Table 1. Regional median rotavirus positivity among countries reporting data to GRSN, 2014.

Region	Median Rotavirus Positivity Among Reporting Countries
African Region (AFR)	34%
Americas Region (AMR)	10%
Eastern Mediterranean Region (EMR)	26%
European Region (EUR)	15%
South-East Asian Region (SEAR)	35%
Western Pacific Region (WPR)	43%

Notes: GRSN – Global RV Surveillance Network.

Figure 1. Countries with the greatest number of rotavirus deaths among children <5 years of age, 2013.



Source: Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013. Clin Infect Dis. 2016;62(suppl_2):S96-S105. doi:10.1093/cid/civ1013. Published by Oxford University Press for the Infectious Diseases Society of America 2016. This work is written by (a) US Government employee(s) and is in the public domain in the US.

Key challenges to improving RV vaccine performance

Though RV vaccination has proven effective overall in preventing hospitalizations of young children and deaths from diarrhea across the globe, two key issues remain: inconsistent duration of protection after the first year of life and reduced vaccine effectiveness in low-income settings.

Studies have shown that in high-income countries, vaccine protection against RV is similar in the first and second years of life. However, increasing evidence indicates that in some countries, effectiveness of RV vaccines is reduced in the second year of life. Studies performed in Moldova, Malawi and Bolivia found that RV1 effectiveness at preventing RV hospitalizations in infants dropped by as much as half after 12 months of age. Similar results were seen with RV5 in Nicaragua (4).

There is a clear disparity in RV vaccine effectiveness between high- and low-income countries, though researchers have yet to definitively determine why. Recent data indicate that RV vaccination has significantly reduced RV hospitalizations in children under five years of age in all regions where this vaccine has been introduced; however, the extent to which it did so varied significantly across regions, achieving hospitalization reductions as high as 94 to 98 percent in high-income countries and as low as 55 to 58 percent in LMIC (4).

Several possible hypotheses for this difference were presented and discussed: blunted vaccine-induced immunity due to other enteropathies, differences in the gut microbiome, genetic polymorphisms in the expression of intestinal glycans, interference by concomitant oral polio vaccine administration and insufficient cross-protection provided by RV strains in the vaccine and the strains circulating in these regions. Some of the proposed molecular mechanisms underlying these hypotheses are discussed in further detail later in this manuscript.

Immune interference with OPV

There has been concern that concomitant oral polio vaccine (OPV) administration may interfere with oral RV vaccine effectiveness. Dr. Umesh Parashar of the CDC Viral Gastroenteritis Epidemiology team presented current knowledge on the impact of a switch from OPV to inactivated polio vaccine on RV vaccine performance. While co-administration with the RV vaccine does not appear to affect OPV performance (5), recent studies have shown a trend toward interference with RV vaccine-induced immune responses by trivalent OPV in South Africa (6) and Bangladesh (7). Parashar presented results from a study his group conducted in Bangladesh to assess the impact of co-administration of bivalent or monovalent OPV on RV1 immunogenicity in healthy infants. Regardless of the formulation, concomitant OPV administration resulted in reduced RV1 immunogenicity as measured by RV IgA seroconversion and RV IgA geometric mean titer (8). Similar results were observed in a study conducted in

Chile assessing the effect of co-administration of bivalent OPV formulation on RV1 (9). One study measuring the effect of OPV co-administration on RV1 effectiveness in six Latin American countries indicated that this drop in immunogenicity does not translate to reduced effectiveness. In the latter study, RV1 was similarly efficacious when administered alone or co-administered with routine national immunization program vaccines, including OPV. Nevertheless, Parashar concluded that though more studies will need to be conducted to assess the downstream effect of this OPV-induced decreased immunogenicity on RV vaccine effectiveness, the consistently reduced RV vaccine immunogenicity observed when co-administered with OPV indicates some negative effect on effectiveness is probable, and that switching to inactivated polio vaccine could be beneficial to RV vaccine performance.

History of adverse events following RV vaccination

Following its introduction in the United States in 1998, an association was identified between RotaShield®, the first vaccine to prevent RV gastroenteritis, and intussusception (10). The risk attributable to RotaShield® vaccination was estimated to be one excess case of intussusception per 10,000 vaccine recipients. Though RotaShield® is no longer in use, intussusception is still monitored as a possible adverse event associated with current RV vaccines. As the occurrence of intussusception following vaccination is rare, randomized clinical trials did not detect a similar level of risk associated with RV1 or RV5 but post-marketing safety assessments have identified an increased risk of intussusception with RV1 and RV5, though significantly less than was associated with RotaShield®.

