EXPERT REVIEWS

Progress with rotavirus vaccines: summary of the Tenth International Rotavirus Symposium

Expert Rev. Vaccines 12(2), 113–117 (2013)

Umesh Parashar*[1], Duncan Steele[2], Kathleen Neuzil[3], Ciro de Quadros[4], Piyanit Tharmaphornpilas[5], Fatima Serhan[6], Mathu Santosham[7], Manish Patel[1] and Roger Glass[8]

[1]*CDC, Atlanta, GA, USA*
[2]*Bill and Melinda Gates Foundation, Seattle, WA, USA*
[3]*Program for Applied Technology in Health, Seattle, WA, USA*
[4]*Sabin Vaccine Institute, Washington, DC, USA*
[5]*Ministry of Health, Bangkok, Thailand*
[6]*WHO, Geneva, Switzerland*
[7]*Johns Hopkins University, Baltimore, MD, USA*
[8]*NIH, Bethesda, MD, USA*
**Author for correspondence: uap2@cdc.gov*

Tenth International Rotavirus Symposium
Bangkok, Thailand, 19–21 September 2012

Over 350 scientific, public and private sector experts from 47 countries convened at the Tenth International Rotavirus Symposium in Bangkok, Thailand on 19–21 September 2012 to discuss progress in the prevention and control of rotavirus, the leading cause of diarrhea hospitalizations and deaths among young children worldwide. Participants discussed data on the burden and epidemiology of rotavirus disease, results of trials of rotavirus vaccines, postmarketing data on vaccine impact and safety from countries that have implemented rotavirus vaccination programs, new insights in rotavirus pathogenesis, immunity and strain diversity, and key issues related to vaccine policy and introduction.

Historical perspective on rotavirus vaccine development

The symposium began with the inaugural Roger Glass Lecture, delivered by Roger Glass (Fogarty International Center, US NIH, MD, USA), who provided a historical perspective on rotavirus vaccine development efforts over the past four decades. In 1973, the seminal work of Ruth Bishop and colleagues led to the discovery of a 70-nm, round-structured virus in the gut of Australian children with acute diarrhea [1]. This virus was subsequently named rotavirus because of its distinct wheel-like appearance (latin, rota=wheel) by electron microscopy. Within a decade, rotavirus was identified to be the most common cause of severe diarrhea in children worldwide, responsible for approximately a third of hospitalizations from diarrhea. The fact that the 'democratic' rotavirus affected children in both industrialized and developing countries indicated that interventions to improve hygiene and sanitation may not be sufficient for disease prevention. This finding, combined with early studies demonstrating that children developed protective immunity after rotavirus infection, led to efforts to develop vaccines for disease prevention.

Remarkably, the first rotavirus vaccine trials began within a decade of the discovery of the virus. Trials of several candidate rotavirus vaccines were conducted in the 1980s and 1990s, culminating in the US licensure in 1998 of Rotashield® (Wyeth, NJ, USA), a rhesus–human reassortant rotavirus vaccine. Rotashield was recommended for routine immunization of US children and was given to over half a million infants in the first year of its introduction. In 1999, however, a rare and unanticipated adverse event, intussusception, was noted in approximately one of 10,000 infants vaccinated with Rotashield, primarily following the first vaccine dose [2]. The manufacturer removed Rotashield from the market and the exuberance around implementation of the first licensed rotavirus vaccine was abruptly replaced by great dismay and uncertainty. Future live oral vaccines in development had to deal with both the untoward legacy of Rotashield and the possibility that they might also be associated with risk of intussusception.

Despite the challenges and uncertainty, the manufacturers of two candidate vaccines in the pipeline – Rotarix®, produced by GlaxoSmithKline (London, UK) and RotaTeq®, produced by

 10.1586/ERV.12.148 ISSN 1476-0584

Merck (NJ, USA) – pursued further clinical testing. The monovalent Rotarix vaccine contains the single most common serotype of rotavirus infecting humans, serotype G1P[8], and is delivered as two oral doses. The pentavalent RotaTeq vaccine is derived from a single bovine strain that is naturally attenuated for humans and is reassorted with the five most common serotypes of human rotavirus; it is administered in a three-dose oral regimen. To assess a possible risk of intussusception of the level seen with Rotashield, trials involving more than 60,000 infants were conducted for both Rotarix and RotaTeq in the USA, Europe and Latin America [3,4]. No risk of intussusception or any other serious adverse event was identified and both vaccines showed high efficacy (85–98%) against severe rotavirus disease. The vaccines were licensed in 2006 and were recommended by the WHO for routine immunization of children in the high- and middle-income regions where their efficacy had been demonstrated.

