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Technical Information for National-level Rotavirus Vaccine Policy Recommendations Summary of available evidence to guide decision-making

A high-level summary of evidence available for national-level technical policy-making around the use of rotavirus vaccine (RVV), with a focus on low- and middle-income countries and adapted to a NITAG-focused decision-making framework. Made possible with support from Gavi, the Vaccine Alliance.

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Purpose and overview

This set of summaries related to rotavirus vaccine (RVV) evidence was developed as a reference by Johns Hopkins' International Vaccine Access Center (IVAC) to facilitate access to recent research around rotavirus vaccine relevant to vaccine use in routine immunization programs worldwide. National Immunization Technical Advisory Group (NITAG) members, Expanded Program on Immunization (EPI) staff and other vaccine decision-makers are the primary audiences for these summaries.

The goal has been to put forth a series of high-level summaries of the best available data that may assist these groups in synthesizing and locating the available evidence needed to formulate decisions regarding introduction or optimal use of RVV in multiple settings. These briefings have been based upon several expert analyses, as described below, which were developed and vetted by a number of international rotavirus and vaccine experts.

The format of this document follows the structure of the SIVAC Initiative's document, *Elements to Consider in Developing a Framework for Issuing Immunization Related Policy Recommendations.* In this overview of evidence around RVV, we have been able to include statements summarizing research in the following areas:

*	Section 1: Rotavirus Vaccine and Immunization Characteristics	p. 4-18
*	Section 2: Rotavirus Disease	p. 19-26
*	Section 3: RVV Economic Considerations	p. 27-34

The 4th section of the *Elements to Consider...* is dedicated to "Health Policy and Programmatic Issues". Given the context-specific nature of the data needed for each country to evaluate issues in this area, we are not able to address and summarize these sections here. Some issues suggested in the SIVAC Framework in section 3, described as Operational Considerations, are also not addressed here because of the country-specific nature of these issues.

The final section of this document is:

 Appendix: Elements to Consider in Developing a Framework for Issuing Immunization Related Policy Recommendations
 p. 35-37

Important notes about this document

- The Rotavirus Vaccine Briefing documents (sections 1-3) were developed in multiple stages as follows:
 - a. In 2016 the Rotavirus Organization of Technical Allies (ROTA Council), co-lead by Johns Hopkins IVAC and PATH, in technical partnership with CDC, produced a synthesis of evidence around rotavirus vaccines aimed at low-, and middle-income countries who have not yet introduced rotavirus vaccines. Having been developed and reviewed by crucial global rotavirus experts, this evidence synthesis, entitled *Rotavirus: common, severe, devastating, preventable*, was mined for key references and data to form the basis of the Rotavirus NITAG Briefing documents. (The ROTA Council publication can be found here: <u>http://rotacouncil.org/resources/101142-004_RotaExecSummary2015_V9r2.pdf</u>)
 - b. Targeted, but non-systematic, literature searches were performed to address the remaining topics outlined in SIVAC's Vaccine Decision-Making Framework. Much of these additional

searches were used to inform section 3 on vaccine economics and societal considerations.

c. On May 1, 2016, the journal *Clinical Infectious Disease* published a supplement entitled *Health Benefits of Rotavirus Vaccination in Developing Countries.* This resource allowed us to update some references and fill in all remaining gaps possible.

Evidence and data gaps for rotavirus vaccines

While the Rotavirus Vaccine Briefing documents represent a synthesis of as much information as could be found relevant to developing nations, there were several areas where information was unavailable to satisfactorily address the potential questions of NITAGs. In particular, these gaps include:

- Information related to costs and financing within a given country. This type of information is likely to be of critical importance in nations who have not yet made a decision to introduce rotavirus vaccines but is not possible to fully assess within the scope of these briefings.
- In general, there is a dearth of information on the effectiveness of rotavirus vaccine in Asian populations, as most low-income nations who have introduced rotavirus vaccines are in Latin America and Africa.
- While several countries in Africa are participating in intussusception surveillance activities both countries currently using rotavirus vaccines and those who have not yet introduced – a similar network is not yet fully established in the Asian region. It may be helpful for decisionmaking in Asia to have a better understanding of background rates of intussusception in the region and to understand how rotavirus vaccine in routine use may or may not affect these rates.
- Much effort is being focused on trying to both understand the reason for lower vaccine efficacy in resource-poor settings, and to boost this lower efficacy. Several studies are underway investigating both questions.
- Questions and comments may be directed to Julie Younkin jbuss2@jhu.edu

Section 1: Rotavirus Vaccine and Immunization Characteristics

Rotavirus Vaccine and Immunization Characteristics Summary

Two oral rotavirus vaccines (RVV), the monovalent Rotarix[®] and the pentavalent RotaTeq[®], have been licensed in over 100 countries and are prequalified by the World Health Organization (WHO) for procurement. In clinical trials and in real world effectiveness studies, these vaccines have a major impact on the morbidity and mortality of rotavirus disease globally, with a sustained response beyond the year of vaccination. In addition, rotavirus vaccines have a substantial impact on rotavirus gastroenteritis-related healthcare utilization. Apart from a low risk of intussusception, the current rotavirus vaccines are considered to represent an acceptable risk-benefit profile, are considered safe and well tolerated. As of December 2016, these RVVs have been implemented nationally in more than 80 countries, 40 of which are low-income GAVI eligible countries.

VACCINE EFFICACY & CHARACTERISTICS

The two Rotavirus vaccines (RVVs), Rotarix[®] and RotaTeq[®] licensed for global use, shown to be safe and effective in large-scale clinical studies and in real-world use, are both prequalified for procurement by the WHO.¹ These RVVs have been licensed in >100 countries worldwide since 2006. As of December 2016, the RVVs have been implemented in the national immunization programs of more than 80 countries, including 40 low-income countries that are eligible for support from Gavi, the Vaccine Alliance. An additional 7 countries have introduced sub-nationally, of which 2 are Gavi-eligible.

Vaccine / Manufacturer	Rotarix ^{® 2} GlaxoSmithKline (GSK)	RotaTeq® ³ Merck & Co., Inc.	
Formulation	Monovalent attenuated human rotavirus strain (RV1)	Pentavalent, human-bovine reassortant vaccine (RV5)	
Strains Present In Vaccine	G1P[8]	G1, G2, G3, G4, and P[8]	
Cross Strain Protection	Yes, broad protection demonstrated	Yes, broad protection demonstrated	
Efficacy Against Severe Rotavirus Diarrhea In	95.8-100%	85-96%	
Children < 1 Year	(High-Income Countries)	(High-Income Countries)	
Efficacy Against Severe Rotavirus Diarrhea In	49-85%	51-64%	
Children < 1 Year	(Low- And Middle-Income Countries)	(Low- And Middle-Income Countries)	
Dosage	At least 106 of live attenuated human G1P[8] particles per dose	A minimum titer of approximately 2.0 to 2.8 x 106 infectious units per reassortant and not greater than 116 x 106 infectious units per aggregate dose	
	2-dose	3-dose	
Administration Schedule	Same schedule as DPT1 and 2	Same schedule as DPT1, 2 and 3	
Product Presentation	 Liquid vaccine in oral, single-dose applicator Liquid vaccine in squeezable, polyethylene single-dose tube Lyophilized vaccine, reconstituted with CaCO₃ buffer, oral applicator 	Liquid vaccine in oral, squeezable tube	
Excipients	Sucrose, dextran 40, sorbitol, amino acids, Dulbecco's modified eagle medium, calcium carbonate, xanthum gum. Calcium carbonate buffer as diluent.	Sucrose, sodium citrate, sodium phosphate, sodium hydroxide, polysorbate 80, cell culture media, trace amounts of fetal bovine serum.	
Shelf Life	36 months	24 months	

Vaccine Vial Monitor Label?	Yes	No
Storage Requirements	2–8º C, not frozen; protect from light	2–8º C, not frozen; protect from light

Chart adapted from *Rotavirus: common, severe, devastating, preventable*, pg. 11.⁴

There are three orally administered rotavirus vaccines licensed for national markets only: ⁵

- ROTAVAC^{®,} manufactured by Bharat Biotech International Limited and licensed for use in India in 2014.
- Rotavin-M1[®], manufactured by the Center for Research and Production of Vaccines and licensed for use in Vietnam in 2007.
- Lanzhou Lamb Rotavirus Vaccine manufactured by the Lanzhou Institute of Biological Products and licensed for use in China in 2000.

Manufacturers in India, China, and Brazil are developing other new vaccines.

VACCINE ADMINISTRATION SCHEDULE

World Health Organization Recommended Vaccination Schedule: 6

Given that a previous vaccine product (which is no longer available) had been shown to be associated with an increase in risk of intussusception – a condition which naturally occurs with greater frequency in older infants (see the sections on **Vaccine Safety** and **Intussusception** below) – the WHO's initial 2009 rotavirus vaccination recommendation was to begin rotavirus vaccination by 15 weeks of age and conclude by 32 weeks of age to minimize any additional intussusception risk. This meant that children older than 15 weeks of age who had not received any rotavirus vaccine would miss out on rotavirus immunization entirely.

After immunization of hundreds of millions of infants worldwide with the two currently available vaccine products, only a very small increase in intussusception (1 to 4 additional cases per 100,000 vaccinated) has been reported by some countries. In controlled clinical trials, neither of the available products was found to be associated with an increase in intussusception.

A 2013 review of all available evidence led the WHO to amend their recommendation for rotavirus vaccine administration, concluding that although early vaccine administration (initiated at or by 6 weeks and completed by 32 weeks of age) is preferable, the benefit of relaxing the age restrictions far outweighed the risks. Indeed, a 2012 study by the US Centers for Disease Control (CDC) estimated that relaxing the age restrictions so that rotavirus vaccine could be administered up to 3 years of age would afford protection to many more children during the period of early childhood with the greatest risk of severe rotavirus infections, and would thus avert more than 47,000 rotavirus deaths worldwide while causing less than 300 additional deaths related to intussusception. The resulting benefit is 154 rotavirus deaths averted per 1 intussusception death.⁷

Specifically, the current WHO recommendation⁶ for rotavirus vaccine administration is as follows:

- *RV1* should be administered in a 2-dose schedule together with DTP1 and DTP2, and with an interval of at least 4 weeks between doses
- *RV5* should be administered in a 3-dose schedule together with DTP1, DTP2 and DTP3 with an interval of at least 4 weeks between doses
- Given that the highest burden of rotavirus gastroenteritis (RVGE) is in children under 2 years of age, it is recommended that the course of immunization be completed before 24 months of age wherever possible.

Note: Differences in rotavirus immunization schedules are generally due to existing routine immunization program schedules and the logistics of delivering multiple vaccines at the same time.

Schedules currently in use

Each country has its own immunization schedule. Both rotavirus vaccines are given orally but differ in the number of doses in the series.

- Low-Income Countries: In general:
 - > RotaTeq[®] (RV5) is given in three doses at 6 weeks, 10 weeks, and 14 weeks of age
 - > Rotarix[®] (RV1) is given in two doses at 6 weeks and 10 weeks of age.

Middle- and Upper-Income Countries

- > RotaTeq[®] is given in three doses at 2 months, 4 months, and 6 months of age
- > Rotarix[®] is given in two doses at 2 months and 4 months of age.

Countries using rotavirus vaccine by product and dosing schedule currently in use (2016):





Source: IVAC's VIEW-hub, December 2016. <u>www.view-hub.org</u>

CORRELATES OF PROTECTION

Research aimed at understanding the variable levels of protection conferred by the two licensed RV vaccines in different settings is hindered by the lack of an established correlate of vaccine-induced protection.⁸

- **Correlates of Protection**: A number of proposed mechanisms of protection against RV infection in humans exist. In many of the efficacy studies reported to date, the induction of RV-specific serum IgA has been used as a marker of vaccine response ⁹⁻²² and, in addition, type-specific neutralizing antibody titers have been reported in some trials.^{9, 10, 18, 19, 21, 23}
- **Seroresponse rates**, either the percentage of infants undergoing seroconversion ('negative' to 'positive') or the percentage of infants with at least a threefold rise in titre, have been reported to indicate a response to the vaccine.²³
- Although homotypic protection may predominate, both vaccines also induce high levels of heterotypic protection.²⁴

VACCINE REAL WORLD EFFECTIVENESS

Rotavirus vaccine effectiveness is similar to efficacy levels found in clinical trials

• Effectiveness Against Rotavirus Hospitalizations: Post licensure effectiveness data of both rotavirus vaccines against rotavirus hospitalizations, in high and upper middle-income countries, and in lower-middle income countries in Latin America, is similar to the efficacy demonstrated in the phase 3 clinical trials. ²⁵⁻⁴⁷



Estimated vaccine effectiveness by study and World Bank income group

Source: Tate, J.E. & Parashar, U.D., Rotavirus Vaccines in Routine Use, p.1296²⁵

Vaccine Efficacy in Low-Income Countries

Unlike with injectable vaccines, live oral vaccines have different efficacy in high-income versus low-income populations. Rotavirus vaccine efficacy ranges from 90% in high socioeconomic populations to 50% in low socioeconomic populations.⁵¹ In addition, over 2 years, vaccine efficacy against severe rotavirus gastroenteritis appeared to be somewhat lower in the African countries than in the Asian countries.^{10, 11, 19, 51}

Several suggestions have been put forth to account for the differential efficacy across regions, including: various immunological factors such as higher titers of transplacental and/or breast-milk antibodies; micronutrient malnutrition; interfering gut flora (tropical enteropathy); intercurrent infections; or an altered distribution of circulating rotavirus strains.^{52, 53}

While naturally acquired rotavirus infections protect against subsequent infections across a range of socioeconomic populations, a key difference is that in low socioeconomic populations, the proportion of infections that result in symptomatic disease does not rapidly decline with each subsequent infection as occurs in high- and middle socioeconomic populations. In the low socioeconomic populations, a similar proportion of primary or secondary infections result in severe rotavirus disease, as do tertiary and subsequent infections.⁵¹

Despite the lower vaccine efficacy rates in populations with low socioeconomic status, vaccines have the potential to prevent significantly more disease given this population's much higher prevalence of disease, severe disease and subsequent severe infections.^{51, 54}

• Select mid- to low-income country data:

- Nicaragua: A regimen of 3 doses of RV5 was estimated to be 58% effective against severe RVGE and 77% effective against very severe RVGE. ⁴⁷
- Bolivia: the adjusted effectiveness of one dose of RV1 against hospital admission for rotavirus was 69% with rotavirus negative controls and 77% with non-diarrhea controls. With both control groups, protection was sustained through two years of life, with similar efficacy against hospital admission among children under 1 year (64% and 77%) and over 1 year of age (72% and 76%). ⁵⁵
- Malawi: Vaccine effectiveness for two doses of RV1 was 64% in test-negative control individuals and 63% in community controls. For children with more severe disease, vaccine effectiveness was 68% in test-negative control individuals and 68% in community controls. Nearly 2 years after vaccine introduction, both the proportion of the under-5 yrs. of age RVGE hospitalizations among infants and the absolute rate of RVGE hospitalizations among infants had fallen significantly.^{4, 56}

DURATION OF PROTECTION

Although published randomized controlled trials (RCTs) were not adequately powered to statistically conclude the degree to which efficacy wanes over time, effectiveness of both the monovalent rotavirus vaccine (RV1) and pentavalent rotavirus vaccine (RV5) currently licensed, extends over the first few years of life.^{13, 14, 48}

- For RV5, one RCT involving 11 countries, reported efficacy against severe rotavirus gastroenteritis (RVGE) at 98%/88% during the first and second rotavirus seasons respectively.¹⁵ An extension of this trial demonstrated a sustained reduction in the number of hospitalizations for RVGE 3 years after vaccination.¹³
 - Sub-Saharan Africa: a 3 country study reported an estimated efficacy of 64.2% during the first and 19.6% in the second year after vaccination.¹⁹
- For RV1, data from RCTs were consistent with little decrease in the efficacy against severe RVGE from season one to the second season of follow-up:
 - > Latin America: from 83% to 79% ⁵⁰
 - > Europe: from 96% to 86% ¹³
 - > Three high- income countries in Asia: sustained efficacy of 100% during the third year of life. 49

VACCINE INDIRECT EFFECTS

Indirect protection of children who were age-ineligible for rotavirus vaccine has been observed in some high- and upper-middle-income countries.²⁵

- Impact on All-Cause Diarrheal Hospitalizations: Significant public health benefit was observed with a decrease in all-cause diarrhea hospitalizations in children 0-2 years of age following RV1 and RV5 vaccine introductions as follows. ⁵⁷
 - > Belgium (RV1 & RV5) 33%
 - > Brazil (RV1) 17-48%
 - > El Salvador (RV1) 28-37%
 - > Mexico (RV1) 40%
 - > Nicaragua (RV5) 40%
 - Indirect Protection of the Unimmunized/Herd Immunity: Rotavirus vaccination is associated with indirect protection of children too old to receive the vaccine and of young adults, demonstrating that the

benefits of rotavirus vaccines extend beyond immunized infants and provide indirect protection to unvaccinated children and adults by reducing the spread of the virus. ⁵⁸

- Rotavirus hospitalizations among children 2–4 years of age who were age-ineligible to receive the vaccine declined by 41%–80%, and all-cause diarrhea hospitalizations declined by 35%–41%. ^{59,60}
- Significant reductions of 8%–30% in unspecified gastroenteritis hospitalizations and 53%–71% in RVGE hospitalizations have also been observed among older children and young adults 5–24 years of age. ^{58,61}

VACCINE EFFECT ON CIRCULATING ROTAVIRUS STRAINS

Risk of Post Vaccine Era RV Strain Shift: Available vaccines have been effective against the range of circulating serotypes, however, close monitoring is needed because small differences in effectiveness against individual serotypes may change future strain distribution. ⁵⁷

In countries with long-term strain surveillance, strains show great diversity over time with no clear pattern, so the ability to link a change in serotype distribution to the introduction of vaccines will take significant time to investigate. ⁵⁷

VACCINE SAFETY INFORMATION

Adverse Events: Large-scale clinical trials for the two approved rotavirus vaccines found them to be safe and efficacious. In a large-scale review of vaccine trial occurrence of fever, diarrhea and vomiting at several time points, there was no difference between vaccine and placebo.⁶² The most common manufacturer reported adverse events include:

- RotaTeq: diarrhea, vomiting, irritability, otitis media, nasopharyngitis and bronchospasm.³
- Rotarix: irritability, cough/runny nose, fever, loss of appetite and vomiting.²

See full manufacturers prescribing information for full report of adverse events.

Intussusception: Intussusception, an acute bowel obstruction, is caused by the telescoping of one part of the bowel into an adjacent section, resulting in obstruction and reduced blood flow. The etiology of intussusception is not well understood and occurs naturally in infants in the absence of vaccination and is typically seen in infants 4-7 months of age, although it can occur at any age. Untreated, it can result in bowel necrosis, perforation and can be fatal. Although rare, in infancy the most common type of intussusception is idiopathic, and is associated with adenoviruses in up to 40% of cases. Idiopathic intussusception occurs with international and ethnic variation in rates and incidence over time. Minimal seasonality is noted. ^{4, 63, 64}

In July 2014, the Rotavirus Organization of Technical Allies (ROTA Council) convened a meeting of technical experts, funders, advocacy organizations and other partners to discuss the available evidence around intussusception and any rotavirus vaccines. Conclusions for the meeting were that the benefits of rotavirus vaccination outweigh any slight increased risk of intussusception but that continued research focus on the mechanisms, causes and rates of intussusception is needed. For more information on this meeting, informing evidence and conclusions, please see: http://www.tandfonline.com/doi/full/10.1080/21645515.2016.1197452

Intussusception Rates: Latest published intussusception rates as of 2013 are as follows:



Source: Jiang, et al. Childhood Intussusception: A Literature Review PLoS One, 2013. 64

Risk for RV Vaccine Associated Intussusception: *Results of a recent meta-analysis showed a small increase in the overall relative risk of intussusception in infants, mostly during the first 7 days after administration of dose 1 and, to a lesser extent, dose 2.⁷⁸ The highest incidence of RV related intussusception occurs day 3-7 following RV vaccination and coincides with the peak period of vaccine virus viral replication.^{77, 79} Several post-licensure surveillance studies have been conducted to assess the risk of intussusception after vaccination in real-world settings.^{62, 65-68, 81-85} Select post-licensure data are as follows:*

- Mexico & Australia a low-level risk of 1-2 excess cases per 100,000 vaccinated children mostly in the first week after the first dose. ⁶⁵⁻⁶⁷
- > **Brazil** no increased risk after the first dose; low risk after the second vaccine dose. ⁶⁶
- > United States a risk of 1-5 excess cases of intussusception per 100,000 vaccinated infants. 68,69

WHO Intussusception Recommendation: Given the significant morbidity and mortality caused by diarrheal disease and rotavirus specifically, the WHO risk-benefit analysis concluded that the benefits of RV vaccination outweighed the low-level risk of intussusception and reaffirmed its recommendation for use in all countries globally. ⁷⁰

Kawasaki Disease: Kawasaki disease following administration of RV vaccines has been reported in a small number of infants. It is unclear whether the rates observed in these vaccinated infants are higher than expected in the normal population. Until further studies are conducted to investigate a potential association, it is currently not thought to be a related occurrence. ^{62, 71}

SAFETY IN SPECIAL POPULATIONS

Data has been collected and recommendations have been made on vaccine use in the following special populations/circumstances:

- **HIV Infected**: Rotavirus vaccines were well tolerated and elicited a satisfactory immune response without aggravating the immunologic or HIV condition. ^{72,73}
- **Breastfeeding and Pre-Term Infants**: Breastfeeding and premature infants do not seem to significantly impair the response to the RV vaccine and can be immunized at their chronological age. In one study (gestation median 34 weeks, range 25-36) there was no increase in adverse events in the vaccinated group. 62,74

• **Blood Transfusion**: Ideally vaccination should not occur within 42 days of receiving an antibodycontaining blood product. However, if the timing of a blood transfusion fell within 42 days of the final dose of rotavirus vaccine in a series, the vaccine should be given on time nonetheless.⁷⁵

VACCINE-REASSORTANT STRAIN SHEDDING:

Rotavirus vaccine strains replicate in the intestinal tract and can be shed in stool following vaccination. Transmission of vaccine or vaccine-reassortant strains is possible. One study estimated that such vaccine-derived reassortant–associated disease occurs at a rate of about 1 per 140 000 vaccinated infants. ⁷⁶

- After dose 1, rotavirus antigen shedding was detected by EIA in 50% to 80% (depending on the study) of infants at approximately day 7 and 0 to 24% at approximately day 30. After dose 2, rotavirus antigen shedding was detected in 4% to 18% of infants at approximately day 7, and 0 to 1.2% at approximately day 30. ⁷⁷
- The potential for transmission of vaccine virus was assessed in a clinical trial among twin pairs in the Dominican Republic. This study showed vaccine strain transmission in 19% of the unvaccinated twins, and seroconversion in 21% of the unvaccinated twins.⁷⁸

CONTRAINDICATIONS TO ROTAVIRUS VACCINE

Administration of Rotavirus vaccination is contraindicated in the following: ⁷⁰

- Hypersensitivity to Vaccine Components: severe hypersensitivity to any of the vaccine components
- **Severe Immunodeficiency**: contraindicated in severe immunodeficiency including severe combined immunodeficiency (SCID)
- **History of Intussusception**: There is no information on the risk of vaccinating infants who have a past history of intussusception. These vaccines are not routinely recommended for infants with a history of intussusception or intestinal malformations.
- Acute Gastroenteritis or Fever: in case of ongoing acute gastroenteritis or fever with moderate to severe illness, vaccination should be postponed.

SECTION 1: REFERENCES

- 1. World Health Organization. (2014, January 10). Vaccines, Rotavirus (online webpage). Retrieved from: http://www.who.int/biologicals/vaccines/rotavirus/en/
- 2. World Health Organization. (ver. 2013). Rotarix Package Insert. Retrieved from: http://www.who.int/immunization_standards/vaccine_quality/pq63_Rotavirus_lyophilised_GSK_product_insert.pdf
- 3. Merck & Co., Inc. (ver. November 2014). RotaTeq Package Insert. Retrieved from: https://www.merck.com/product/usa/pi circulars/r/rotateq/rotateq pi.pdf
- 4. Rota Council, (2016). *Rotavirus: common, severe, devastating, preventable*. Retrieved from: <u>http://rotacouncil.org/resources/101142-004 RotaExecSummary2015 V9r2.pdf</u>
- 5. Rosen, C.J. (2015). Rotavirus Disease and Vaccines: Frequently Asked Questions. PATH. Retrieved from: http://sites.path.org/rotavirusvaccine/files/2015/01/PATH-Rotavirus-Disease-and-Vaccines-FAQs-EN-2015.01.09.pdf
- 6. World Health Organization. (2013). Rotavirus vaccines: WHO Position Paper. *Weekly Epidemiological Record*. 88(5), 49-64. http://www.who.int/wer/2013/wer8805.pdf?ua=1
- Patel, M., Clark, A., Sanderson, C., Tate, J., Parashar, U. (2012) Removing the Age Restrictions for Rotavirus Vaccination: A Benefit-Risk Modeling Analysis. *PLoS Med*, 9(10). doi: 10.1371/journal.pmed.1001330 <u>http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001330</u>
- Parashar, U., Steele, D., Neuzil, K., Quadros, C., Tharmaphornpilas, P., Serhan, F, & Glass, R. (2013). Progress with rotavirus vaccines: summary of the Tenth International Rotavirus Symposium. *Expert Reviews Vaccines*, 12(2), 113–117. doi: 10.1586/ERV.12.148. Retrieved from: <u>https://www.researchgate.net/publication/235646612 Parashar U et al Progress with rotavirus vaccines summary of the Tenth I</u> <u>nternational Rotavirus Symposium Expert Rev Vaccines 12 113-117</u>
- Armah, G.E., Breiman, R.F., Tapia, M.D., Dallas, M.J., Neuzil, K.M., Binka, F.N., . . . Steele, A.D. (2012). Immunogenicity of the pentavalent rotavirus vaccine in African infants. *Vaccine*, 30(Supplement 1), A86–A93. doi: 10.1016/j.vaccine.2011.10.006. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/22520142</u>.
- Zaman, K., Dang, D.A., Victor, J.C., Shin, S., Yunus, M., Dallas, M.J... Ciarlet, M. (2010). Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Lancet*, 376(9741), 615–623. doi: 10.1016/S0140-6736(10)60755-6. Retrieved from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60755-6/abstract.
- 11. Madhi, S.A., Cunliffe, N.A., Steele, D., Witte, D., Kirsten, M., Louw, C, . . . Neuzil, K.M. (2010). Effect of human rotavirus vaccine on severe diarrhea in African infants. *N. Engl. J. Med.* 362, 289–298. doi: 10.1056/NEJMoa0904797. Retrieved from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0904797
- 12. Lau, Y.L., Nelson, E.A., Poon, K., Chan, P., Chiu, S., Sung, R, ... Bock, H. (2013). Efficacy, safety and immunogenicity of a human rotavirus vaccine (RIX4414) in Hong Kong children up to three years of age: a randomized, controlled trial. *Vaccine*, 31, 2253–2259. http://dx.doi.org/10.1016/j.vaccine.2013.03.001
- Vesikari, T., Karvonen, A., Prymula, R., Schuster, V., Tejedor, J.C., Cohen, R, . . . Bouckenooghe, A. (2007). Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomized, double-blind controlled study. *Lancet*, 370(9601), 1757–1763. doi: <u>http://dx.doi.org/10.1016/S0140-6736(07)61744-9</u>. Retrieved from: <u>http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)61744-9/abstract</u>.
- Kawamura, N., Tokoeda, Y., Oshima, M., Okahata, H., Tsutsumi, H., Van Doorn, L.J... Han, H.H. (2011). Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. *Vaccine* 29(37), 6335–6341. doi: 10.1016/j.vaccine.2011.05.017. Retrieved from: <u>https://www.researchgate.net/publication/51191081 Kawamura N et al Efficacy safety and immunogenicity of RIX4414 in Japane</u> <u>se infants during the first two years of life Vaccine 29 6335-6341</u>
- Ruiz-Palacios, G.M., Pérez-Schael, I., Velázquez, F.R., Abate, H., Breuer, T., Clemens, S.C... O'Ryan, M., for the Human Rotavirus Vaccine Study Group. (2006). Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N. Engl. J. Med*, 354(1), 11– 22. Retrieved from: <u>http://www.nejm.org/doi/pdf/10.1056/NEJMoa052434</u>
- 16. Tregnaghi, M.W., Abate, H.J., Valencia, A., Lopez, P., Da Silveira, T.R., Rivera, L, ... Han, H.H. (2011). Human rotavirus vaccine is highly efficacious when coadministered with routine expanded program of immunization vaccines including oral poliovirus vaccine in Latin America. *Pediatric Infectious Disease Journal*. 30(6), e103–e108. doi: 10.1097/INF.0b013e3182138278. Abstract retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21378594.
- 17. Cunliffe, N.A., Witte, D., Ngwira, B.M., Todd, S., Bostock, N.J., Turner, A.M, ... Neuzil, K.M. (2012). Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial.