Regional impacts, challenges and opportunities of RV vaccination

Southeast Asia and Western Pacific

Though global RV vaccine uptake is improving, serious gaps remain in Asia. Globally, the Southeast Asia and Western Pacific regions had the two highest median RV percent positivity (i.e., the percentage of positive rotavirus results) between 2013 and 2015. Two of the three countries with the highest number of under-five RV deaths – India and Pakistan – contributed to 29 percent of the global under-five RV deaths between 2013 and 2015. RV vaccine uptake is also relatively low in these regions. Only 27 percent of countries in the Western Pacific region and zero percent in the Southeast Asian region have implemented a national RV vaccination program as of September 2016.

Two countries in the Southeast Asian region applied for Gavi support for RV vaccine introduction. Gavi approved Pakistan's application for phased RV vaccine introduction beginning in Punjab in 2017. In 2016, Bangladesh submitted a Gavi application for 2018 RV vaccination introduction. Dr. Tajul Islam A. Bari of the Bangladesh Ministry of Health and Family Welfare presented the results of a study conducted in advance of Bangladesh's Gavi application that estimated mass RV vaccination will prevent 135,000 hospitalizations and 2,723 deaths in the country annually. However, it was stressed that before implementing a national RV immunization program, Bangladesh will need to improve cold chain capacity and realistically assess feasibility considering the need to simultaneously monitor for intussusception during RV vaccine administration.

In his keynote address, Dr. Pradeep Haldar of the Indian Ministry of Health and Family Welfare, presented the state of RV vaccine introduction in India. In 2015, India recommended RV vaccination for a universal immunization program and began phased regional introduction of ROTAVAC®, a live, oral, monovalent RV vaccine produced in India by Bharat Biotech. RV vaccination was implemented in March 2016 in four pilot states, targeting 2.32 million children. In order to prepare health systems in these states to effectively implement these programs, health workers at national, state, district and block levels received standardized training, and media workshops were conducted before the program launch in order to enhance coverage and promote media advocacy in support of the program. Additionally, databases and immunization records were updated to include RV, and a cold chain assessment was performed to identify and strengthen any potential weak points. Ongoing challenges include ensuring a continuous supply of RV vaccine, optimizing vaccine usage to reduce waste, and accounting for additional children coming from neighboring states to be immunized.

The Thailand Advisory Committee first recommended RV vaccination be included in the national immunization program in 2010. Following a preliminary study in one province in 2011, an effectiveness study including RV1 conducted between 2012 and 2014 identified approximately 88 percent vaccine effectiveness in the country.

In 2010, the Philippines became the first country in Southeast Asia to include RV vaccination in its national immunization program. However, the 2016 health budget no longer included RV vaccination, in part because an impact study had not been performed to justify inclusion of the vaccine in the budget. According to Dr. Elvira Dayrit of the Philippines Department of Health, "decision-making shortcuts" including poor long-term planning and forecasting, lack of an operations manual, and modest communication and community mobilization played a large role in the lapse in RV vaccination in the Philippines. Moving forward, she recommends organizing an integrated all-cause diarrhea prevention program including full-scale communication activities and community mobilization in select priority areas with known high diarrheal disease burden. Once such a program is successfully established, a full nation-wide RV vaccination program can be re-implemented. Dayrit stressed that in order to sustain vaccination efforts following RV vaccine introduction, it is important to demonstrate vaccine impact, which can

only happen with good surveillance and data collection; she emphasized that this is particularly critical for maintaining support for rotavirus vaccination in a changing political environment. RV vaccination has been reinstated in the Philippines' 2017 health budget, but at a much smaller scale and without a multi-year, sustainable plan in place.

Fiji was the first low- to middle-income country in the Asia-Pacific region to show a decline in RV and all-cause diarrhea hospital admissions following RV vaccine introduction in September 2012. RV surveillance commenced in Fiji in 2005. Pre-vaccination, RV positivity among children hospitalized with acute diarrhea in Fiji was 39 percent (11). Dr. Fiona Russell of the Murdoch Children's Research Institute presented a vaccine evaluation project conducted in Fiji between 2012 and 2016 that assessed impact of concurrent RV, pneumococcal and human papilloma virus vaccine introduction for all 3 diseases, as well as impact of the pneumococcal conjugate vaccine on nasopharyngeal carriage. In October 2012, RV1 was administered in infants at six and 14 weeks of age. Investigators measured all-cause diarrhea hospitalization, all-cause diarrhea mortality, RV positivity (inpatient and outpatient) and intussusception rates. Post-RV vaccine introduction in Fiji, under-five all-cause and RV diarrhea hospital admissions decreased by 29 and 70 percent, respectively. Active intussusception surveillance revealed that RV vaccination may cause approximately two additional cases of intussusception every five years compared to the pre-vaccination baseline; however, it was noted that access to surgery to treat intussusception was good in Fiji, and no intussusception deaths occurred during the study. Together, these results indicate that RV vaccine introduction was successful, though Russell emphasized the importance of continued surveillance was important to monitor vaccine impact and safety.