Because many live oral vaccines have performed less well in low-income settings compared with richer countries, the WHO mandated that rotavirus vaccines be tested for efficacy in low-income African and Asian settings before making a global recommendation for vaccine use. Data from trials of both rotavirus vaccines in developing countries became available in 2009 [5–7], and indeed vaccine efficacy was modest compared with high-income settings, ranging from 51 to 64% in the first year of life. The reasons for the lower efficacy of rotavirus vaccines in low-income settings are not completely understood, but could be related to interference by oral polio vaccine, higher titers of maternal antibodies in the infant, concurrent gut infection with other microbes, micronutrient deficiencies (e.g., zinc or vitamin A), altered gut microbiome or other host factors (e.g., comorbidities such as diarrhea) [8]. Importantly, despite lower efficacy, the absolute number of severe rotavirus gastroenteritis cases prevented by vaccination of a given number of children is greater in low-income countries because of the substantially greater baseline rotavirus burden in these settings. These considerations led the WHO to make a recommendation for global use of rotavirus in 2009 [9].

Burden & epidemiology of rotavirus disease

The public health need for a rotavirus vaccine is evident from the tremendous health burden of rotavirus disease. Data from the WHO-coordinated global network for rotavirus surveillance at 185 sentinel sites in 64 countries showed rotavirus detection rates of 37–53% in children hospitalized with diarrhea in 2011 in regions of the world where vaccines have not been widely implemented (Fatima Serhan, WHO, Geneva, Switzerland). By applying rotavirus detection rates from these surveillance networks as well as those from a review of the scientific literature to global figures of total mortality from childhood diarrhea, an estimate of 453,000 annual global deaths from rotavirus gastroenteritis was derived (Jacqueline Tate, CDC, GA, USA) [10]. More than 90% of the estimated global rotavirus deaths occur in low-income countries in Africa and Asia, with five countries (India, Nigeria, Pakistan, Democratic Republic of Congo and Ethiopia) accounting for more than half of the deaths.

The implications for vaccination programs of variations in the epidemiology of rotavirus disease in different settings were examined. Analysis of the age distribution of rotavirus mortality showed that timely vaccination of young children is vital to maximize the impact of vaccination, especially in countries where severe rotavirus disease occurs at a very young age and/or delays in the timing of routine vaccination are common (Colin Sanderson, London School of Tropical Medicine and Hygiene, London, England). Data on rates and outcomes of rotavirus infection in prospective follow-up from birth to 3 years of age of a cohort of 453 children in South India were compared with findings from a similar evaluation conducted in Mexican children in the early 1990s (Gagandeep Kang, Christian Medical College, Vellore, India [11,12]). Two notable differences were observed between the natural history of rotavirus infections among Indian and Mexican children. First, rotavirus infections occurred at a younger age among infants in India compared with Mexico (53% infected vs 34% infected by 6 months of age, respectively). Second, while no child developed moderate/severe rotavirus diarrhea with their third or subsequent rotavirus infection in the Mexican cohort, 22% of third or later rotavirus infections in the cohort of Indian children led to moderate/severe diarrhea. These differences in natural history parameters were incorporated into a mathematical model to estimate vaccine efficacy in different settings (Ben Lopman, CDC, GA, USA [13]). The model predicted greater efficacy in high- and middle-income settings compared with low-income settings, with a gradient in efficacy estimates that was very similar to that observed in clinical trials of rotavirus vaccine in different socioeconomic settings. Furthermore, the model reaffirmed that the absolute benefits of vaccination in terms of number of cases of severe rotavirus disease prevented by vaccination of a given number of children was greater in developing countries as compared with higher resource settings.