Vaccine, 30(Supplement 1), A36–A43. doi: 10.1016/j.vaccine.2011.09.120. Retrieved from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982044/.

- Vesikari, T., Matson, D.O., Dennehy, P., Van Damme, P., Santosham, M., Rodriguez, Z, . . . Heaton, P.M. (2006). Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N. Engl. J. Med*, 354(1), 23–33. Retrieved from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa052664.
- Armah, G.E., Sow, S.O., Breiman, R.F., Dallas, M.J., Tapia, M.D., Feikin, D.R, ... Neuzil, K.M. (2010). Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet*, 376(9741), 606–614. doi: 10.1016/S0140-6736(10)60889-6. Retrieved from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60889-6.
- Sow, S.O., Tapia, M., Haidara, F.C., Ciarlet, M., Diallo, F., Kodio, M, . . . Levine, M.M. (2012). Efficacy of the oral pentavalent rotavirus vaccine in Mali. *Vaccine*, 30(Supplement 1), A71–A78. doi: 10.1016/j.vaccine.2011.11.094. Abstract retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22520140.
- Shin, S., Anh, D.D., Zaman, K., Yunus, M., Mai, L.T., Thiem, V.D., . . . Ciarlet, M. (2012). Immunogenicity of the pentavalent rotavirus vaccine among infants in two developing countries in Asia, Bangladesh and Vietnam. *Vaccine*, 30(Supplement 1), A106–A113. doi: 10.1016/j.vaccine.2011.11.091. Retrieved from: https://www.researchgate.net/publication/230613985 Shin S et al Immunogenicity of the pentavalent rotavirus vaccine among in fants in two developing countries in Asia Bangladesh and Vietnam Vaccine 30 Suppl 1 A106-A113.
- Narang, A., Bose, A., Pandit, A.N., Dutta, P., Kang, G., Bhattacharya, S.K, ... Bock, H.L. (2009). Immunogenicity, reactogenicity and safety of human rotavirus vaccine (RIX4414) in Indian infants. *Human Vaccines*, 5(6), 414–419. Retrieved from: http://www.landesbioscience.com/journals/vaccines/article/8176.
- Ward, R.L., Knowlton, D.R., Zito, E.T., Davidson, B.L., Rappaport, R. & Mack, M. (1997). Serologic correlates of immunity in a tetravalent reassortant rotavirus vaccine trial. US Rotavirus Vaccine Efficacy Group. *Journal of Infectious Diseases*, 176, 570–577. Retrieved from: http://jid.oxfordjournals.org/content/176/3/570.full.pdf
- Clarke, E. & Desselberger, U. (2015). Correlates of protection against human rotavirus disease and the factors influencing protection in low-income settings. *Mucosal Immunology*, 8(1), 1–17. doi:10.1038/mi.2014.114, published online 3 December 2014. Retrieved from: <u>http://www.nature.com/mi/journal/v8/n1/full/mi2014114a.html</u>.
- 25. Tate, J.E., & Parashar, U.D. (2014). Rotavirus vaccines in routine use. *Clinical Infectious Diseases*. 59(9), 1291-301. doi: 10.1093/cid/ciu564. Retrieved from: <u>http://cid.oxfordjournals.org/content/59/9/1291.long</u>.
- Patel, M., Pedreira, C., De Oliveira, L.H., Umana, J., Tate, J., Lopman, B, ... Parashar, U. (2012). Duration of protection of pentavalent rotavirus vaccination in Nicaragua. *Pediatrics*. 130(2), e365–72. doi:10.1542/peds.2011-3478. Retrieved from: <u>http://pediatrics.aappublications.org/content/130/2/e365.long</u>.
- Snelling, T.L., Schultz, R., Graham, J., Roseby, R., Barnes, G.L., Andrews, R.M. & Carapetis, J.R. (2009). Rotavirus and the indigenous children of the Australian outback: monovalent vaccine effective in a high-burden setting. *Clinical Infectious Diseases*. 49(3), 428–31. doi: 10.1086/600395. Retrieved from: <u>http://cid.oxfordjournals.org/content/49/3/428.long</u>.
- Braeckman, T., Van Herck, K., Meyer, N., Pirçon, J., Soriano-Gabarró, M., Heylen, E., . . . Damme, P.V. (2012). Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. BMJ; 345, e4752. doi: 10.1136/bmj.e4752. Retrieved from: http://www.bmj.com/content/345/bmj.e4752.long.
- Correia, J.B., Patel, M.M., Nakagomi, O., Montenegro, F.M., Germano, E.M., Correia, N.B., ... Nakagomi, T. (2010). Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by sero-typically unrelated G2P[4] strains in Brazil. *Journal of Infectious Diseases*, 201(3), 363–369. doi: 10.1086/649843. Retrieved from: <u>http://jid.oxfordjournals.org/content/201/3/363.long</u>.
- Justino, M.C., Linhares, A.C., Lanzieri, T.M., Miranda, Y., Mascarenhas, J.D., Abreu, E, . . . Colindres, R.E. (2011). Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for severe G2P[4] rotavirus gastroenteritis in Belem, Brazil. *Pediatric Infectious Disease Journal*, 30(5), 396–401. doi: 10.1097/INF.0b013e3182055cc2. Abstract retrieved from: http://journals.lww.com/pidj/pages/articleviewer.aspx?year=2011&issue=05000&article=00010&type=abstract.
- 31. Gagneur, A., Nowak, E., Lemaitre, T., Segura, JF., Delaperrière, N., Abalea, L, ... Oger, E. (2011). Impact of rotavirus vaccination on hospitalizations for rotavirus diarrhea: the IVANHOE study. *Vaccine*, 29(21), 3753–3759. doi: 10.1016/j.vaccine.2011.03.035. Abstract retrieved from: http://www.sciencedirect.com/science/article/pii/S0264410X11004038.
- Adlhoch, C., Hoehne, M., Littmann, M., Marques, A.M., Lerche, A., Dehnert, M, ... Koch J. (2013). Rotavirus vaccine effectiveness and case-control study on risk factors for breakthrough infections in Germany, 2010–2011. *Pediatric Infectious Disease Journal*, 32(2), e82–9. doi: 10.1097/INF.0b013e3182720b71. Abstract retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23334342.
- Muhsen, K., Shulman, L., Kasem, E., Rubinstein, U., Shachter, J., Kremer, A, ... Cohen, D. (2010). Effectiveness of rotavirus vaccines for prevention of rotavirus gastroenteritis-associated hospitalizations in Israel: a case-control study. *Human Vaccines*, 6(6), 450–454. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/20448471</u>.

- 34. Yen, C., Figueroa, J.R., Uribe, E.S., del Carmen-Hernandez, L., Tate, J.E., Parashar, U.D., . . . Lopez-Collado, R. (2011). Monovalent rotavirus vaccine provides protection against an emerging fully heterotypic G9P[4] rotavirus strain in Mexico. *Journal of Infectious Diseases*, 204(5), 783–786. doi: 10.1093/infdis/jir390. Epub 2011 Aug 2. Retrieved from: http://jid.oxfordjournals.org/content/204/5/783.full.
- Martinon-Torres, F., Bouzon, A.M., Redondo, C.L., Lastres, J.M.S., Díaz, S.P., Pillado, T.S, & Sánchez, J.M.M. (2011). Effectiveness of rotavirus vaccination in Spain. *Human Vaccines*, 7(7), 757-761. doi: 10.4161/hv.7.7.15576. Retrieved from: http://www.tandfonline.com/doi/abs/10.4161/hv.7.7.15576.
- Castilla, J., Beristain, X., Martinez-Artola, V., Navascuésd, A., García Cenoza, M., Álvareze, N, . . . Barricartea, A. (2012). Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. *Vaccine*, 30(3), 539–543. doi:10.1016/j.vaccine.2011.11.071. Abstract retrieved from: <u>http://www.sciencedirect.com/science/article/pii/S0264410X11018676</u>.
- Boom, J.A., Tate, J.E., Sahni, L.C., Rench, M., Quaye, O., Mijatovic-Rustempasic, S, ... Parashar, U.D. (2010). Sustained protection from: pentavalent rotavirus vaccination during the second year of life at a large, urban United States pediatric hospital. *Pediatric Infectious Disease Journal*, 29(12), 1133–1135. doi: 10.1097/INF.0b013e3181ed18ab. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/20634776</u>.
- Boom, J.A., Tate, J.E., Sahni, L.C., Rench, M.A., Hull, J.J., Gentsch, J.R, ... Parashar, U.D. (2010). Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. *Pediatrics*, 125(2), e199–207. doi: <u>http://dx.doi.org/10.1542/peds.2009-1021</u>.
- Staat, M.A., Payne, D.C., Donauer, S., Weinberg, G.A., Edwards, K.M., Szilagyi, P.G. . . . Parashar, U.D. (2011). Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics*, 128(2), e267–75. doi:10.1542/peds.2010-3722. Retrieved from: <u>http://pediatrics.aappublications.org/content/pediatrics/128/2/e267.full.pdf</u>
- Payne, D.C., Boom, J.A., Staat, M.A., Edwards, K.M., Szilagyi, P.G., Klein, E.J... Parashar, U.D. (2013). Effectiveness of pentavalent and monovalent rotavirus vaccines in concurrent use among US children <5 years of age, 2009–2011. *Clinical Infectious Diseases*, 57(1):13– 20. doi: 10.1093/cid/cit164. Epub 2013 Mar 13. Retrieved from: http://cid.oxfordjournals.org/content/57/1/13.full.pdf+html
- Desai, S.N., Esposito, D.B., Shapiro, E.D., Dennehy, P.H., Vazquez, M. (2010). Effectiveness of rotavirus vaccine in preventing hospitalization due to rotavirus gastroenteritis in young children in Connecticut, USA. *Vaccine*, 28(47), 7501–7506. doi: 10.1016/j.vaccine.2010.09.013. Epub 2010 Sep 17. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/20851087</u>.
- Cortese, M.M., Immergluck, L.C., Held, M., Jain S., Chan, T., Grizas, A.P. . . . Vazquez, M. (2013). Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics*, 132(:e25–33. 132(1):e25-33. doi: 10.1542/peds.2012-3804. Epub 2013 Jun 17. Retrieved from: <u>http://pediatrics.aappublications.org/content/pediatrics/132/1/e25.full.pdf</u>
- Cortese, M.M., Leblanc, J., White, K.E., Jerris, R.C., Stinchfield, P., Preston, K.L, . . . Immergluck, L.C. (2011). Leveraging state immunization information systems to measure the effectiveness of rotavirus vaccine. *Pediatrics*, 128(6), e1474–81. doi: 10.1542/peds.2011-1006. Epub 2011 Nov 14. Retrieved from: <u>http://pediatrics.aappublications.org/content/pediatrics/128/6/e1474.full.pdf</u>
- 44. Wang, F.T., Mast, T.C., Glass, R.J., Loughlin, J., Seeger, J.D. (2010). Effectiveness of the pentavalent rotavirus vaccine in preventing gastroenteritis in the United States. *Pediatrics*, 125(2), e208–13. doi: 10.1542/peds.2009-1246. Epub 2010 Jan 25. Retrieved from: http://pediatrics.aappublications.org/content/125/2/e208
- Chang, W.C., Yen, C., Wu, F.T., Huang, Y.C., Lin, J.S., Huang, F.C., . . . Hsiung, C.A. (2014). Effectiveness of 2 rotavirus vaccines against rotavirus disease in Taiwanese infants. *Pediatric Infectious Disease Journal*, 33(3), e81–6. doi: 10.1097/INF.00000000000105. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/24569388</u>.
- 46. Snelling, T.L., Andrews, R.M., Kirkwood, C.D., Culvenor, S. & Carapetis, J.R. (2011). Case-control evaluation of the effectiveness of the G1P[8] human rotavirus vaccine during an outbreak of rotavirus G2P[4] infection in central Australia. *Clinical Infectious Diseases*, 52(2), 191–199. doi: 10.1093/cid/ciq101. Retrieved from: <u>http://cid.oxfordjournals.org/content/52/2/191.full</u>.
- Patel, M., Pedreira, C., De Oliveira, L.H., Tate, J., Orozco, M., Mercado, J.... Parashar, U.D. (2009). Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. *JAMA*, 301(21), 2243–2251. doi: 10.1001/jama.2009.756. Retrieved from: <u>http://jama.jamanetwork.com/article.aspx?articleid=184013</u>
- 48. Vesikari, T., Karvonen, A., Ferrante, S.A & Ciarlet, M. (2010). Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study. *European Journal of Pediatrics*, 169(11), 1379–86. doi: 10.1007/s00431-010-1242-3. Retrieved from: https://www.researchgate.net/publication/44684324 Vesikari T Karvonen A Ferrante SA et al Efficacy of the pentavalent rotavir us vaccine RotaTeqR in Finnish infants up to 3 years of age the Finnish extension study.
- 49. Phua, K.B., Lim, F.S., Lau, L.Y., Nelson, E.A., Huang, L.M., Quak, S.H., . . . Han, H.H. (2012). Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. *Vaccine*, 30, 4552–4557. doi: 10.1016/j.vaccine.2012.03.030. Retrieved from:

http://www.academia.edu/19749878/Rotavirus vaccine RIX4414 efficacy sustained during the third year of life A randomized cli nical trial in an Asian population