Africa

Sixty-one percent of the countries on the African continent (33 of 54) have introduced a RV vaccine into their national immunization program, including six Gavi non-eligible countries. The first country in the African region to introduce RV vaccination was South Africa – regionally in 2008 followed by a national roll-out in 2009. There was a rapid increase in the number of countries that introduced RV vaccine from six in 2012 to 30 in 2015. This increase slowed significantly between 2016 and 2017 with only four countries – Guinea-Bissau, Liberia, Uganda and Côte d'Ivoire – launching RV vaccination programs in 2016.

The issues preventing the remaining countries in the African region from introducing a RV vaccine are primarily due to a lack of sustainable financing for a RV immunization program and the need to address other competing priorities. Though five countries are not Gavi eligible, many are Gavi-approved but implementation of the program has been delayed. Other countries are awaiting a decision on a Gavi application. Some countries meet the

financial criteria for Gavi eligibility but have DPT3 coverage less than 70 percent and thus are ineligible to apply for support for RV vaccine introduction.

A well-established, WHO-coordinated rotavirus surveillance network exists in the African region. The African Rotavirus Surveillance Network (AFRSN), which was first formed in 2006, works to strengthen capacity in the region in a variety of areas, including laboratory, surveillance, research and human resources. This network contributes data for documentation of regional and country disease burden associated with rotavirus diarrhea in children under the age of five, documents circulating rotavirus genotypes in the African region and monitors for intussusception in areas where the vaccine has been introduced. AF RSN has also developed a system for monitoring disease trends over time, vaccine impact and serotype shift following vaccine introduction. Lastly, AF RSN works to raise rotavirus disease burden awareness, as well as support for rotavirus vaccine introductions.

According to Dr. Jason Mwenda of the WHO Regional Office for Africa, 15 of the 31 countries in the African region that introduced the RV vaccine conducted post-introduction evaluations (PIE) to learn and document programmatic implications of RV immunization. The PIEs identified key strengths of the program which included the availability of national and subnational plans, strong collaboration with partners, and training funded by the government and its partners, which was conducted before RV vaccine introduction. Additional strengths identified by the PIEs include proper use, development and updating of immunization reporting and recording tools; supportive supervision of immunization activities, including written feedback for healthcare workers; communication materials prepared specifically by each country; good overall acceptance of RV vaccination by communities and healthcare providers; and the availability of budget lines for traditional vaccines and full financing or co-financing of new vaccines in many countries. Key weaknesses of the immunization programs revealed by the PIEs were inadequate duration of training and inadequate or lack of reference materials in some areas; inadequate data recording, reporting and distribution; inadequate cold-chain capacity at sub-national levels; and stock-outs resulting from under-estimation of new vaccine requirements.

As presented by Dr. Jacqueline Tate of the U.S. CDC, the 2012 introduction of RV5 in Rwanda resulted in a significant reduction in under-five RV hospitalizations (61 to 70 percent), under-five acute gastroenteritis admissions (45 to 49 percent), under-five all-cause diarrhea hospitalization (17 to 23 percent), all-cause diarrheal hospitalizations during RV season (27 to 40 percent) and the proportion of diarrhea hospitalizations attributable to RV (55 to 62 percent). This last effect was greatest in the RV vaccine-eligible age group, though the benefit was also seen in non-vaccinated age groups, indicating RV vaccination in Rwanda had a herd protective effect. RV5 was found to be 80 percent effective in preventing hospitalizations overall, an effect that persisted through at least 18 months of age.

Dr. David Goldfarb of the University of British Columbia described declines in RV mortality and hospitalizations following RV1 introduction in Botswana in 2012. This decline was most prominent in infants and during RV season, and correlates with a significantly reduced RV positivity post-vaccine introduction. Interestingly, while the full series of RV1 exhibited about 54 percent effectiveness, one dose of RV1 conferred a similar level of protection against severe RV diarrhea among infants less than six months old (approximately 48 percent effectiveness) (12). This is notable, as a large number of RV deaths in Botswana occur in children under six months of age, and many do not return for a second dose. Protection was also found to increase with severity of illness, suggesting potential benefits of vaccination against severe RV diarrhea, which can be fatal. This study also found that in Botswana, co-infections with other enteric diseases did not appear to affect RV1 effectiveness.

Malawi's VacSurv program measured RV vaccine morbidity and mortality impact and cost-effectiveness through a series of population demographic surveillance, large-scale cohort studies, sentinel surveillance, case-control studies, costing studies and household transmission studies. RV vaccination in Malawi, which began in 2012, resulted in a 54 percent reduction in infant RV cases (13) and a 49 percent reduction in RV mortality, averting an estimated 281 deaths and 54,000 RV cases in the 2015 birth cohort alone.