Impact & effectiveness of rotavirus vaccination

By 2012, approximately 40 countries worldwide have introduced rotavirus vaccine in their national childhood immunization programs. The first introductions happened in many countries in Latin America beginning in 2006, and vaccines have had a notable impact on mortality, hospitalizations and outpatient visits for diarrhea in this region (Lucia Oliveira, Pan American Health Organization, Washington, DC, USA). Perhaps the most exciting postlicensure data pertains to the effect of rotavirus vaccination in reducing deaths from childhood diarrhea, an outcome that was not assessed in prelicensure trials [14]. In Mexico, following introduction of Rotarix into the national immunization program in 2007, diarrhea mortality declined 35% in 2008 compared with the prevaccine baseline (2003–2006) and this decline in mortality has now been sustained for 4 years from 2008 to 2011 (Edgar Sanchez Uribe, Ministry of Health, Mexico City, Mexico). Substantial declines of 17–55% in all-cause gastroenteritis hospitalization and even larger declines of 49–89% in rotavirus gastroenteritis hospitalizations among children <5 years of age have been observed within the first 2 years following rotavirus vaccine introduction in many middle- and high-income countries, including the

USA, South Africa and Israel (Nicola Page, National Institute of Communicable Disease, Johannesburg, South Africa; Umesh Parashar, CDC, GA, USA; Ron Dagan, Ben-Gurion University, Beer-Sheva, Israel [15]). Of note, declines in acute gastroenteritis hospitalizations of 8–29% among older children and adults 5–24 years of age during the rotavirus season were observed in the USA following rotavirus vaccine introduction, indicating an unappreciated burden of rotavirus disease in these older populations and additional indirect benefits of vaccination beyond the target vaccinated age groups [16].

Intussusception

Although the two large prelicensure trials of RotaTeq and Rotarix did not find an increased risk of intussusception, postmarketing studies have found a low risk of intussusception (one to two cases per 100,000 infants) in the first week after the first dose of rotavirus vaccine in some settings, but the results are variable. Studies in Mexico and Australia reported an increased intussusception risk with the first dose whereas in Brazil a risk was identified after the second dose but not the first dose; no risk has been identified in active monitoring in the USA. No studies to date have examined risk of intussusception in low-income settings and limited data on the baseline epidemiology and incidence of intussusception from these locations are available (Julie Bines, Murdoch Children's Research Institute, Melbourne, Australia). Generating data from developing countries is important because even a few isolated reports of intussusception that are temporally but not causally related to vaccination could have an adverse impact on the vaccine program. Furthermore, recognizing that the benefits of vaccination far outweigh the potential short-term risk of intussusception, the WHO has recently recommended removing the current age restrictions on rotavirus vaccination in developing countries to allow more flexibility for countries to improve vaccine coverage, but at the same time also strongly recommended implementing intussusception surveillance in these settings to monitor safety of vaccination (Manish Patel, CDC, GA, USA) [17].

Pipeline of rotavirus vaccine candidates

Updates on the status of the two licensed international RotaTeq and Rotarix vaccines were provided (Michelle Goveia, Merck and Company, PA, USA and Bernd Benninghoff, GSK, Belgium). In addition, several candidate vaccines are in various stages of clinical development. One candidate based on a neonatal rotavirus strain, 116E, is being developed by Bharat Biotech International Limited (Sai Prasad, Bharat Biotech International Limited, Hyderabad, India). The 116E vaccine strain is a natural reassortant between a human rotavirus virus G9P[11] strain with the VP4 protein from a bovine rotavirus strain. This strain was originally isolated from a neonate with an asymptomatic rotavirus infection in New Delhi, India. The 116E vaccine demonstrated good immunogenicity in Indian children [18], and is currently in the late stages of a Phase III efficacy trial with results expected in 2013. Earlier in the pipeline are vaccines being developed by the Serum Institute of India and Shantha Biotechnics based on the UK bovine–human reassortant strains. In Vietnam, a monovalent rotavirus vaccine, Rotavin™, containing a human G1P[8] rotavirus strain attenuated by serial passage in cell culture, has demonstrated good immunogenicity and was licensed for use in April 2012 [19] (Nguyen Trang, National Institute of Health and Epidemiology, Vietnam). Another candidate vaccine based on a neonatal rotavirus strain, RV3 (G3P[7]), has shown good safety in Phase I studies and will soon be tested in larger trials (Julie Bines and Margie Danchin, Murdoch Children's Research Institute, Melbourne, Australia). Next, the previously withdrawn Rotashield® (Wyeth, NJ, USA) vaccine has recently completed a Phase II study in Ghana. In this trial, the vaccine was given on a two-dose schedule with one dose each in the first 2 months of life, with the intent to administer the vaccine prior to age 3 months when the incidence of intussusception is very low (George Armah, Noguchi Memorial Research Institute, Ghana). Finally, several nonreplicating rotavirus vaccine candidates, including those based on inactivated rotavirus strains, virus-like particles and VP6 or VP8 subunits are in preclinical development (Baoming Jiang, CDC, GA, USA).