- 50. Linhares, A.C., Velazquez, F.R., Perez-Schael, I., Sáez-Llorens, X., Abate, H., Espinoza, F., . . . Bouckenooghe, A., Human Rotavirus Vaccine Study Group. (2008). Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet*, 371(9619), 1181– 1189. doi: 10.1016/S0140-6736(08)60524-3. Retrieved from: <u>http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60524-3/abstract</u>.
- Lopman, B.A., Pitzer, V.E., Sarkar, R., Gladstone, B., Patel, M., Glasser, J., . . . Parashar, U.D. (2012). Understanding Reduced Rotavirus Vaccine Efficacy in Low Socio-Economic Settings. *PLoS One*. 7(8), e41720. doi: 10.1371/journal.pone.0041720. Retrieved from: <u>http://journals.plos.org/plosone/article/asset?id=10.1371%2Fjournal.pone.0041720.PDF</u>.
- Patel, M., Shane, A.L., Parashar, U.D., Jiang, B., Gentsch, J.R., & Glass, R.I. (2009). Oral Rotavirus Vaccines: How Well Will They Work Where They Are Needed Most? [Supplement: Rotavirus Vaccine Challenges]. *Journal of Infectious Diseases*. 200(Supplement 1), S39-S48. doi: 10.1086/605035. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3673012/</u>.
- Moon, S.S., Wang, Y., Shane, A.L., Nguyen, T., Ray, P., Dennehy, P., & Jiang, B. (2010) Inhibitory effect of breast milk on infectivity of live oral rotavirus vaccines. *Pediatric Infectious Disease Journal*. 29(10), 919–923. doi: 10.1097/INF.0b013e3181e232ea. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3704726/.
- 54. Nelson, E.A., & Glass, R.I. (2010) Rotavirus: realising the potential of a promising vaccine [Comment]. *Lancet.* 376, 568–570. doi: 10.1016/S0140-6736(10)60896-3. <u>http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041720</u>.
- 55. Patel, M.M., Patzi, M., Pastor, D., Nina, A., Roca, Y., Alvarez, L., . . . De Oliveira, L.H. (2013). Effectiveness of monovalent rotavirus vaccine in Bolivia: case-control study. *BMJ*, 346:f3726. doi: 10.1136/bmj.f3726. Retrieved from: <u>http://www.bmj.com/content/bmj/346/bmj.f3726.full.pdf</u>
- 56. Bar-Zeev, N., Kapanda, L., Tate, J.E., Jere, K.C., Iturriza-Gomara, M., Nakagomi, O, ... Cunliffe, N.A. (2015). Effectiveness of a monovalent rotavirus vaccine in infants in Malawi after programmatic roll-out: an observational and case-control study. *Lancet Infectious Diseases*, 15(4), 422-428. doi: org/10.1016/S1473-3099(14)71060-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4374102/.
- 57. Patel, M.M., Glass, R., Desai, R., Tate, J.E. & Parashar, U.D. (2012). Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infectious Diseases*, 12(7), 561-570. doi: <u>http://dx.doi.org/10.1016/S1473-3099(12)70029-4</u>.
- Lopman, B., Curns, A.T., Yen, C., Parashar, U. (2011). Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *Journal of Infectious Diseases*. 204(7), 980–986. doi: 10.1093/infdis/jir492. Retrieved from: <u>http://jid.oxfordjournals.org/content/204/7/980.full.pdf+html</u>
- Yen, C., Tate, J.E., Wenk, J.D., Harris, J.M., & Parashar, U.D. (2011). Diarrhea associated hospitalizations among US children over 2 rotavirus seasons after vaccine introduction. *Pediatrics*; 127(1), e9–e15. doi: 10.1542/peds.2010-1393. Epub 2010 Dec 20. Abstract retrieved from: <u>http://pediatrics.aappublications.org/content/127/1/e9</u>.
- 60. Cortese, M.M., Tate, J.E., Simonsen, L., Edelman, L., & Parashar, U.D. (2010). Reduction in gastroenteritis in United States children and correlation with early rotavirus vaccine uptake from national medical claims databases. *Pediatric Infectious Disease Journal*. 29(6), 489–494. doi: 10.1097/INF.0b013e3181d95b53. Abstract retrieved from: http://journals.lww.com/pidj/pages/articleviewer.aspx?year=2010&issue=06000&article=00003&type=abstract
- Gastanaduy, P.A., Curns, A.T., Parashar, U.D., & Lopman, B.A. (2013). Gastroenteritis hospitalizations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. *JAMA*. 310(8), 851–853. doi:10.1001/jama.2013.170800. Retrieved from: http://jama.jamanetwork.com/article.aspx?articleid=1733704
- Soares-Weiser, K., Maclehose, H., Bergman, H., Ben-Aharon, I., Nagpal, S., Goldberg, E., Pitan, F., Cunliffe, N. (2012). Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database of Systematic Reviews*. 11. Art. No.: CD008521. doi: 10.1002/14651858.CD008521.pub3. Retrieved from: <u>http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008521.pub2/abstract;jsessionid=E66B357A067D09A0A3378CCC2EE194</u> <u>A4.f02t04</u>.
- 63. Buttery, J.P., Standish, J., Bines, J.E. (2014). Intussusception and rotavirus vaccines: consensus on benefits outweighing recognized risk (ESPID Reports and Reviews). *The Pediatric Infectious Disease Journal*. 33(7), 772-773. doi: 10.1097/INF.000000000000359. Retrieved from http://journals.lww.com/pidj/Fulltext/2014/07000/Intussusception and Rotavirus Vaccines Consensus.23.aspx
- 64. J., Jiang, B., Parashar, U., Nguyen, T., Bines, J., & Patel, M.M. (2013). Childhood intussusception: a literature review. *PLoS One*. 8(7), e68482. doi:10.1371/journal.pone.0068482. Retrieved from: <u>http://journals.plos.org/plosone/article/asset?id=10.1371%2Fjournal.pone.0068482.PDF</u>
- 65. Buttery, J.P., Danchin, M.H., Lee, K.J., Carlin, J.B., McIntyre, P.B., Elliott, E.J., ... Bines, J.E., PAEDS/APSU Study Group. (2011). Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in

Australia. *Vaccine*. 29(16), 3061-3066. doi: 10.1016/j.vaccine.2011.01.088. Abstract retrieved from: http://www.sciencedirect.com/science/article/pii/S0264410X11001605

- 66. Patel, M.M., Lopez-Collada, V.R., Bulhoes, M.M., De Oliveira, L.H., Bautista Márquez, A., Flannery, B., . . . Parashar, U.D. (2011). Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *New England Journal of Medicine*. 364(24), 2283–2292. doi: 10.1056/NEJMoa1012952. Retrieved from: <u>http://www.nejm.org/doi/full/10.1056/NEJMoa1012952</u>.
- Velazquez, F.R., Colindres, R.E., Grajales, C., Hernández, M.T., Mercadillo, M.G., Torres, F.J., ... Verstraeten, T. (2012). Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. *Pediatric Infectious Disease Journal*. 31(7), 736–744. doi: 10.1097/INF.0b013e318253add3. Retrieved from: http://journals.lww.com/pidi/Fulltext/2012/07000/Postmarketing Surveillance of Intussusception.16.aspx
- 68. Weintraub, E.S., Baggs, J., Duffy, J., Vellozzi, C., Belongia, E.A., Irving, S., . . . DeStephano, F. (2014). Risk of intussusception after monovalent rotavirus vaccination. *New England Journal of Medicine*. 370, 513–519. doi: 10.1056/NEJMoa1311738. Retrieved from: http://www.nejm.org/doi/full/10.1056/NEJMoa1311738?rss=searchAndBrowse
- 69. Yih, W.K., Lieu, T.A., Kulldorff, M., (2014). Intussusception risk after rotavirus vaccination in U.S. infants. *New England Journal of Medicine*. 370(6), 503–512. doi: 10.1056/NEJMoa1303164. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1303164.
- 70. World Health Organization. (January 2013). Rotavirus vaccines: WHO position paper-January 2013. *Weekly Epidemiological Record*. 88(5), 49–64. Retrieved from: <u>http://www.who.int/wer/2013/wer8805/en/</u>
- 71. World Health Organization. (January 2008). Global Advisory Committee on vaccine safety. *Weekly Epidemiological Record*. 83, 37-44. Retrieved from: <u>http://www.who.int/wer/2008/wer8304.pdf?ua=1</u>
- 72. Steele, A.D., Madhi, S.A., Louw, C.E., Bos, P., Tumbo, J.M., Werner, C.M., ... Han, H.H. (2011). Safety, reactogenicity, and immunogenicity of human rotavirus vaccine RIX4414 in human immunodeficiency virus-positive infants in South Africa. *Pediatric Infectious Disease Journal*, 30(2), 125–130. doi: 10.1097/INF.0b013e3181f42db9. Abstract retrieved from: http://journals.lww.com/pidi/Abstract/2011/02000/Safety, Reactogenicity, and Immunogenicity of.7.aspx.
- 73. Laserson, K.F., Nyakundi, D., Feikin, D.R., Nyambane, G., Earnest Cook, Janet Oyieko, Joel Ojwando, Stephen B. Rivers, Max Ciarlet, Kathleen M. Neuzil and Robert F. Breiman. (2012). Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq®, in Kenya, including among HIV-infected and HIV-exposed infants. *Vaccine*, 30, (Supplement 1), A61–A70. Retrieved from: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0264410X11014320.
- 74. Goveia, M.G., Rodriguez, Z.M., Dallas, M.J., Itzler, R.F., Boslego, J.W., Heaton, P.M., & REST Study Team. (2007). Safety and efficacy of the pentavalent human-bovine (WC3) reassortant rotavirus vaccine in healthy premature infants. *Pediatric Infectious Diseases Journal*. 26(12), 1099-104. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/18043445</u>.
- 75. American Academy of Pediatrics Committee on Infectious Diseases. (2007). Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. *Pediatrics*. 119(1), 171-82. Retrieved from: <u>http://pediatrics.aappublications.org/content/119/1/171.long</u>.
- 76. Payne, D.C., Edwards, K.M., Bowen, M.D., Keckley, E., Peters, J., Esona, M.D., & Gentsch, J.R. (2010). Sibling transmission of vaccinederived rotavirus (RotaTeq) associated with rotavirus gastroenteritis. *Pediatrics*, 125(2), e438–e441. doi: 10.1542/peds.2009-1901. Abstract retrieved from: <u>http://pediatrics.aappublications.org/content/125/2/e438</u>.
- 77. Rotavirus. (2015). Epidemiology and Prevention of Vaccine-Preventable Diseases, *The Pink Book: Course Textbook (13th Ed)*. Retrieved from: <u>http://www.cdc.gov/vaccines/pubs/pinkbook/rota.html</u>.
- Rivera, L., Mendez Pena, L., Stainier, I., Gillard, P., Cheuvart, B., Smolenov, I., & Han, H.H. (2011). Horizontal transmission of a human rotavirus vaccine strain – a randomized, placebo-controlled study in twins. *Vaccine*. 29(51), 9508–9513. doi:10.1016/j.vaccine.2011.10.015. <u>http://www.sciencedirect.com/science/article/pii/S0264410X11016094#</u>
- Rosillon, D., Buyse, H., Friedland, L.R., Ng, S-P., Velázquez, F.R., & Breuer, T. (2015). Risk of intussusception after rotavirus vaccination: meta-analysis of post-licensure studies [Vaccine Reports]. *The Pediatric Infectious Disease Journal*. 34(7), 763-768. doi: 10.1097/INF.000000000000715. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/26069948</u>.
- Yen, C., Jakob, K., Esona, M.D., Peckham, X., Rausch, J., Hull, J.J., . . . LaRussa, P. (2011). Detection of fecal shedding of rotavirus vaccine in infants following their first dose of pentavalent vaccine. *Vaccine*. 29(24), 4151–4155. doi: 10.1016/j.vaccine.2011.03.074. Epub 2011 Apr 6. Abstract retrieved from: <u>http://www.sciencedirect.com/science/article/pii/S0264410X11004567</u>
- Escolano, S., Farrington, C.P., Hill, C., & Tubert-Bitter, P. (2011). Intussusception after rotavirus vaccination–spontaneous reports [Correspondence]. *New England Journal of Medicine*. 365(22), 2139. doi: 10.1056/NEJMc1107771. Retrieved from: <u>http://www.nejm.org/doi/pdf/10.1056/NEJMc1107771</u>
- 82. Shui, I.M., Baggs, J., Patel, M., Parashar, U.D., Rett, M., Belongia, E.A., . . . Weintraub, E. (2012). Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA*. 307(6), 598–604. doi: 10.1001/jama.2012.97. Retrieved from: http://www.nejm.org/doi/full/10.1056/NEJMoa1311738?rss=searchAndBrowse

- Loughlin, J., Mast, T.C., Doherty, M.C., Wang, F.T., Wong, J., & Seeger, J.D. (2012). Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *The Pediatric Infectious Disease Journal*. 31(3), 292–296. doi: 10.1097/INF.0b013e3182421390. Abstract retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22173146.
- Carlin, J.B., Macartney, K.K., Lee, K.J., Quinn, H.E., Buttery, J., Lopert, R., & McIntyre, P.B. (2013). Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. *Clinical Infectious Diseases*. 57(10), 1427–1434. doi: 10.1093/cid/cit520. Retrieved from: <u>http://cid.oxfordjournals.org/content/57/10/1427.full.pdf+html</u>.
- 85. Haber, P., Patel, M., Pan, Y., Baggs, J., Haber, M., Museru, O., & Parashar, U.D. (2013). Intussusception after rotavirus vaccines reported to US VAERS, 2006-2012. *Pediatrics*. 131(6), 1042–1049. doi: 10.1542/peds.2012-2554. Epub 2013 May 13. Retrieved from: http://pediatrics.aappublications.org/content/131/6/1042.long.

Rotavirus Disease Summary

Diarrhea is one of the world's leading killers of children, and rotavirus is the most common cause of severe diarrhea. Rotavirus gastroenteritis (RVGE) is highly contagious, spreading easily from person to person. Rotaviruses (RV) live on hands and surfaces from hours to days, respectively. In the body, RV destroys the surface tissue of the small intestines, preventing absorption of nutrients, causing diarrhea¹. Children who do not have timely access to medical care can develop severe RVGE disease, which can result in rapid dehydration, shock, electrolyte imbalance and death. In 2013 RV was the cause of approximately 215,000^{3, 49} deaths in young children and hundreds of thousands of hospitalizations.