In collaboration with the International Maternal Pediatric Adolescent AIDS Clinical Trials network, Merck conducted a randomized, multicenter, double-blind clinical trial evaluating RV5 safety and immunogenicity in Human Immunodeficiency Virus (HIV)-positive and HIV-exposed infants in Botswana, Tanzania, Zambia and Zimbabwe. Dr. Susan Kaplan of Merck & Co. presented data from that trial showing that RV5 was similarly immunogenic in both groups such that antibody titers after three doses of RV5 did not differ based on HIV status. Additionally, RV5 shedding in stool was similar to that previously reported and was not prolonged in HIV-positive infants. Given these results, this study concluded that RV5 was safe and well-tolerated in HIV-positive and HIV-exposed infants.

Americas

In 2006, Latin America and the Caribbean (LAC) became the first region in the world to introduce RV vaccination in the public health sector. Dr. Lucia De Oliveira of the Pan American Health Organization (PAHO), WHO Regional Office for the Americas, discussed the state of RV vaccine uptake and impact in Latin America. At approximately 81 percent regional coverage, RV vaccine uptake is relatively high in the Americas region.

Since 2006, 19 countries in the Americas region have introduced RV vaccines into their national immunization programs. An estimated 91.7 percent of the Latin American 2015 live birth cohort lived in a country where RV vaccination is part of the national immunization program. According to De Oliveira, disease burden and cost-

effectiveness were key determinants in the decision-making process surrounding RV vaccine introduction in LAC. Data from RV sentinel surveillance was used to measure RV vaccine impact.

Between 2006, when the first seven countries introduced RV vaccines, and 2015, RV positivity in LAC dropped 55 percent. A meta-analysis revealed that RV vaccine administration consistently protected against diarrhea hospitalizations in LAC. Between 2008 and 2015, under-five RV hospitalizations declined 47 percent, under-five all-cause diarrhea hospital admissions declined 30 percent and under-five diarrhea mortality declined 52 percent. The vaccine appeared to have higher effectiveness in children under 12 months of age. 2013 estimates indicate that RV vaccination averted between 6,903 and 8,621 deaths in the region.

De Oliveira highlighted key lessons learned from RV vaccine introduction in LAC. She indicated that in areas where vaccine coverage was not universal, it was difficult to accurately measure coverage and impact due to children moving from one municipality to another. The fact that RV vaccine requires more cold chain storage than other vaccines included in these countries' national programs posed an additional challenge; cold chain capacity in these countries had to be strengthened prior to RV vaccine introduction in order to avoid vaccine waste. De Oliveira emphasized that training needs to be comprehensive and should occur at all levels of the immunization program.

De Oliveira made recommendations for RV vaccination programs in LAC. Countries should increase the RV vaccine administration age range to include children up to one year of age. She stated that surveillance and impact studies are essential to ensure continued success of the RV vaccine programs. De Oliveira warned that because RV vaccine impact is directly related to coverage, care needs to be taken to ensure uptake is not affected by the simultaneous introduction of more than one vaccine. She concluded by emphasizing that political and technical commitment, financial sustainability and collaboration between countries to share lessons learned and build on past experiences are essential for successful new vaccine introduction.

According to Dr. Daniel Payne of the U.S. CDC, RV activity in the USA has decreased substantially every RV season since RV vaccine introduction in 2006. RV positivity has decreased by 74 to 90 percent since 2006, correlating negatively with RV vaccine coverage. RV-positive acute gastroenteritis hospitalizations under three years of age have dropped from 51 to 5 percent since 2006. Reports indicate under-five RV hospitalizations have declined 63 to 94 percent post-vaccine introduction, resulting in an estimated 50,000 averted under-five hospitalizations. Despite the positive impact of RV vaccination in the United States, RV vaccine coverage remains around 73 percent. This level of coverage has resulted in a shift from the annual distribution of RV observed in the U.S. before vaccine introduction to a biennial distribution, indicating that sufficient numbers of infected individuals remain to maintain disease transmission in the United States, but only every other year.

Both RV1 and RV5 are recommended for use in the United States. Studies performed by the U.S. CDC and presented by Dr. Bernd Benninghoff of GlaxoSmithKline have observed no significant difference in vaccine effectiveness in the United States between RV1 and RV5, and both vaccines exhibit broad protection against heterologous RV strains (14-16). The most significant vaccine protection is against severe disease, but protection has also been observed broadly against mild to moderate RV disease. RV vaccination has been shown to induce herd immunity in the US, inducing reductions in RV infections in both adults and children too old or young to have been vaccinated. Interestingly, RV vaccination in the U.S. is also associated with an 18 to 20 percent reduction in risk of seizures requiring hospitalization in the year following vaccination, an effect that was also seen in studies in Australia and Spain. A shift in circulating RV genotypes has been observed post-vaccination.