New insights in rotavirus pathogenesis, immunity & strain diversity

B V Venkataran Prasad (Baylor College of Medicine, TX, USA) presented emerging data showing that rotaviruses exhibit genotype-dependent variations in glycan specificity that may have implications in host specificity, tissue tropism, susceptibility, pathogenesis and interspecies transmission [20]. Specific recognition of A-type histo blood group antigens (HBGA) may be the basis for interspecies transmission observed in P[14] rotaviruses. The glycan binding site in globally dominant P[4] viral protein (VP)8 is distinct and, in addition, H-type P[4] VP8 can bind to Lewis HBGA; this might perhaps be a basis for increased prevalence of this strain.

A correlate of immune protection for rotavirus infection and vaccination has not been identified to date, and is eagerly sought since it could simplify clinical testing of future rotavirus vaccine candidates (i.e., vaccines could be licensed based on immunogenicity data alone versus the current standard of substantially larger efficacy trials) and also help evaluate the effect of interventions to improve the performance of rotavirus vaccines in developing countries. Data from clinical trials of Rotarix were re-examined to assess for a correlate of efficacy against any rotavirus gastroenteritis and severe rotavirus gastroenteritis in vaccinated children (Htay Htay Han, GSK, PA, USA). A separate review examined published data of immunogenicity and efficacy trials of RotaTeq and Rotarix to assess for correlation between serum IgA antibody titers and efficacy in WHO regions with low, medium and high under-5 mortality rate (u5MR) (Manish Patel, CDC, GA, USA). Serum IgA antibody titers and seroconversion rates were inversely correlated with levels of u5MR, and efficacy during the first 2 years of life was significantly lower among countries with lower median IgA titers [21,22]. These data suggest that serum antirotavirus IgA antibody is potentially a useful marker of immunity to rotavirus infection and this issue should be further examined with both available data and data that will be gathered in clinical trials of future rotavirus vaccines.

New insights in rotavirus strain diversity and evolution were reviewed. Although a large genetic diversity exists among human rotaviruses with respect to the G/P genotypes, the diversity is much smaller on the level of complete genomes and only Wa and DS-1-like rotavirus strains are of significant epidemiological importance in humans (Jelle Matthijnssens, University of Leuven, Belgium). The genotype constellation of rotavirus strains circulating in Africa and Asia seems to be similar to strains from the rest of the world, suggesting that the lower vaccine efficacy observed in these settings is most likely not due to circulation of rotavirus strains with a distinct genotype constellation but rather other host and environmental factors.

Vaccine-derived reassortant rotaviruses have been detected in association with gastroenteritis in a limited number of patients in a few countries that have implemented rotavirus vaccination programs [23–25]. The rotavirus genome is composed of 11 double-stranded RNA gene segments, and two rotavirus strains infecting the same cell can swap genomic segments (reassortment) to produce progeny with a mosaic genome containing individual genes from each parent. RotaTeq contains five live-attenuated strains derived through laboratory reassortment of human rotavirus strains with a bovine rotavirus strain. Three RotaTeq strains each contain a single human rotavirus gene segment and ten bovine rotavirus segments while two strains contain two human strain segments and nine bovine strain segments. In studies in Australia, USA and Finland, some children with gastroenteritis were infected with a vaccine-derived G1P[8] strain, believed to be the product of a genetic reassortment event in which the human G1 gene segment of one of the RotaTeq vaccine strains is inserted into the other vaccine strain containing the human P[8]. Additional studies were recommended to further document the frequency, distribution and disease severity associated with such vaccine-derived rotavirus strains.