DISEASE BURDEN

Rotavirus (RV) is the most common cause of vaccine preventable severe and fatal diarrhea among infants and young children estimated to have resulted in 215,000 deaths in 2013.⁴⁹

- **Mortality**: Diarrhea is one of the leading infectious causes of death in children younger than 5 years and caused an estimated 578,000 deaths globally in 2013.⁴⁹
 - Rotavirus specifically killed about 123,000 African and 80,000 Southern and Southeast Asian children under the age of 5 in 2013—more than 336 and 220 each day respectively.⁴⁹ (See Table 1 of Tate et al 2016 for additional disease burden estimates by region. ⁴⁹)
- **Morbidity**: Rotavirus is ubiquitous and infects nearly every child by 3-5 years of age and is the leading cause of severe dehydrating and fatal diarrhea in young children worldwide. Globally, the highest rates of severe rotavirus disease occur at age 6-24 months.^{2,4}
- Low-Income Countries: In low-income countries, the median age of the primary rotavirus infection is 6-9 months with 80% of first infections occurring before 1 year of age.⁵
- Seasonality: In high-income countries with temperate climates, a winter peak in RV seasonality is observed. In most low-income countries in Asia and Africa, rotavirus epidemiology is characterized by one or more periods of intense rotavirus circulation against a background of year-round transmission.⁴ Recent data suggest that level of country development is a stronger predictor of seasonal intensity of RV than geography.⁶
- **Hospitalizations**: Rotavirus is responsible for 38% of all diarrhea-related hospitalizations globally in children under 5 years of age.^{3, 7}
 - The World Health Organization (WHO) Global Surveillance Network for Rotavirus reports the proportion of children < 5 years of age hospitalized for diarrhea caused by rotavirus in East Asia/South-East Asia/Africa as 47%/42%/42% respectively.⁸
- Gender Predominance: Boys appear to have increased susceptibility to rotavirus infection compared to girls, and are more likely to be hospitalized.⁹ The reported ratios of male predominance in India, Nigeria, Bahrain, Malaysia and Mauritius were 1.6:1/1.8:1/1.5:1/1.6.3:1/1.6:1 respectively.^{10, 11, 12, 46, 48} Although in some countries the difference in gender did not reach statistical significance, a similar male gender prevalence was reported.^{12, 45}
 - According to the WHO Scientific Advisory Group of Experts (SAGE) on Immunizations, the number of affected males was up to 20% higher than the number of females in some studies. It is not known whether this is due to a greater susceptibility to rotavirus exposure in boys or a greater likelihood of parents of affected boys seeking medical care.^{13, 14}

• **Risk Factors**: Biological factors that put children at risk for severe RV disease include infants younger than 6 months who are not exclusively breastfed, infants with undernutrition, premature birth, immunodeficiency and zinc deficiency.^{15,2}

CLINICAL CHARACTISTICS

- **Rotavirus Classification**: Rotavirus, a non-enveloped RNA virus, is classified according to 2 surface proteins the VP7 (glycoprotein or G protein) and the VP4 (protease cleaved protein or P protein) which elicit the production of neutralizing antibodies. Rotavirus strains are commonly referred to by their G protein classification.^{4, 16}
- **Rotavirus Strains**: Currently, 5 G-P combinations (G1P[8], G2P[4], G3P[8], G4P[8]) and G9P[8]) account for approximately 90% of all human rotavirus infections in many parts of the world; type G1P[8] is the most prevalent combination.⁴
- **Pathophysiology**: Rotavirus primarily infects the small intestine, destroying the surface tissue and preventing the absorption of nutrients, causing diarrhea.¹
- Clinical Course: The incubation period for rotavirus diarrhea is short, usually 1-3 days. The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. As a result of protection mediated primarily by transplacental transfer of maternal antibodies, children less than or equal to 3 months of age infected with rotavirus seldom have symptomatic disease. The first infection after 3 months of age is generally the most severe. Infection may cause watery diarrhea that ultimately resolves itself without treatment, or it may result in severe dehydration (10–20 bowel movements per day), electrolyte imbalance, metabolic acidosis and vomiting. Up to one-third of infected children may have a temperature greater than 102°F (39°C). The gastrointestinal symptoms generally resolve in 3 to 7 days but may last for up to 2–3 weeks. Although in most cases, recovery is complete, fatalities do occur, mainly in children ≤1 year of age.^{4, 5, 17, 18, 19, 35}
- Viral Shedding: During rotavirus infection, viruses are shed for several days in high concentrations (i.e., 10¹² virus particles per gram of stool during the acute illness) in the stools of infected children, before and several days after clinical disease. Very few infectious particles (virions) are needed to cause disease.^{20, 4}
- **Immunocompetence**: Rotavirus infection may last longer among children who are immunocompromised because of certain congenital immunodeficiency disorders and may be detected in the stool of these children for more than 30 days after infection.^{17, 21, 22, 23}
- **Treatment**: No specific therapy is available for treating rotaviruses. WHO-recommended treatment such as low-osmolarity oral rehydration solutions (ORS), zinc supplements, and treatment with intravenous (IV) fluids, when needed, can help rehydrate children until the intestine repairs and recovers.^{4, 24, 44}
- Protective Immunity: Recovery from a first rotavirus infection usually does not lead to permanent immunity. After a single natural infection, 38% of children are protected against any subsequent rotavirus infection, 77% are protected against rotavirus diarrhea, and 87% are protected against severe diarrhea.²³ Reinfection can occur at any age. This protection is mediated by humoral and cellular components of the immune system. Following the first infection, the serological response is directed mainly against the specific viral serotype (i.e. a homotypic response), whereas a broader, heterotypic antibody response is elicited following ≥1 subsequent rotavirus infections.²⁵
- Long-term Sequelae: For children in low-income and middle-income countries, the occurrence of several episodes of diarrhea per year can lead to nutritional deficits. The odds of growth stunting by age 2 years increased by 1.13 (95% CI 1.07–1.19) for every five episodes of diarrhea. Growth stunting is indicative of a long-term nutritional deficit, which is associated with decreased cognitive function.^{26,27}

USE/COST OF HEALTHCARE

In addition to the morbidity and mortality imposed by rotaviral disease, treating rotavirus carries significant cost burden for families and countries.

- Global Health Utilization:
 - Researchers found that prior to rotavirus vaccination, in 2010 there would have been 23 million outpatient cases and 3.3 million inpatient cases of RV totaling US\$987 million in treatment costs.²⁸
 - ▶ The average length of hospitalization for RVGE is 4-5 days with a range of 1 21 days.^{45, 47}
- Select Country-Specific Treatment Cost Burdens:
 - In India, the total cost of a RV hospitalization can range from \$32 to more than \$135, equal to up to 2 months of income for an average Indian family. Hospitalization and outpatient visits cost India approximately \$78 million and \$86 million each year, respectively.^{29,30}
 - In Bangladesh, treatment of one episode of rotavirus can amount to nearly 85% of the average family's monthly income.³¹
 - In Malaysia, rotavirus hospitalization for a child costs more than one-quarter of the average monthly income.³² The median cost of providing inpatient care for an episode of rotavirus gastroenteritis is estimated to be US\$212.³³
 - In Uganda, inpatient admission for one episode of severe rotavirus diarrhea costs 10% of the average family's monthly income.³⁴

PREVENTATIVE/CONTROL MEASURES

Rotaviruses are ubiquitous, easily spread and resistant to routine methods of disinfection.

- **Spread**: Rotavirus is commonly spread from person-to-person. It is highly contagious and passes easily through the fecal-oral route by way of contact with contaminated hands or objects, such as toys and surfaces, or through tainted food or water.^{18, 19, 36-39}
- **Control and Prevention**: Rotaviruses are highly infectious and relatively resistant to inactivation by chemical disinfectants and antiseptics.³⁵ Unfortunately, interventions that prevent bacterial and parasitic causes of diarrhea, such as improvements in hygiene, sanitation and drinking water, do not adequately prevent the spread of rotavirus. The virus is incredibly resilient and can live on hands for hours and surfaces for days.²⁴
 - WHO/UNICEF Recommended Preventative Strategies: The integrated Global Action Plan For Pneumonia and Diarrhoea (GAPPD) recommends the following diarrheal disease control strategies:⁴⁴
 - Exclusive breastfeeding for 6 months and continued breastfeeding with appropriate complementary feeding to reduce onset and severity of diarrhoea
 - Standardized guidelines for identification and treatment of diarrhoea in the community at first-level health facilities and at referral hospitals.
 - Water, sanitation and hygiene interventions.

REGIONAL/INTERNATIONAL CONSIDERATIONS

Based on efficacy, effectiveness and vaccine impact data, WHO recommends that all National Immunization Programs (NIP) adopt rotavirus immunization into their routine immunization schedules.

- WHO Recommendations: WHO's Strategic Advisory Group of Experts (SAGE) reviewed additional data from clinical studies in Africa and Asia, as well as post-licensure data from the Americas, and expanded their recommendation that all countries should include rotavirus vaccines in their national immunization programs, particularly in those countries with high child mortality due to diarrhea.⁴⁰⁻⁴²
 - To allow for greater vaccine coverage, in 2013 WHO recommended that there be no age restrictions on rotavirus vaccination in high-mortality regions; co-administration is recommended with routine childhood vaccines.⁴
 - > About 60% of countries in sub-Saharan Africa have introduced rotavirus vaccine
- Global Vaccine Introduction Status: At least 80 countries have introduced rotavirus vaccines into their NIP, and 7 countries have introduced rotavirus vaccines regionally (see map below).⁴³

Introduced – National (84)

Introduced – Subnational (6)



Source: Adapted from IVAC's VIEW-hub, December 2016. www.view-hub.org

• **GAVI Country Status**: Forty-one (56%) of the 73 Gavi countries have introduced rotavirus vaccine. An additional 19 Gavi countries are planning to introduce rotavirus vaccine, five of which have already received approval (with/without clarification) for Gavi support.⁴³

Introduced – National (40)

Introduced – Subnational (1)

Not Introduced (32)



Source: Adapted from IVAC's VIEW-hub, December 2016. www.view-hub.org

- WHO/UNICEF GOALS: The Global Action Plan for Pneumonia and Diarrhoea (GAPPD) outlines the following WHO/UNICEF goals of reducing the health impact of diarrheal disease by 2025:⁴⁴
 - Reduce mortality from diarrhoea in children less than 5 years of age to fewer than 1 per 1000 live births.
 - Reduce the incidence of severe diarrhea by 75% in children less than 5 years of age compared to 2010 levels.
 - Reduce by 40% the global number of children less than 5 years of age who are stunted compared with 2010 levels.

SECTION 2: REFERENCES

- 1. Estes, M.K., Kapikian, A.Z. (2001). Rotaviruses. In Knipe, D., Howley, P.M., Griffin, D., Lamb, R., Martin, M, & Roizman, B (Eds.), *Fields Virology* (Vol. 1). Philadelphia (EUA): Lippincott Williams & Wilkins.
- Walker, C.L., Rudan I, Liu L, Nair, H., Theodoratou, E., Bhutta, Z.A, . . . Black, R.E. (2013). Global burden of childhood pneumonia and diarrhoea. *Lancet.* 381(9875), 1405-1416. doi: 10.1016/S0140-6736(13)60222-6. Retrieved from: <u>http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60222-6/abstract</u>.
- Lanata, C.F., Fischer-Walker, C.L., Olascoaga, A.C., Torres, C.X., Aryee, M.J. & Black, R.E. (for the Child Health Epidemiology Reference Group of the WHO and UNICEF). (2013). Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. *PLoS One*. 8(9), e72788. doi: <u>http://dx.doi.org/10.1371/journal.pone.0072788</u>.
- 4. World Health Organization. (2013). Rotavirus vaccines: WHO position paper: February 2013. *Weekly Epidemiological Record*. 88(5), 49-64. Retrieved from: <u>http://www.who.int/wer/2013/wer8805.pdf</u>
- 5. Sanderson, C., Clark, A., Taylor, D. & Bolanos, B. (2011). Global review of rotavirus morbidity and mortality data by age and WHO region. Report to WHO/IVB. Keppel Street, London: London School of Hygiene and Tropical Medicine. Retrieved from: <u>http://www.who.int/immunization/sage/meetings/2012/april/Sanderson et al SAGE April rotavirus.pdf?ua=1</u>
- Patel, M.M., Pitzer, V.E., Alonso, W.J., Vera, D., Lopman, B., Tate, J., & Parashar, U.D. (2013). Global Seasonality of Rotavirus Disease. *Pediatric Infectious Disease Journal*. 32(4), e134-e147. doi: 10.1097/INF.0b013e31827d3b68. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103797/pdf/nihms428024.pdf</u>
- Parashar, U.D., Gibson, C.J., Bresee, J.S., & Glass, R.I. (2006). Rotavirus and severe childhood diarrhea. *Emerging Infectious Diseases*. 12(2), 304-306. doi: 10.3201/eid1202.050006. Retrieved from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3373114/pdf/05-0006.pdf.
- World Health Organization. (2011). Global Rotavirus Information and Surveillance Bulletin, October 2011 (Reporting period: January to December 2010). 4, 1-10. Retrieved from: http://www.who.int/immunization/diseases/rotavirus/Final RV bulletin Jan Dec 2010 Data.pdf.
- 9. Bass, C.W., & Dorsey, K.N. (2004). Rotavirus and other agents of viral gastroenteritis. In Richard, E., & Behrman, F. (Eds.), Nelson Textbook of Pediatrics (pp. 67-110). Philadelphia: Raven Press.
- 10. Junaid, S.A., Umeh, C., Olabode, A.O., & Banda, J.M. (2011). Incidence of rotavirus infection in children with gastroenteritis attending Jos university teaching hospital, Nigeria. *Virology Journal*, 8(2330). doi: 10.1186/1743-422X-8-233. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3107812/pdf/1743-422X-8-233.pdf</u>
- 11. Dutta, S.R., Khalfan, S.A., Baig, B.H., Philipose, L., & Fulavfil, R. (1990). Epidemiology of rotavirus diarrhea in children under five years in Bahrain. *International Journal of Epidemiology*. 19(3), 722-727. doi: <u>10.2147/CLEP.S46822</u>.
- 12. Salim, H., Karyana, P.G., Sanjaya-Putra, G.N., Budiarsa, S., & Soenarto Y. (2014). Risk factors of rotavirus diarrhea in hospitalized children in Sanglah Hospital, Denpasar: a prospective cohort study. *BMC Gastroenterology*. 14(54). DOI: 10.1186/1471-230X-14-54© Salim et al.; licensee BioMed Central Ltd. 2014. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986934/pdf/1471-230X-14-54.pdf</u>
- Borade, A., Bais, A.S., Bapat, V., & Dhongade, R. (2010). Characteristics of rotavirus gastroenteritis in hospitalized children in Pune. *Indian Journal of Medical Sciences*. 64(5), 210-218. doi: 10.4103/0019-5359.98942. Retrieved from: <u>http://www.indianjmedsci.org/text.asp?2010/64/5/210/98942</u>.
- 14. World Health Organization Scientific Working Group. (1980). Rotavirus and other viral diarrhoeas: Bulletin of the World Health Organization. 58(2), 183-198. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2395787/</u>
- 15. Huppertz, H., Salman, N., & Giaquinto, C. (2008). Risk factors for severe rotavirus gastroenteritis. *Pediatric Infectious Disease Journal*. 27(1), s11-19. doi: 10.1097/INF.0b013e31815eee0a. Retrieved from: http://journals.lww.com/pidj/Abstract/2008/01001/Risk Factors for Severe Rotavirus Gastroenteritis.3.aspx
- 16. Kobayashi, N., Ishino, M., Wang, Y.H., Chawla-Sarkar, M., Krishnan, T., & Naik, T.N. (2007). Diversity of G-type and P-type of human and animal rotaviruses and its genetic background. In Mendez-Vilaz, A., & Diaz, J. (Eds.) *Modern Research And Educational Topics In Microscopy*. Formatex, pp. 847-858.
- 17. Estes, M.K., & Greenberg, H.B. (2013). Rotaviruses. In Knipe, D.M., & Howley, P.M. (Eds.) *Fields virology* (pp. 1347–1401). Philadelphia: Kluwer/Lippincott, Williams and Wilkins.
- 18. PATH. (2009). Common virus and senseless killer: A briefing paper on rotavirus. Retrieved from: http://www.path.org/publications/detail.php?i=1685
- Rodriguez, W.J., Kim, H.W., Brandt, C.D., Schwartz, R.H., Gardner, M.K., Jeffries, B., . . . Kapikian, A.Z. (1987). Longitudinal study of rotavirus infection and gastroenteritis in families served by a pediatric medical practice: clinical and epidemiologic observations. *Pediatric Infectious Disease Journal*. 6(2), 170-176. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/3031575</u>.
- 20. Bishop, R.F. (1996). Natural history of human rotavirus infection (Supplement). Archives of Virology. 12, 119-128.