Europe

Ten countries in Western Europe and three in Eastern Europe have introduced RV vaccination to date, beginning in 2006 and most recently in 2015. Current data suggests RV vaccination in Europe will have a significant impact on RV morbidity but not mortality, due to relatively low baseline severe disease and mortality rates because of prompt treatment and access to medical care, especially for severe disease. European countries have been included in several RV vaccine impact studies, including RotaBIS in Belgium and the RV Efficacy and Safety Trial (REST), which included a trial in Finland. RV vaccine uptake in Western European countries that have introduced RV vaccination is high, reaching up to 90 and 93 percent in Belgium and the United Kingdom, respectively.

Dr. Timo Vesikari of the University of Tampere presented data showing that RV vaccines are highly effective in a Western European setting. REST found RV5 was 82 to 95 percent effective in preventing diarrhea hospitalizations and emergency room visits in Finland. Separate pre-licensure studies confirmed these results, finding that even one dose of RV5 was 81 percent effective and resulted in a 70.2 percent reduction in all-cause hospitalization and all-cause acute gastroenteritis. Indirect protection in individuals who were non-eligible to receive the vaccine was also observed following inclusion of either RV1 or RV5 in national immunization programs in Belgium, Finland, Austria, Australia, the United Kingdom, Mexico and the United States, though this protection was found to wane over time in some countries (17-26). As in the U.S., a shift in circulating RV genotypes was observed post-vaccination, though RV vaccination was still protective against these new strains.

Three Eastern European countries have introduced RV vaccines into their national immunization programs: Armenia, Moldova and Georgia. RV vaccination was effective in reducing RV hospitalizations in these countries, though less so than in Western Europe. Following vaccine introduction, under-five RV hospitalizations dropped 69 and 67 percent in Armenia and Moldova, respectively. Vaccine effectiveness was slightly higher in infants under

12 months of age, reducing RV hospitalizations in this age group by 73 to 75 percent. As in Western Europe, an indirect protective effect was seen in groups too young or too old to be immunized against RV.

Demand, cost-effectiveness and financing

Key issues for RV vaccine policy in Gavi-graduating countries

As of September 2016, 39 countries had introduced RV vaccine with Gavi support, and five additional countries have been approved for future RV vaccine introduction. The overall objective of Gavi's model is to put countries on a trajectory towards financial sustainability, while enabling them to introduce vaccines sooner than they otherwise would have been able to. As countries graduate from Gavi support, they co-finance a fraction of the weighted average price of the vaccine presentation used in the country, which increases by 15 percent annually until a country is fully self-financed. This new price-related co-financing for countries in the preparatory transition phase has several implications for RV vaccine policy in Gavi-graduating countries.

According to Melissa Ko, Senior Programme Manager at Gavi, the increasing number of Gavi-graduating countries that include RV vaccination in their national programs may have an impact on RV1 versus RV5 demand. Though the Gavi co-pay for a full course of both RV vaccines is identical, RV1 is currently less expensive than RV5 in the absence of Gavi support and requires only two doses compared to the three doses required for RV5. As a result, RV1 could be more attractive for inclusion in immunization programs as countries transition away from Gavi support. Any change of presentation during this transition phase will impact total co-financing amounts.

Additional measures are being put into place to support access to pricing that would allow recently Gavi-transitioned countries to sustain RV immunization programs that were begun with Gavi support. Fully self-financing countries can also choose to be included in UNICEF tenders on behalf of Gavi countries, or develop approaches to procure vaccines via UNICEF's Vaccine Independence Initiative revolving fund or the PAHO Revolving Fund. RV vaccine manufacturers are assisting by offering reduced prices to recently Gavi-transitioned countries. GlaxoSmithKline, which produces Rotarix® (RV1), is offering a ten-year price freeze to fully self-financing countries that introduced RV1 with Gavi support. Merck, which produces RotaTeq® (RV5), has extended the Gavi price to Gavi-transitioned countries with a Gross National Income per capita not exceeding 3,200 USD until 2025.

Global market for RV Vaccines: Price and value

The global demand for RV vaccines is growing. According to Dr. Carsten Mantel of the WHO, the global market for RV vaccines rose from 12 million courses in 2010 to approximately 36 million courses – about 1.3 billion USD – in 2015. The market is projected to grow approximately 130 percent through 2025 and global demand is expected to exceed more than 100 million RV courses administered per year by 2025, particularly in low- to middle-income countries.