Translating science to policy

On the final afternoon, panelists and audience members gathered to discuss the data presented at the symposium and the best ways to translate these data into country decisions and action on rotavirus vaccine introduction. The introductory talk by Kathy Neuzil (Program for Applied Technology in Health [PATH], WA, USA) reported that 38 countries, including nine Global Alliance for Vaccines and Immunisation (GAVI)-eligible countries, had introduced rotavirus vaccines as of September 2012. Many additional introductions in GAVI-eligible countries, particularly in Africa and the Middle East, are anticipated in the coming months. The successful dual launch of rotavirus and pneumococcal vaccines in Ghana in April 2012 was discussed by George Armah (Noguchi Memorial Research Institute, Ghana). A presentation by Andy Seale (PATH, WA, USA) provided the audience with strategies to more effectively communicate with decision makers, and emphasized the critical role of partnerships in moving an agenda forward. Mathuram Santosham (Johns Hopkins University, MD, USA) shared lessons learned from the HiB initiative. The slow uptake of rotavirus vaccines in Asia was discussed, with Tony Nelson (Chinese University of Hong Kong, Hong Kong, China) emphasizing the importance of knowledge translation and the need for enhanced advocacy in Asian countries. The panelists, who all represented the ROTA Council, invited audience members to share their experiences and ask questions, and also provided Web-based resources to assist audience members with advocacy and communication [101,102].

Two additional issues related to maximizing the benefits of rotavirus vaccination in developing countries were discussed during the symposium. The first was the need to ensure equitable distribution of rotavirus vaccines to ensure that they reach the most vulnerable children who are at greatest risk for severe outcomes of rotavirus diarrhea and are thus likely to benefit the most from vaccination (Rick Rheingans, University of Florida, FL, USA). The second was to examine the optimal timing and number of doses of rotavirus vaccination to achieve maximum protection from rotavirus disease in developing countries (Duncan Steele, Bill and Melinda Gates Foundation, WA, USA). Vaccination at a younger age would be ideal to provide maximum protection against rotavirus disease that occurs early in life; however, greater levels of passively transferred maternal antibody among younger infants could adversely affect vaccine performance. The benefits of adding a third dose of Rotarix to the primary immunization schedule should be examined, as this would allow initiation of vaccination at a young age while at the same time providing a third dose at a later age that would be less subject to interference by maternal antibody. Adding a third Rotarix dose would have implications in terms of vaccine supply, cost and cold chain capacity; thus, the benefits of this additional dose would have to be weighed against these and other considerations.

The symposium concluded with presentations on the cost–effectiveness of rotavirus vaccines in Thailand, and the value of these data for decision making. The recent launch of rotavirus vaccines in the Philippines was celebrated with a talk by Eric Tayag, Assistant Secretary of the Department of Health.

Conclusion

Overall, the Tenth International Rotavirus symposium was a success, with a record number of participants and a record number of countries with rotavirus vaccination programs. Surveillance and modeling continue to confirm rotavirus as the cause of a substantial proportion of severe, dehydrating diarrhea in diverse settings and populations. A highlight of the conference was the impact data demonstrating significant reductions in severe gastroenteritis, death and other important outcomes under 'real world' conditions of use in diverse settings. The rotavirus vaccine pipeline has promising new candidates in various stages of development, and important research continues into rotavirus pathogenesis, immunity, improving the performance of vaccines and correlates of protection.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

Financial & competing interests disclosure

M Santosham has served on the Scientific Advisory Board of both Merck and GlaxoSmithKline. He is also the chair of the Data & Safety Monitoring Board for 116E (Bharat Biotech) vaccine trial. K Neuzil is employed at PATH, which receives grants related to rotavirus vaccine development

and research from the GAVI Alliance and the Bill and Melinda Gates Foundation. C de Quadros is employed at the Sabin Institute, which has received grants from both GlaxoSmithKline and Merck that were used to support the Rotavirus Symposium held in Bangkok. R Glass is a government employee and through CDC has been involved with patents for an inactivated rotavirus vaccine and the Indian neonatal vaccine strain, 116E, being developed by the Government of India and the Gates Foundation, CDC and NIH, and Stanford. The CDC has received royalties from companies interested in testing the inactivated rotavirus vaccines and R Glass has received some funds from these agreements. F Serhan works at the WHO, which receives funds from the GAVI Alliance to support the rotavirus global surveillance network. U Parashar and M Patel are CDC employees and do not have any relevant financial disclosures. D Steele and P Tharmaphornpilas do not have any financial disclosures. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Bishop RF, Davidson GP, Holmes IH, Ruck BJ. Virus particles in epithelial cells of duodenal mucosa from children with acute non-bacterial gastroenteritis. *Lancet* 2(7841), 1281–1283 (1973).