- 21. Cortese, M.M., Parashar, U.D. (2009). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations Report. 58(RR-2), 1–25. Retrieved from: <u>http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5802a1.htm.</u>
- 22. Yolken, R., & Wilde, J. (1994). Assays for detecting human rotavirus. In Kapikian, A.Z. (Ed.). *Viral infections of the gastrointestinal tract.* (pp. 251–78). New York: Marcel-Dekker.
- 23. Rotavirus. (2015). Epidemiology and Prevention of Vaccine-Preventable Diseases, The Pink Book: Course Textbook (13th Ed). Retrieved from: <u>http://www.cdc.gov/vaccines/pubs/pinkbook/rota.html</u>.
- 24. ROTA Council, (2016). Rotavirus: common, severe, devastating, preventable. Retrieved from: http://rotacouncil.org/resources/101142-004_RotaExecSummary2015_V9r2.pdf.
- 25. Angel, J., Franco, M.A., & Greenberg, H.B. (2012). Rotavirus immune responses and correlates of protection. *Current Opinions in Virology*. 2(4), 419–425. doi:10.1016/j.coviro.2012.05.003. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422408/pdf/nihms379950.pdf</u>
- 26. Checkley, W., Buckley, G., Gilman, R.H., Assis, A.M., Guerrant, R.L., Morris, S.S., ... Black, R.E. for Childhood Malnutrition and Infection Network. (2008). Multi-country analysis of the effects of diarrhoea on childhood stunting. *International Journal of Epidemiology*. 37, 816–830. doi:10.1093/ije/dyn099. Retrieved from: <u>http://ije.oxfordjournals.org/content/37/4/816.full.pdf+html</u>
- 27. Walker, S.P., Wachs, T.D., Grantham-McGregor, S., . (2011). Inequality in early childhood: risk and protective factors for early child development. *Lancet.* 378(9799), 1325–1338. doi: 10.1016/S0140-6736(11)60555-2. Retrieved from: http://www.sciencedirect.com/science/article/pii/S0140673611605552
- 28. Palermina-Caicedo, A., De la Hoz-Restrepo, F., & Alvis-Guzman, N. (2015). Epidemiological and economic impact of monovalent and pentavalent rotavirus vaccines in low and middle income countries: a cost-effectiveness modeling analysis. *The Pediatric Infectious Disease Journal*, 34(7), e176-e184. doi: 10.1097/INF.00000000000727. Abstract retrieved from: <u>http://journals.lww.com/pidj/Abstract/2015/07000/Epidemiological and Economic Impact of Monovalent.17.aspx?trendm</u> <u>d-shared=0</u>.
- 29. Johns Hopkins Bloomberg School of Public Health. (2015). For Rotavirus, prevention is the best medicine. *Global Health Now*. http://www.globalhealthnow.org/news/for-rotavirus-prevention-is-the-best-medicine.
- 30. John, J., Sarkar, R., Mulliyil, J., Bhandari, N., Bhan, M., & Kang, G. (2014). Rotavirus gastroenteritis in India, 2011-2013: revised estimates of disease burden and potential impact of vaccines [Supplement]. *Vaccine*. 32S, A5-A9. doi: 10.1016/j.vaccine.2014.03.004. Retrieved from <u>http://www.sciencedirect.com/science/article/pii/S0264410X14003429</u>.
- 31. icddr,b. Preliminary analysis from "The economic burden of rotavirus infection resulting in hospitalization among children <5 years of age in selected hospitals of Bangladesh". icddr,b. Protocol# 14009.
- 32. Chai, P.L, & Lee, W.S. (2009). Out-of-pocket costs associated with rotavirus gastroenteritis requiring hospitalization in Malaysia [Supplement]. *Vaccine*. 27(5), F112-F115. doi:10.1016/j.vaccine.2009.08.069. Retrieved from: <u>http://europepmc.org/abstract/MED/19931708</u>.
- 33. Lee, W.S., Poo, M.I., & Nagaraj, S. (2007). Estimates of economic burden of providing inpatient care in childhood rotavirus gastroenteritis from Malaysia. *Journal of Paediatric and Child Health*. 43(12), 818–825. doi: 10.1111/j.1440-1754.2007.01160.x Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1754.2007.01160.x/full.
- 34. Sigei, C., Odaga, J., Mvundura, M., Madrid, Y., Clark, A.D., & Kenya ProVac Technical Working Group/Uganda ProVac Technical Working Group. (2015). Cost-effectiveness of rotavirus vaccination in Kenya and Uganda [Supplement]. *Vaccine.* 33(1), A109-118. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624336/</u>.
- 35. Esona, M.D., & Gautam, R. (2015). Rotavirus. *Clinics in Laboratory Medicine*. 35(2), 363–391. doi: <u>http://dx.doi.org/10.1016/j.cll.2015.02.012</u>. Retrieved from: <u>http://www.sciencedirect.com/science/article/pii/S0272271215000311.</u>
- 36. Black, R.E., Lopez de Romana, G., Brown, K.H., Bravo, N., Bazalar, O.G., & Kanashiro, H.C. (1989). Incidence and etiology of infantile diarrhea and major routes of transmission in Huascar, Peru. *American Journal of Epidemiology*. 129(4), 785-799. http://aje.oxfordjournals.org/content/129/4/785.full.pdf
- 37. Mrukowicz, J., Szajewska, H., & Vesikari, T. (2008). Options for the prevention of rotavirus disease other than vaccination [Supplement]. Journal of Pediatric Gastroenterology and Nutrition. 46(2), S32-37. Retrieved from: <u>http://mobile.journals.lww.com/jpgn/_layouts/15/oaks.journals.mobile/articleviewer.aspx?year=2008&issue=05002&article=00005</u>.
- 38. Simhon, A., Mata, L., Vives, M., Rivera, L., Vargas, S., Ramirez, G., . . . Azofeifa, J. (1985). Low endemicity and low pathogenicity of rotaviruses among rural children in Costa Rica. *Journal of Infectious Diseases*. 152(6), 1134-1142. Retrieved from: <u>http://jid.oxfordjournals.org/content/152/6/1134.abstract</u>.
- 39. Zaki, A.M., DuPont, H.L., el Alamy, M.A., Arafat, R.R., Amin, K., Awad, M.M., . . . Wyatt, R.G. (1986). The detection of enteropathogens in acute diarrhea in a family cohort population in rural Egypt. *American Journal of Tropical Medicine and Hygiene*. 35(5), 1013-1022. Retrieved from: <u>http://scicurve.com/paper/2876656</u>.

- 40. World Health Organization. (2009). Meeting of the immunization Strategic Advisory Group of Experts: conclusions and recommendations. *Weekly Epidemiological Record*. 84(23), 220-236. Retrieved from: http://www.who.int/wer/2009/wer8451_52.pdf
- 41. World Health Organization. (2009). Meeting of the Strategic Advisory Group of Experts on immunization, October 2009 conclusions and recommendations. *Weekly Epidemiological Record*. 84(50), 517-532. Retrieved from: http://www.who.int/wer/2009/wer8450.pdf?ua=1.
- 42. World Health Organization. (2009). Rotavirus vaccines: an update. *Weekly Epidemiological Record*. 84(50), 533-540. Retrieved from: <u>http://www.who.int/wer/2009/wer8451_52.pdf</u>.
- 43. VIEW-hub Quarterly Report: Global Vaccine Introduction and Implementation, International Vaccine Access Center. (December 2016) <u>http://www.ihsph.edu/research/centers-and-institutes/ivac/resources/publications.html</u>
- 44. World Health Organization/The United Nations Children's Fund (UNICEF). (2013). Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025: the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) Retrieved from: http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/
- 45. Ahmed, S., Kabir, L., Rahman, A., Hussain, M., Khatoon, S., & Hannan, A. (2009). Severity of Rotavirus Diarrhea in Children: one Year Experience in a Children Hospital of Bangladesh. *Iran Journal of Pediatrics*. 19(2), 108-116. Retrieved from: <u>http://www.bioline.org.br/pdf?pe09017</u>.
- 46. Hung, L.C., Wong, S.L., Chan, L.G., Rosli, R., Ng, A.N., & Bresee, J.S. (2006). Epidemiology and strain characterization of rotavirus diarrhea in Malaysia. *International Journal of Infectious Diseases*. 10(6), 470–474. doi: 10.1016/j.ijid.2006.05.008. Retrieved from: <u>http://www.sciencedirect.com/science/article/pii/S1201971206001305</u>.
- 47. Phua, K.B., Tee, N., Tan, N., Ramakrishnan, G., Teoh, Y., Bock, H., & Liu, Y. (2013). A Hospital-based Surveillance of Rotavirus Gastroenteritis in Children <5 Years of Age in Singapore. *Pediatric Infectious Disease Journal*. 32, e426–e431 doi: 10.1097/INF.0b013e31829f2cb0. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/23958814</u>.
- 48. Pursem, V.N., Peeroo, B.M., Mangar, I., Sohawon, F.M., Seheri, L.M., Mphahlele, M.J., ... Manraj, S.S. (2014). Epidemiology of Rotavirus Diarrhea and Diversity of Rotavirus Strains Among Children Less Than 5 Years of Age with Acute Gastroenteritis in Mauritius: June 2008 to December 2010 [Supplement]. *The Pediatric Infectious Disease Journal*. 33(1), S49-S53. doi: 10.1097/INF.00000000000051. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/24343614</u>.
- 49. Tate, J.E., Burton, A.H., Boschi-Pinto, C., & Parashar, U.D. for the World Health Organization–Coordinated Global Rotavirus Surveillance Network. (2016). Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013. *Clinical Infectious Diseases*. 62(Supplement 2), S96-S105. Retrieved from: <u>http://cid.oxfordjournals.org/content/62/suppl_2/S96.full</u>.

Rotavirus Vaccine Economic Considerations Summary

As the most common cause of severe diarrheal disease, rotavirus contributes substantially to the heavy economic and social costs of diarrhea. Beyond the important economic burden of treatment on health systems and families, some studies have demonstrated a lifelong negative impact of early childhood diarrhea on cognition and school performance.

Economic evaluations of rotavirus vaccines have found them to be cost-effective across low-, middle- and high-income countries and across a range of vaccine prices, and the use of these vaccines in low- and lower-middle income countries stands to result in significant cost savings for health systems.