While the price of RV vaccines are higher than most widely implemented vaccines; they are consistently offered at a lower price than other new vaccines such as aP-containing vaccines, HPV and PCV vaccines. RV vaccine prices are tiered approximately by country income level, with some overlap between income groups. Regional location may also influence pricing. The current weighted average price of RV vaccines for Gavi is 4.80 USD per course – 4.17 USD per course for RV1 and 10.50 USD per course for RV5. PAHO receives RV1 for 6.50 USD per course. UNICEF has access to RV1 and RV5 at 4.26 USD and 10.50 USD per course, respectively. The U.S. CDC pays the highest price for RV vaccines, at 173.50 USD per course for RV1 and 199.47 USD per course for RV5.

RV1 is in use by most countries seeking to include RV vaccines in their national immunization programs due to its smaller cold chain footprint, its two-dose regimen compared to RV5's three-dose regimen and the vaccine vial monitor built into its cap that clearly indicates to healthcare workers whether or not a vial of vaccine can be used. 95 percent of countries that have introduced RV vaccine globally purchase RV1, representing 77 percent of the global volume of RV vaccines purchased. The Gavi co-pay is the same for RV1 and RV5 – approximately 0.30 USD per course. Many countries procure through UNICEF (42 percent, 8 countries: all Gavi-eligible or in transition), while all non-eligible UMICs and HICs (11 countries) self-procure the vaccine. Though the Gavi co-pay is equal for both vaccines – approximately 0.30 USD per course – this price difference is important for countries to consider as they design rotavirus immunization programs that will be sustainable beyond Gavi graduation.

Challenges affecting demand level and timing: Country readiness for vaccine introduction and sustainable financing once introduced

Several major issues face countries introducing RV vaccines into their national immunization program. Delayed country readiness can cause setbacks to effective vaccine introduction. This can include insufficient cold chain and health systems preparation, and lack of training of healthcare workers and immunization professionals.

Concerns surrounding budgeting for RV vaccine programs have been identified as important potential barriers to RV vaccine introduction. Competing priorities for national health budgets, such as inactivated polio vaccine introduction or outbreaks of emerging infections such as Ebola, can make it difficult to secure funding for RV vaccine programs. Additionally, concerns about long-term sustainability of a RV vaccination program can reduce political will for RV vaccine introduction.

63 of the 81 countries (78 percent) that have introduced RV vaccines into their national immunization program have included RV1 (four countries have included both RV1 and RV5). According to Dr. Duncan Steele of the Bill and Melinda Gates Foundation, this preference for one vaccine presentation combined with the lack of locally-produced vaccines in most countries can contribute to supply problems despite the availability of another effective vaccine. However, uncertain short- and long-term demand in developing countries increases risk for manufacturers, reducing the number of market entrants, delaying development efforts and keeping prices higher than desired.

Dr. Steele provided supply- and demand-side interventions that he indicated could address these problems, helping lower market entry barriers and costs. Supply-side interventions included that research and discovery efforts be largely publicly funded, including transfer and availability of intellectual property rights, and that clinical development costs be shared with public health partners or governments. Additionally, he suggested sharing costs of vaccine clinical trials and other studies in low-resource settings, as well as providing technical assistance and support for developing country manufacturers, including development, production, regulatory and legal expertise. Demand-side interventions included WHO policy-making to reduce risk for vaccine manufacturers and support country decision-making, vaccines subsidized by donors such as Gavi, and country support for immunization system strengthening and vaccine introduction.

Cost-effectiveness and affordability

The WHO's Vaccine Product Price and Procurement Project (V3P) was designed to gather information that can be used to inform countries and stakeholders on vaccine policy and programming (27). V3P identifies price ranges and budget spending to facilitate country planning and budgeting for RV vaccination programs. It also helps countries develop a better understanding of the market and what factors influence prices in order to shed light on the possible factors behind the price a country will pay for RV vaccines. It enables countries to make informed decisions regarding the prices they are willing and able to pay by helping them compare prices to those paid by other, similar countries. Through these activities, V3P aims to make the vaccine market – including the RV vaccine market – more transparent and to measure progress toward improved vaccine affordability.

Dr. Clint Pecenka of PATH presented the results of a RV vaccination cost-effectiveness study in Bangladesh and the implications of those results for immunization policy in Asia. This study examined nationwide RV vaccine introduction in infants in 2016 using the Provac Initiative's TRIVAC model that was designed for use at a country level to perform national and sub-national cost-effectiveness evaluations. Examining baseline mortality and vaccine price paid, the study concluded that RV vaccination in infants was cost-effective in Bangladesh, even without Gavi support or even with relatively low mortality rates. Dr. Pecenka also concluded that hospitalization, vaccine, delivery and household costs are the most likely to affect cost-effectiveness in Asia compared to regions with higher RV mortality.

New RV vaccines

The RV vaccine pipeline

A rich RV vaccine pipeline currently exists with candidates in all stages of development (Table 2).