2 Murphy TV, Gargiullo PM, Massoudi MS *et al.*; Rotavirus Intussusception Investigation Team. Intussusception among infants given an oral rotavirus vaccine. *N. Engl. J. Med.* 344(8), 564–572 (2001).

3 Vesikari T, Matson DO, Dennehy P *et al.*; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N. Engl. J. Med.* 354(1), 23–33 (2006).

4 Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR *et al.*; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N. Engl. J. Med.* 354(1), 11–22 (2006).

5 Madhi SA, Cunliffe NA, Steele D *et al.* Effect of human rotavirus vaccine on severe diarrhea in African infants. *N. Engl. J. Med.* 362(4), 289–298 (2010).

6 Armah GE, Sow SO, Breiman RF *et al.* 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 (2010).

7 Zaman K, Dang DA, Victor JC *et al.* 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 (2010).

8 Patel M, Shane AL, Parashar UD, Jiang B, Gentsch JR, Glass RI. Oral rotavirus vaccines: how well will they work where they are needed most? *J. Infect. Dis.* 200(Suppl. 1), S39–S48 (2009).

9 WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2009 – conclusions and recommendations. *Wkly Epidemiol. Rec.* 84(50), 518 (2009).

10 Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis.* 12(2), 136–141 (2012).

11 Gladstone BP, Ramani S, Mukhopadhya I *et al.* Protective effect of natural rotavirus infection in an Indian birth cohort. *N. Engl. J. Med.* 365(4), 337–346 (2011).

12 Velázquez FR, Matson DO, Calva JJ *et al.* Rotavirus infections in infants as protection against subsequent infections. *N. Engl. J. Med.* 335(14), 1022–1028 (1996).

13 Lopman BA, Pitzer VE, Sarkar R *et al.* Understanding reduced rotavirus vaccine efficacy in low socio-economic settings. *PLoS One* 7(8), e41720 (2012).

14 Richardson V, Hernandez-Pichardo J, Quintanar-Solares M *et al.* Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. *N. Engl. J. Med.* 362(4), 299–305 (2010).

15 Patel MM, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect. Dis.* 12(7), 561–570 (2012).

16 Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *J. Infect. Dis.* 204(7), 980–986 (2011).

17 Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit–risk modeling analysis. *PLoS Med.* 9(10), e1001330 (2012).

18 Bhandari N, Sharma P, Taneja S *et al.*; Rotavirus Vaccine Development Group. A dose-escalation safety and immunogenicity study of live attenuated oral rotavirus vaccine 116E in infants: a randomized, double-blind, placebo-controlled trial. *J. Infect. Dis.* 200(3), 421–429 (2009).

19 Dang DA, Nguyen VT, Vu DT *et al.*; Rotavin-M1 Vaccine Trial Group. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. *Vaccine* 30(Suppl. 1), A114–A121 (2012).

20 Hu L, Crawford SE, Czako R *et al.* Cell attachment protein VP8* of a human rotavirus specifically interacts with A-type histo-blood group antigen. *Nature* 485(7397), 256–259 (2012).

21 Armah GE, Breiman RF, Tapia MD *et al.* Immunogenicity of the pentavalent rotavirus vaccine in African infants. *Vaccine* 30(Suppl. 1), A86–A93 (2012).

22 Shin S, Anh DD, Zaman K *et al.* Immunogenicity of the pentavalent rotavirus vaccine among infants in two developing countries in Asia, Bangladesh and Vietnam. *Vaccine* 30(Suppl. 1), A106–A113 (2012).

23 Hemming M, Vesikari T. Vaccine-derived human-bovine double reassortant rotavirus in infants with acute gastroenteritis. *Pediatr. Infect. Dis. J.* 31(9), 992–994 (2012).

24 Donato CM, Ch'ng LS, Boniface KF *et al.* Identification of strains of RotaTeq rotavirus vaccine in infants with gastroenteritis following routine vaccination. *J. Infect. Dis.* 206(3), 377–383 (2012).

25 Boom JA, Sahni LC, Payne DC *et al.* Symptomatic infection and detection of vaccine and vaccine-reassortant rotavirus strains in 5 children: a case series. *J. Infect. Dis.* 206(8), 1275–1279 (2012).

Websites

101 ROTA Council: Advocacy Toolkit. http://rotacouncil.org/toolkit

102 Rotavirus Vaccine Access and Delivery. http://sites.path.org/rotavirusvaccine