ECONOMIC IMPACT OF INTERVENTION ON IMMUNIZATION PROGRAM/HEALTH SECTOR

There are several types of economic evaluations. Cost-effectiveness analysis (CEA) is the most common type of economic evaluation. The results of cost-effectiveness analyses are expressed as incremental cost-effectiveness ratios (ICERs), where the costs are represented in monetary units and the health effects or outcomes are measured as follows:¹

- > Life Years Gained (LYG) measures health effects in "natural units"
- Disability-adjusted Life Years (DALYs) measure a health loss; more commonly used in Lowto Middle-Income Countries
- Quality-adjusted Life Years (QALYs) measure a health gain; are more commonly used in highincome countries

With the objective of providing policy-makers with evidence for deciding on interventions and programs that maximize health for the available resources in their country, the WHO-CHOICE (Choosing Interventions that are Cost-Effective) initiative was developed. This provides country-level information for analyses on health interventions. WHO-CHOICE uses a multiple of country per capita gross domestic product (GDP) as an indicator of cost-effectiveness. Using GDP, the range of incremental cost effectiveness ratio (ICER) calculation will lead to one of the following categories of cost-effectiveness: ^{2,3}

- > ICER less than the per capita GDP is considered "highly cost-effective"
- > ICER less than three times the per capita GDP is considered "cost-effective"
- > ICER equal to or greater than 3 times per capita GDP is "not cost-effective"

Several studies on the cost-effectiveness of rotavirus vaccination have been published.⁴⁻²⁷ These studies vary widely in both methodologies employed and key input variables such as price of vaccine, associated delivery costs, vaccine effectiveness, and other factors such as herd effect. Despite the heterogeneity of approaches to estimate cost-effectiveness, the vast majority of countries modeled demonstrate a positive economic value for the introduction of rotavirus vaccine into their respective NIPs. One such study demonstrated that in all GAVI-eligible countries, introducing rotavirus vaccine from 2011 through 2030, would prevent 2.46 million childhood deaths and 83 million DALYs with annual reductions of 180,000 childhood deaths a year at peak vaccine uptake.²⁸

Country/ Region	Vaccine Price	Vaccine / Number of Doses	Vaccine Effectiveness	Vaccine Coverage/ Dose	Deaths Averted	Hospitalization Averted	Savings to Healthcare System	ICER	Ref
India (select regions)	\$1.25	RV 5 - 3	50% (variable)	(Various)	35,000			\$105-298/ DALY	21
India	\$0.15 \$1.00 \$7.00	RV1 - 2	50%	73%/63%	44,000	293,000	\$20.6M	Cost Savings \$21.41/DALY \$200/DALY	20
Thailand	\$7.00	RV1 – 2	85-90%	96%	419	46,542	\$6.4M	\$370/DALY	19
Tanzania	\$8.40	RV1 - 2	57-70%	93%				\$112/DALY	13
Somalia*	\$0.15	RV1 - 2	40-50%	47%	908	19,758	\$0.063M	\$5.30/DALY	10
Kenya	¢0.20	DI/1 2	13-34% /	95%	60,935	216,454	\$30M	\$38/DALY	14
Uganda	φ0.20	1111-2	27-67%	100%	70,236	329,779	\$10M	\$34/DALY	14
Indonesia	\$5.00	RV5 - 3	70 - 84%	94%	5,450		\$5.1M	\$174/QALY	18

Results from select Cost-Effectiveness Studies:

Break-Even Analysis: Break-even analysis involves finding the value of an input variable that produces a zero benefit level. In this case, the input variable is the price per dose of rotavirus vaccine, where the healthcare costs saved as a result of preventing rotavirus gastroenteritis exactly offset the cost of vaccination. This break-even price can be calculated from both the healthcare system and societal perspectives.⁵ These assessments can help calculate a "break-even" price that can be used as a basis for negotiations with manufacturers or purchasing agencies. An economic evaluation of rotavirus disease and rotavirus vaccines in developing countries found that from the healthcare system perspective, the "break-even" prices for rotavirus vaccines would be <US\$0.53 for lower-middle-income countries and <US\$2.00 for upper-middle-income countries.⁵

VACCINE RELATED COSTS AND RESOURCE USE

Rotavirus vaccine use has been shown to be cost-effective for reducing rotavirus gastroenteritis-related mortality and morbidity in high-, middle- and low-income countries. The amount of resources required for implementation of new vaccines into National Immunization Programs (NIP) depends on factors such as vaccine attributes, immunization schedules and ease of access to the intended vaccine recipient populations. These resources vary by country and can be costly. Additional elements to consider in calculating cost for vaccine delivery include elements such as personnel, training, transportation, cold chain, and waste. Accurate information on the cost and financing of vaccine programs is essential for NIP planning and management.

Multiple peer-reviewed articles on the topic of costs have been published²⁹⁻³¹, including the following recent references from the EPIC^a Immunization Costing project³² which discuss this issue in more detail:

Rotavirus Technical Briefings, Section 3: Rotavirus Vaccine Economic Considerations Last updated January 2017

^{*} Routine Immunization (RI) program data only

^a EPIC I is a coordinated set of immunization costing and financing studies (2012-2014) financed by the Bill & Melinda Gates Foundation

- 1. Andrus, J., & Walker, D. (2015). Perspectives on expanding the evidence base to inform vaccine introduction: Program costing and cost-effectiveness analyses. *Vaccine*, 33(Supplement 1), A2–A3. doi:10.1016/j.vaccine.2015.01.001 [link]
- Brenzel, L., Young, D., & Walker, D. (2015). Costs and financing of routine immunization: Approach and selected findings of a multi-country study (EPIC). *Vaccine*, 33(Supplement 1), A13–A20. doi:10.1016/j.vaccine.2014.12.066 [link]
- Gargasson, J., Nyonator, F., Adibo, M., Gessner, B., & Colombini, A. (2015). Costs of routine immunization and the introduction of new and underutilized vaccines in Ghana. *Vaccine*, 33(Supplement I), A40-A46. http://dx.doi.org/10.1016/j.vaccine.2014.12.081 [link]
- Schütte, C., Chansa, C., Marinda, E., Guthrie, T., Banda, S., Nombewu, Z., . . . Kinghorn, A. (2015). Cost analysis of routine immunisation in Zambia. *Vaccine*, 33(Supplement 1), A47-A52. http://dx.doi.org/10.1016/j.vaccine.2014.12.040 [link]
- Janusz, C., Castañeda-Orjuela, C., Aguilera, I., Garcia, A., Mendoza, L., Díaz, I., & Resch, S. (2015). Examining the cost of delivering routine immunization in Honduras. *Vaccine*, 33(Supplement I), A53-A59. http://dx.doi.org/10.1016/j.vaccine.2015.01.016 [link]
- Goguadze, K., Chikovani, I., Gaberi, C., Maceira, D., Uchaneishvili, M., Chkhaidze, N., & Gotsadze, G. (2015). Costs of routine immunization services in Moldova: Findings of a facility-based costing study. *Vaccine*,33(Supplement I), A60-A65. http://dx.doi.org/10.1016/j.vaccine.2014.12.034 [link]
- Ahanhanzo, C., Huang, X., Gargasson, J., Sossou, J., Nyonator, F., Colombini, A., & Gessner, B. (2015). Determinants of routine immunization costing in Benin and Ghana in 2011. Vaccine,33(Supplement I), A66-A71. http://dx.doi.org/10.1016/j.vaccine.2014.12.069 [link]
- 8. Levin, C. (2016, February 18). Meeting Report: Convening on immunization delivery costs (Rep.). [link]
- Brenzel, L., Schütte, C., Goguadze, K., Valdez, W., Gargasson, J., & Guthrie, T. (2016). EPIC Studies: Governments Finance, On Average, More Than 50 Percent Of Immunization Expenses, 2010–11 *Health Affairs*, 35, 259-265. [link]

VACCINE AVAILABILITY

UNICEF entered into two Long Term Arrangements for the supply of Rotavirus Vaccine (RVV) with two manufacturers for 83.4 Million courses that extend through 2016. To date, no new manufacturers are expected to enter the market with a WHO prequalified Rotavirus Vaccine prior to 2019. As of mid-2014, there was an unbalanced demand for rotavirus vaccine available due to country selection of one product over another and manufacturing issues. The demand for RVV was expected to exceed available supply by 2017/2018, which may result in delays in country introductions or additional contractual awards to increase supply to meet this demand.^{33, 34} Countries should consult with UNICEF Supply Division for the most up-to-date information regarding available rotavirus vaccine supply.

VACCINE PRICE/AFFORDABILITY

Support for Procurement of Rotavirus Vaccines

Low Income Countries

For all low-income Gavi-eligible countries, a \$0.20/dose co-financing payment will be required. For countries preparing for or entering the transition phase, the price per dose will depend on the country's gross national

income (GNI) per capita on average over the previous three years.^b A diagram of Gavi's current transition policy illustrates the relationship between financing and country eligibility over time: ³⁵



In August, 2016 both manufacturers currently supplying rotavirus vaccines to Gavi countries have agreed to guarantee Gavi pricing after transition. Merck (Rotateq) and GSK (Rotarix) have each guaranteed a 10 year price freeze to Gavi countries from the date a country assumes full self-financing, meaning that for the first 10 years after transition, the country can procure vaccine from the manufacturer at Gavi prices (see table below for Gavi pricing) with no increase in cost. Eligibility for the price guarantee varies by vaccine and details may be found here:

www.gavi.org/Library/GAVI-documents/Supply-procurement/FAQ--Merck-pricing-commitments-forcountries-transitioning-out-of-Gavi-s-financial-support/

Lower-middle- and Middle-income Countries

- For countries in the PAHO region, a Revolving Fund exists to help with vaccine purchase. Information can be found at <u>http://www.paho.org/immunization/toolkit/vaccine-procurement-fund.html</u>
- UNICEF <u>http://www.unicef.org/supply/index 54052.html</u>, UNICEF price data can be found at <u>http://www.unicef.org/supply/index 57476.html</u>
- Some vaccine manufacturers offer tiered pricing agreements with individual countries to providing vaccine at affordable prices.

select publicly available rotavirus vaccine prices			
ROTAVIRUS VACCINE PRICES*			
COUNTRY/REGION	VACCINE*	PRICE (US\$/COURSE)	
Cost to Gavi	Rotarix / RotaTeq	US\$2.13 (1.88€) / 3.56 (per dose prices)	
Cost to Gavi-eligible, low- income countries**	Rotarix / RotaTeq	US\$0.40-0.60 (Subsidized co-pay price)	
РАНО	Rotarix	US\$13.00	
United Kingdom	Rotarix	US\$45 (estimated)	
United States of America	Rotarix / RotaTeq	US\$174-209 (CDC) US\$219-235 (private market)	

Select publicly available rotavirus vaccine prices

Table adapted from Rotavirus: common, severe, devastating, preventable, p. 28 (* as of Feb. 2016)³⁶⁻⁴⁰

^b Gavi's full co-financing policy may be found at: <u>http://www.gavi.org/about/governance/programme-policies/co-financing/</u>

* Rotarix is recommended as a 2-dose course while RotaTeq is recommended as a 3-dose course.

** The maximum co-financing cost for Gavi countries is 100% of the Gavi price per dose (\$2.13-3.56, depending on the vaccine product selected)

SOCIO-ECONOMIC IMPACTS OF DISEASE

Data from some settings suggest that diarrheal disease has important and far-reaching consequences on early childhood education and cognition.

- In a study of children in a Brazilian shantytown, researchers found that the greater the number of episodes of persistent diarrhea before age two, the more delayed a child was in terms of school readiness. Overall, each episode of diarrhea delayed a child's starting school by 0.7 months. Likewise, 6-10 years later, increasing episodes of diarrhea before age two predicted delays in age-appropriate educational attainment.⁴¹
- In a separate study from Brazil, children with a high incidence of diarrhea in the first two years of life scored significantly lower on 3 out of 5 types of tests measuring cognitive function at ages 6-10 compared to children who did not suffer recurrent bouts of early childhood diarrhea.⁴²

COSTS TO FAMILIES

See *Section 2: Rotavirus Disease* of this brief for a summary of studies evaluating rotavirus disease treatment costs to individuals and families.

SECTION 3: REFERENCES

- World Health Organzation. (2003). Making choices in health: WHO guide to cost-effectiveness analysis. Edited by T. Tan-Torres Edejer *et al.* Geneva: World Health Organization. Available from: http://www.who.int/choice/publications/p 2003 generalised cea.pdf
- 2. World Health Organization. (2014). Choosing interventions that are cost-effective [Internet]. Geneva: World Health Organization. Available from: <u>http://www.who.int/choice/en/</u> [cited 2016 April 8].
- 3. World Health Organization. (2015). Cost effectiveness and strategic planning (WHO-CHOICE). [13 November 2015]. Available from: <u>http://who.int/choice/costs/CER levels/en/</u>.
- 4. Paternina-Caicedo, A., De la Hoz-Restrepo, F., & Alvis-Guzman, N. (2015). Epidemiological and economic impact of monovalent and pentavalent rotavirus vaccines in low and middle income countries. *The Pediatric Infectious Disease Journal*. 34(7), e176-e184. doi: 10.1097/INF.00000000000727. Abstract retrieved from: http://journals.lww.com/pidj/Abstract/2015/07000/Epidemiological and Economic Impact of Monovalent.17.aspx?trendmd_-shared=0
- Rheingans, R.D., Antil, L., Dreibelbis, R., Podewils, L.J., Bresee, J.S., & Parashar, U.D. (2009). Economic costs of rotavirus gastroenteritis and cost-effectiveness of vaccination in developing countries. *The Journal of Infectious Diseases*. 200 (Supplement 1), S16-S27. doi: 10.1086/605026. Retrieved from: http://jid.oxfordjournals.org/content/200/Supplement 1/S16.long
- Abbott, C., Tiede, B., Armah, G., & Mahmoud, A. (2012). Evaluation of cost-effectiveness of live oral pentavalent reassortant rotavirus vaccine introduction in Ghana. *Vaccine*. 30(15), 2582–2587. doi:10.1016/j.vaccine.2012.01.076. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/22321664</u>
- Bar-Zeev, N., Tate, J.E., Pecenka, C., Chikafa, J., Mvula, H., Wachepa, R., ... Cunliffe, N.A. for the VACSURV Consortium. (2016). Cost-effectiveness of monovalent rotavirus vaccination of infants in Malawi: a post-introduction analysis using individual patient–level costing data. *Clinical Infectious Diseases*. 62 (Supplement 2), S220-S228. doi: 10.1093/cid/civ1025.
- Berry, S.A., Johns, B., Shih, C., Berry, A.A., & Walker, D.G. (2010). The cost-effectiveness of rotavirus vaccination in Malawi. *The Journal of Infectious Diseases*. 202(Supplement 1), S108-S115. doi: 10.1086/653578. Retrieved from: http://jid.oxfordjournals.org/content/202/Supplement 1/S108.long
- Diopa, A., Atherly, D., Faye, A., Sall, F.A., Clark, A.D., Nadiel, L., . . . Ba, M. (2015). Estimated impact and cost-effectiveness of rotavirus vaccination in Senegal: A country-led analysis. *Vaccine*. 33(Supplement), A119-A125. <u>http://dx.doi.org/10.1016/j.vaccine.2014.12.065</u>
- Gargano, L.M., Tate, J.E., Parashar, U.D., Omer, S.B., & Cookson, S.T. (2015). Comparison of impact and cost-effectiveness of rotavirus supplementary and routine immunization in a complex humanitarian emergency, Somali case study. *Conflict and Health.* 9(5), 1-10. doi: 10.1186/s13031-015-0032-y. Retrieved from: <u>http://conflictandhealth.biomedcentral.com/articles/10.1186/s13031-015-0032-y</u>.
- Jan van Hoek, A., Ngama, M., Ismail, A., Chuma, J., Cheburet, S., Mutonga, D., & Nokes, D.J. (2012). A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: comparison between rotarix and rotateq vaccines. *PLoS ONE*. 7(10), e47511. doi:10.1371/journal.pone.0047511. Retrieved from: <u>http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0047511</u>
- Melliez, H., Boelle, P.Y., Baron, S., Moutona, Y., & Yazdanpanah, Y. (2007). Effectiveness of childhood vaccination against rotavirus in sub-Saharan Africa: the case of Nigeria. *Vaccine*. 25. 298-305. doi:10.1016/j.vaccine.2006.07.038. Retrieved from: <u>http://anothersample.net/effectiveness-of-childhood-vaccination-against-rotavirus-in-sub-saharan-africa-the-case-of-nigeria</u>
- Ruhago, G.M., Ngalesoni, F.N., Robberstad, B., & Norheim, O.F. (2015). Cost-effectiveness of live oral attenuated human rotavirus vaccine in Tanzania. *Cost Effectiveness and Resource Allocation*. 13(7), 1-12. doi: 10.1186/s12962-015-0033-0. Retrieved from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4422135/
- 14. Sigeia, C., Odaga, J., Mvundura, M., Madrid, Y., Clark, A.D., & Kenya ProVac Technical Working Group/Uganda ProVacTechnical Working Group. (2015). *Vaccine*. 33(Supplement), A109-A118. <u>http://dx.doi.org/10.1016/j.vaccine.2014.12.079</u>
- Tate, J.E., Kisakye, A., Mugyenyi, P., Kizza, D., Odiit, A., & Braka, F. (2011). Projected health benefits and costs of pneumococcal and rotavirus vaccination in Uganda. *Vaccine*. 29(17), 3329-3334. doi: 10.1016/j.vaccine.2010.12.122. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/21241733</u>.
- Tate, J.E., Rheingans, R.D., O'Reilly, C.E., Obonyo, B., Burton, D.C., Tornheim, J.A., ... Widdowson, M. (2009). Rotavirus disease burden and impact and cost-effectiveness of a rotavirus vaccination program in Kenya. *The Journal of Infectious Diseases*. 200(Supplement 1), S76-S84. doi: 10.1086/605058. Retrieved from: http://iid.oxfordiournals.org/content/200/Supplement 1/S76.long