Table 2. Rotavirus vaccine development pipeline*****

Vaccine	Manufacturer	Stage of development	Mode of Administration	References
BRV-PV	Serum Institute of India	Phase I (liquid); Phase III (lyophilized)	Oral	30
BRV-PV	Epicentre	Phase III	Oral	31
BRV-PV	Shantha	Discontinued after Phase III	Oral	32-34
RV3-BB	Murdoch Childrens Research Institute, BioFarma	Phase IIb	Oral	35, 36
CDC-9	U.S. Centers for Disease Control and Prevention	Pre-clinical	Oral; Intradermal	37-41
P2-VP8	Medical Research Council Respiratory and Meningeal Research Unit	Phase I/II	Parenteral	42, 43

Notes: *Data compiled as of August 2017. BRV-PV – Pentavalent bovine-human reassortant rotavirus vaccine; BRV-TV – Tetravalent bovine-human reassortant rotavirus vaccine; RV3-BB – human neonatal rotavirus vaccine; CDC-9 – Monovalent CDC-9 G1P8 reassortant inactivated rotavirus vaccine; P2-VP8 – Non-replicating parenteral P2-VP8 subunit vaccine.

New RV vaccines will ensure adequate global vaccine supply and diversity, and likely resulting market pressure will help lower RV vaccine prices. Additionally, novel vaccines have the potential to improve effectiveness and impact in developing settings, and may reduce risk of intussusception even further (28, 29). New technologies may also help reduce cold chain requirements that pose a challenge for immunization programs in low-income countries.

Inactivated RV vaccines

Significant advances have been made in developing inactivated RV vaccines (IRV). IRV could have important advantages over current live-attenuated RV vaccines. An inactivated, non-replicating vaccine is more likely than live-attenuated, oral RV vaccines to yield a comparable immune response in children in any setting, as it faces fewer challenges such as interference by oral polio vaccines, micronutrient deficiencies or existing infection with other enteric diseases (29). Such vaccines could also be administered concomitantly with other vaccines and are not expected to cause intussusception (30, 31). They also would be less costly to develop, as clinical trials to demonstrate efficacy could be smaller and take less time to complete due to the lack of concern for intussusception. IRV would also allow for greater ease of implementation by eliminating separate cold chain requirements; RV vaccines currently in use have different cold chain requirements from routine national immunization program vaccines, which can make implementation logistically difficult.

Improving existing vaccine performance and delivery

While the development of new RV vaccines is critical to improving RV vaccine access and uptake, strategies and technologies for improving the performance and delivery of existing RV vaccines was also an important topic of conversation at this year's meeting. Dr. Carl Kirkwood of the Bill and Melinda Gates Foundation proposed that one way to improve performance of existing RV vaccines was to alter the currently recommended delivery schedule. For example, RV1 is used in a two-dose product administered at six and 10 weeks of age. However, a three-dose course has been shown to have improved IgA seroconversion and exhibited a trend toward improved effectiveness compared to the two-dose regimen. Thus, implementing a three-dose course could be an effective means of improving RV1 vaccine effectiveness in regions where RV vaccines have been shown to be relatively less effective in reducing disease burden. Kirkwood also proposed that a booster dose at nine months of age or neonatal immunization may be effective methods of increasing RV vaccine effectiveness by improving RV vaccine-induced protection.

Researchers at the MSD Wellcome Trust Hilleman Labs are developing a thermostable RV vaccine formulation that would allow for greater stability and reduce cold chain burden. This thermostable vaccine consists of a live,

oral, pentavalent, lyophilized (RV5 antigen bulk) vaccine that is immunologically non-inferior and similar to RV5 in safety and tolerability. The lyophilized vaccine is distributed in a two-chambered integrated reconstitution and administration device (IRAD) as a single dose that is stable for more than six months at 45 degrees Celsius, 20 months at 37 degrees Celsius, and for more than three years at 2-25 degrees Celsius. Two rounds of user acceptability trials yielded an IRAD that was very well accepted by immunization professionals. A Phase I/II clinical trial showed the thermostable RV5 formulation was safe and well-tolerated in healthy adults. Results of a Phase IIb clinical trial conducted in an infant cohort which was completed in December 2016 are forthcoming.

New insights into RV pathogenesis and immunology

Researchers presented the latest insights into RV pathogenesis and immunology, with a particular focus on addressing why RV vaccines exhibit lower effectiveness in low income regions.

Innate immune interference with RV vaccination

Dr. Sashi Ramani and Dr. Mary Estes of the Baylor College of Medicine reported that innate intestinal health may be affecting vaccine effectiveness. Endogenous interferon production does not limit RV replication; however, exogenous administration of Type I interferons restricted virus replication, indicating that extra-endothelial sources of Type I interferons may be critical for limiting viral replication in the gut. These results led the study authors to hypothesize that high cytokine concentrations in the gut induced by pre-existing enteric infections at the time of vaccination could interfere with vaccine virus replication, limiting the development of vaccine protection.

Intestinal glycan polymorphisms impact on RV strain susceptibility and vaccine effectiveness

A topic that is currently of particular interest to the RV field is the effect of genetic polymorphisms in the expression of intestinal glycans on susceptibility to RV strains and vaccines. VP8 of human RV bind histoblood group antigens (HBGA). RV researchers hypothesize that differences in these HBGA may lead to differential susceptibility to RV infection and may affect the response to oral RV vaccines.

Ramani, Estes and colleagues found that antibodies blocking the HBGA α-(1,2) fucosylated glycans protected human intestinal epithelial cells cultured *in vitro* from infection with the P[8] VP8* RV strain. An ongoing study in

this lab is investigating whether HBGA-blocking antibodies are present in infant serum, and whether or not these antibodies could be a correlate of protection against acute RV gastroenteritis or of vaccine failure. The study authors hypothesize that vaccination is less likely to induce protection in infants with higher pre-vaccination levels of HBGA-blocking antibodies, and that infants who showed a boost in HBGA-blocking antibodies post-vaccination are more likely to be protected against acute RV gastroenteritis.

Dr. Lennart Svennson and his colleagues at Linkoping University presented their finding that differences in Lewis antigen secretor status influenced susceptibility to different RV genotypes and the response to RV vaccines. Lewis A-expressing individuals (non-secretors) were found to be strongly resistant to P8 RV strains, while Lewis-negative individuals were more susceptible to P6 strains, independent of secretor status. Interestingly, non-secretors exhibited no or little immune response to P8-based RV vaccines, which may have an effect on RV vaccine effectiveness and impact.

Gut microbiome modulation of RV vaccine response

Recent studies indicate that in addition to the gut immune response and HBGA expression, the composition of the gut microbiome may also be playing a significant role in modulating the infant immune response following RV vaccination. Dr. Vanessa Harris's group at the University of Amsterdam found significant differences in the gut microbiomes of vaccine responders and non-responders. The gut microbiome compositions of vaccine responders were more similar to those of responders in different countries than to non-responders from their own birth cohort. These studies suggest that the RV vaccine immune response may be related to the immune-stimulatory capacity of bacteria in the microbiome, though further studies are required to better understand this connection.

Recommendations and Conclusions

Global RV vaccine uptake has been slower than expected, with serious gaps remaining in Asia. Despite this, global vaccine uptake is increasing and RV vaccination will have averted an estimated 2.4 million deaths between 2007 and 2025. In order to improve RV vaccine uptake, health care workers should be well-informed on the risks and benefits of RV vaccination.

Experts at the meeting made several recommendations to improve RV vaccine uptake and effectiveness. In spite of the disparity in RV vaccine effectiveness between low- and high-income countries, RV vaccination is recommended for inclusion in all national immunization programs due to the significant drop in all-cause diarrhea

hospitalizations associated with RV vaccination, regardless of the setting. RV vaccination should be included as part of a comprehensive strategy to control diarrheal disease, including clean water, sanitation, oral rehydration therapy, breast feeding and zinc treatment.

Further research will be required to identify the mechanisms underlying reduced RV vaccine effectiveness in developing country settings. Current research indicates immune responses induced by pre-existing enteric infections, differences in the gut microbiome, genetic polymorphisms in the expression of intestinal glycans and interference by concomitant oral polio vaccine administration may all be playing a role in this disparity. Novel vaccines currently in clinical development or alternative dosing schedules for existing vaccines have the potential to improve RV vaccine effectiveness in low-income countries.

Studies assessing the impact of withholding breastfeeding prior to RV vaccination have concluded that breastfeeding infants does not interfere with RV vaccine-induced immune protection. Due to the health benefits and reduced risk of diarrheal disease associated with breastfeeding, it is not recommended mothers stop breastfeeding in advance of RV vaccine administration.

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) lifted age restrictions on RV vaccination in 2013. Despite that, age restrictions on RV vaccination are still in place in 60 percent of countries administering the vaccine. It is recommended that countries ensure timely administration of RV vaccine doses. The first dose should be administered before RV gastroenteritis is likely to occur – as soon as possible after six weeks of age, concurrent with the first dose of diphtheria, tetanus and pertussis vaccine.

In order to continue monitoring the safety of RV vaccines, it is recommended that, where possible, countries enhance routine Adverse Events Following Immunization reporting and management systems, collect sufficient surveillance data to establish a baseline rate of natural intussusception before vaccine introduction, conduct self-controlled case-series studies where appropriate, and monitor epidemiological impact of RV vaccination through high-quality surveillance.

RV vaccination has successfully reduced the burden of RV disease in countries around the world. The 12th International Rotavirus Symposium served as an excellent opportunity for experts and stakeholders in the field to come together to assess RV vaccine impact and plan future efforts to ensure continued progress.

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