- 17. Muangchana, C., Riewpaiboon, A., Jiamsiri, S., Thamapornpilas, P., & Warinsatian, P. (2012). Economic analysis for evidencebased policy-making on a national immunization program: A case of rotavirus vaccine in Thailand. *Vaccine*. 30(18), 2839-2847. doi:10.1016/j.vaccine.2012.02.047. Abstract retrieved from: <u>http://europepmc.org/abstract/med/22387220</u>.
- 18. Suwantika, A.A., Tu, H.A., & Postma, M.J. (2013). Cost-effectiveness of rotavirus immunization in Indonesia: taking breastfeeding patterns into account. *Vaccine*. 31, 3300-3307. <u>http://dx.doi.org/10.1016/j.vaccine.2013.04.055</u>
- Chotivitayatarakorn, P., Chotivitayatarakorn, P., & Poovorawan, Y. (2010). Cost-effectiveness of rotavirus vaccination as part of the national immunization program for Thai children. *Southeast Asian Journal of Tropical Medicine and Public Health*. 41(1), 114-125. Retrieved from: <u>https://www.unboundmedicine.com/medline/citation/20578490/Cost effectiveness of rotavirus vaccination as part of the</u> national immunization program for Thai children
- Esposito, D.H., Tate, J.E., Kang, G., & Parashar, U.D. (2011). Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008. *Clinical Infectious Diseases*. 52(2), 171-177. doi: 10.1093/cid/ciq094. Retrieved from: <u>http://cid.oxfordjournals.org/content/52/2/171.long</u>.
- Rheingans, R., Anderson, J.D., Anderson, B., Chakraborty, P, Atherly, D., & Pindolia, D. (2014). Estimated impact and costeffectiveness of rotavirus vaccination in India: effects of geographic and economic disparities. *Vaccine*. 32 (Supplement), A140-A150. <u>http://dx.doi.org/10.1016/j.vaccine.2014.05.073</u>
- Vergueta, S., Murphya, S., Anderson, B., Johansson, K.A., Glass, R., & Rheingans, R. (2013). Public finance of rotavirus vaccination in India and Ethiopia: an extended cost-effectiveness analysis. *Vaccine*. 31, 4902-4910. <u>http://dx.doi.org/10.1016/j.vaccine.2013.07.014</u>
- Wilopo, S.A., Kilgore, P., Kosen, S., Soenarto, Y., Aminah, S., Cahyono, A., . . . Tholib, A. (2009). Economic evaluation of a routine rotavirus vaccination programme in Indonesia. *Vaccine*. 27 (Supplement 5), F67-F74. doi:10.1016/j.vaccine.2009.09.040. Abstract retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/19931723</u>.
- Ozawa, S., Clark, S., Portnoy, A., Grewal, S., Brenzel, L., & Walker, D.G. (2016). Return on investment from childhood immunization in low- and middle-income countries 2011-2020. *Health Affairs*. 35(2), 199-207. doi: 10.1377/hlthaff.2015.1086. Retrieved from: <u>http://content.healthaffairs.org/content/35/2/199.full.html</u>
- Jit, M., Yuzbashyan, R., Sahakyan, G., Avagyan, T., & Mosina, L. (2011). The cost-effectiveness of rotavirus vaccination in Armenia. *Vaccine*. 29(48), 9104-9111. doi:10.1016/j.vaccine.2011.08.127. Abstract retrieved from: <u>http://europepmc.org/abstract/med/21945959</u>.
- 26. Kotsiopoulos, N., Connolly, M.P., Postma, M.J., & Hutubessy, R.C. (2013). Fiscal consequences of changes in morbidity and mortality attributed to rotavirus immunization. *Vaccine*. 31, 5430-5434. <u>http://dx.doi.org/10.1016/j.vaccine.2013.09.002</u>
- 27. Shakerian, S., Lakeh, M.M., Esteghamati, A., Zahraei, M., & Yaghoubi, M. (2015). Cost-effectiveness of rotavirus vaccination for under-five children in Iran. *Iranian Journal of Pediatrics*. 25(4), e2766. doi: 10.5812/ijp.2766. Retrieved from: http://cdn.neoscriber.org/cdn/serve/8a/f9/8af9e4b6569af3c8bf986912d25b03b2779b97e7/ijp-25-2766.pdf
- Atherly, D., Lewis, K.D., Tate, J., Parashar, U.D., & Rheingans, R.D. (2012). Projected health and economic impact of rotavirus vaccination in GAVI-eligible countries: 2011–2030. *Vaccines*. 30(Supplement 1), A7-A14. Abstract retrieved from: http://www.sciencedirect.com/science/article/pii/S0264410X11020457.
- Portnoy, A., Ozawa, S., Grewal, S., Norman, B.A., Rajgopal, J., Gorham, K.M., & Lee, B.Y. (2015). Costs of vaccine programs across 94 low- and middle-income countries. *Vaccines*. 33(Supplement 1), A99-A108. <u>http://dx.doi.org/10.1016/j.vaccine.2014.12.037</u>.
- Andrus, J.K., & Walker, D.G. (2015). Perspectives on expanding the evidence base to inform vaccine introduction: program costing and cost-effectiveness analyses. *Vaccines*. 33(Supplement 1), A2-A3. Available at: http://www.sciencedirect.com/science/article/pii/S0264410X1500002X.
- Madsen, L.B., Ustrup, M., Hansen,K.S., Nyasulu, P.S., Bygbjerg, I.C., & Konradsen, F. (2014). Estimating the costs of implementing the rotavirus vaccine in the national immunisation programme: the case of Malawi. *Tropical Medicine and International Health*. 19(2), 177–185. doi:10.1111/tmi.12233 Abstract retrieved from: http://onlinelibrary.wiley.com/doi/10.1111/tmi.12233/epdf
- 32. EPIC, Immunization Costing. Retrieved on April 8, 2016 from: <u>http://www.immunizationcosting.org/publications/</u>
- 33. UNICEF. (2014). Vaccine Manufacturer Consultation, Copenhagen, October 2014. Retrieved from: http://www.unicef.org/supply/files/4.Market updates.pdf
- 34. UNICEF Supplies and Logistics. (October 2015). Overview of Rotavirus Through UNICEF. Presentation retrieved from: http://www.unicef.org/supply/files/4 f VIC 2015 New Vaccines Presentation - Consolidated.pdf
- 35. GAVI, The Vaccine Alliance. (2016). Support, transition process. (<u>http://www.gavi.org/support/apply/graduating-countries/</u>).

- Nelson EA, de Quadros CA, Santosham M, Parashar UD, Steele D. Overcoming perceptions of financial barriers to rotavirus vaccine introduction in Asia. *Human Vaccine Immunotherapy*. 2013;9(11):2418-26. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981852/</u>.
- 37. UNICEF. Product menu for vaccines supplied by UNICEF for Gavi, The Vaccine Alliance. 30 March 2015. Available from: http://www.unicef.org/supply/files/Product Menu 31 March 2015.pdf
- 38. CDC. Vaccines for Children Program (VFC). [April 2016]. Available from: <u>http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html</u>.
- 39. PAHO. PAHO Revolving Fund. [2015]. Available from: http://new.paho.org/hq/index.php?option=com_content&task=view&id=1864&Itemid=2234&lang=en.
- 40. Rota Council, (2016). *Rotavirus: common, severe, devastating, preventable*. Retrieved from: <u>http://rotacouncil.org/resources/101142-004_RotaExecSummary2015_V9r2.pdf</u>
- 41. Lorntz B, Soares AM, Moore SR, *et al.* Early childhood diarrhea predicts impaired school performance. *Pediatric Infectious Disease Journal.* 2006:25(6):513-20. Retrieved from: <u>http://www.ncbi.nlm.nih.gov/pubmed/?term=16732149</u>
- 42. Niehaus. Early Childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. *American Journal of Tropical Medicine and Hygeine*. 2002:68(5);590-3. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12201596





ELEMENTS TO CONSIDER IN DEVELOPING A FRAMEWORK FOR ISSUING IMMUNIZATION RELATED POLICY RECOMMENDATIONS

Ational Immunization Technical Advisory Groups (NITAGs) provide evidence based recommendations for the development of immunisation policies. These recommendations are generated from a systematic, credible and transparent process of selecting, reviewing and synthesising evidence.

In generating evidence-based recommendations NITAG begins with defining a recommendation framework. This recommendation framework

outlines the elements on which evidence should be gathered. For each element, specific data required is identified. NITAG will then rank this data as critical (high priority), important (intermediate priority) or noncritical (low priority). Structured and comprehensive reviews of evidence are conducted for all critical and important data requirements.

The table provided lists key elements to be considered when developing an immunization recommendation. These elements may be related to the vaccine characteristics disease, economic or operational considerations, or health policy and programmatic issues.

ISSUE	ELEMENT		
	Safety	Type, consequences and frequency of short and long-term adverse events following vaccination	
		Risk groups or risk factors for adverse events	
		Contraindications	
	Efficacy and Effectiveness	Type specific protection afforded	
TICS		Critical determinants of the immune response associated with protection	
RIS		Duration of protection and waning of immunity if any	
Ē		Interference regarding protection or immunity with other vaccines	
AC		Impact on resistance to antibiotics and antivirals	
IAR		Herd immunity	
TION CH	Vaccine indirect effects	Potential negative population impact through change in age of infection for unprotected individuals e.g. rubella or varicella vaccine or emergence of non-vaccine serotypes	
ZAI	Vaccine characteristics	Vaccine presentation and formulation	
IN		Dosage and route of administration	
CINE		Administration schedule and possibility of co-administration with other vaccines	
AC ND		Flexibility of vaccination schedules	
P < 7		Cold chain and logistic requirements	
	Burden of disease	Incidence of morbidity and mortality, age specific morbidity and mortality, risk groups, serotype/serogroup distribution, epidemic potential, disease occurrence over time, changes in epidemiology over time	
	Clinical characteristics disease	Signs and symptoms of disease, severe forms of disease, long term complications of disease, medical management of disease	
	Use and costs of health care	Primary/secondary/tertiary care implications, short and long term use of health care (e.g. treatments, hospitalization)	
	Alternative preventive and control measures	Alternative preventive and control measures (e.g. health education, hygiene, vector control) and their effectiveness, costs and practicality	
B		Other existing vaccines against the same disease and their effectiveness, costs and practicality	
SEA	Regional and international considerations	Existence of regional and global recommendations	
2 . DIS		Disease potential for international spread and pandemic potential	

ISSUE		ELEMENT	SPECIFIC DATA		
		Vaccine related costs and resource use	Direct and indirect costs to administer the vaccine as they compare to those of other existing vaccines or other prevention or control measures		
	ONAL	Vaccino availabilit.	Availability of vaccine and long term supply		
		vaccine availability	Available suppliers and competition dynamic in the market		
		Vaccine affordability	Availability of fiscal space to effectively implement and sustain the recommendation in the programme		
	ERATI		Prevailing prices for the vaccine in the market and price estimations for the specific country		
	OPE		School and work absenteeism		
		Socio-economic	Indirect costs to patients and families		
	AN	and social impact of disease	Productivity losses		
	IIC		Stigma around a disease		
	IDE	Economic impact	Reduction in health care costs		
	NO	of intervention on immunization program as well as health sector	Health gain (years of life saved, QALY gained, etc)		
ຕ	C C C C C C C C C C C C C C C C C C C		Cost effectiveness ratio of vaccination program		
		Interaction with a th			
		existing intervention and control strategies	Impacts of program (catch up) on safety and efficacy of other vaccines and other health care sectors		
		Feasibility	Accessibility of target population		
			Availability of the vaccine and long term supply in public and private sector including collaborations with insurance sector		
		Vaccine registration and regulations	National regulatory authorities requirements for licensing the vaccine and/or its use in a different schedule as originally recommended		
	SUES	Impact on resources	Availability of human, technical and financial resources for distribution (including cold chain sustainability); consider additional training needs of health workers		
	VTIC ISS	Ability to evaluate	Availability of information systems to manage the vaccine supply chain and measure related performance metrics i.e. coverage and vaccine utilisation		
	× IM		Existence and reliability of surveillance system		
	OLIC SRAM	Acceptability	Perception of the public and medical community about the disease and the vaccine		
	ALTH P	Equity	Universality, accessibility and gratuity of services for all the inhabitants in the country including vulnerable, hard to reach and immigrant populations		
4	HE, ANI	Social considerations	Non health related effects of vaccination, ethical considerations, legal implications etc.		