Maternal antibody interference contributes to reduced rotavirus vaccine efficacy in developing countries

Claire E. Otero, Stephanie N. Langel, Maria Blasi, Sallie R. Permar

1 Duke Human Vaccine Institute, Duke University Medical Center, Durham, North Carolina, United States of America,
2 Department of Pathology, Duke University School of Medicine, Durham, North Carolina, United States of America,
3 Department of Pediatrics, Duke University Medical Center, Durham, North Carolina, United States of America,
4 Department of Medicine, Duke University Medical Center, Durham, North Carolina, United States of America

*sallie.permar@duke.edu

Abstract

Rotavirus (RV) vaccine efficacy is significantly reduced in lower- and middle-income countries (LMICs) compared to high-income countries. This review summarizes current research into the mechanisms behind this phenomenon, with a particular focus on the evidence that maternal antibody (matAb) interference is a contributing factor to this disparity. All RV vaccines currently in use are orally administered, live-attenuated virus vaccines that replicate in the infant gut, which leaves their efficacy potentially impacted by both placentally transferred immunoglobulin G (IgG) and mucosal IgA Abs conferred via breast milk. Observational studies of cohorts in LMICs demonstrated an inverse correlation between matAb titers, both in serum and breast milk, and infant responses to RV vaccination. However, a causal link between maternal humoral immunity and reduced RV vaccine efficacy in infants has yet to be definitively established, partially due to limitations in current animal models of RV disease. The characteristics of Abs mediating interference and the mechanism(s) involved have yet to be determined, and these may differ from mechanisms of matAb interference for parenterally administered vaccines due to the contribution of mucosal immunity conferred via breast milk. Increased vaccine doses and later age of vaccine administration have been strategies applied to overcome matAb interference, but these approaches are difficult to safely implement in the setting of RV vaccination in LMICs. Ultimately, the development of relevant animal models of matAb interference is needed to determine what alternative approaches or vaccine designs can safely and effectively overcome matAb interference of infant RV vaccination.

Rotavirus vaccine efficacy is reduced in lower- and middle-income countries (LMICs)

Despite the development of effective vaccines, which have reduced rotavirus (RV)-related morbidity and mortality by 67% [1], RV is still one of the most common causes of diarrheal disease in childhood [1,2]. There are currently 4 vaccines endorsed by the World Health...
Organization (WHO) to prevent RV-induced gastroenteritis: Rotarix, Rotateq, Rotavac, and RotaSiil, but only Rotarix and Rotateq are widely used globally [3]. These vaccines are orally administered, live-attenuated formulations, each containing different human and/or bovine serotypes of RV (Table 1). In first-world countries, RV vaccines are highly efficacious (80% to 90%), but in LMICs, efficacy plummets to 40% to 60% [4,5]. Due to this disparity in vaccine efficacy, RV infections still cause significant morbidity and mortality in LMICs [2].

Several reasons for low RV vaccine efficacy in LMICs have been proposed, including higher RV exposure, greater diversity of RV G and P serotypes, malnutrition, microbiome composition, maturation stage of the immune system, reduced vaccine replication due to other enteric pathogens, coadministration of the oral polio virus vaccine, different expression of histo-blood group antigens, skewed T helper 1 (Th1)/T helper 2 (Th2) balance and antibody response to vaccination, and higher incidence of maternal antibody (matAb) interference [15–18]. While it is likely that multiple factors contribute to the reduced RV vaccine efficacy observed in LMICs, matAb interference is likely a major contributor due to greater RV exposure, leading to greater maternal immunity, and higher rates and longer duration of breastfeeding in LMICs [19–21]. This review focuses on current evidence supporting matAb interference as a contributor, remaining questions, and proposed modifications to increase the efficacy of current vaccine regimens.

Evidence supports matAb interference as a mechanism of reduced RV vaccine efficacy

MatAbs are transferred to the infant via 2 distinct routes: (1) placental transfer of immunoglobulin G (IgG) into infant circulation; and (2) breast milk transfer of primarily IgA into the infant gastrointestinal tract [22,23]. Most studies investigating the role of matAb interference focus on placently transferred IgG [24]. However, evidence from both population-level observational and animal modeling studies suggest that breast milk–derived matAb also interferes with RV vaccine efficacy [10,25,26].

Rotavac is a recently developed RV vaccine derived from a naturally attenuated and reassorted neonatal RV strain (116E). A clinical trial of this vaccine in Indian infants identified a significant inverse relationship between RV-specific maternal IgG and infant Rotavac vaccine responses. However, matAb inhibition was overcome by increasing the vaccine dose [10]. While the Rotavac trial did not investigate breast milk Abs as a contributor to matAb interference, modeling of RV infection using the murine RV strain Epizoonotic Diarrhea of Infant Mice (EDIM) showed that seropositive BALB/c dams conferred Abs to their pups, primarily through breastfeeding, which impaired pups’ immune responses to live RV inoculation [26].

| Vaccine | Developer | WHO prequalified | Composition | matAb interference reported? |
|---------|-----------|-----------------|-------------|-----------------------------|
| RotaTeq | Merck (United States) | 2008 | Pentavalent human–bovine reassortant G1–G4 and P[6] [7] | Yes [8] |
| Rotarix | GlaxoSmithKline (Belgium) | 2009 | Monovalent human G1P[6] | Yes [9] |
| Rotavac | Bharat Biotech (India) | 2018 | Monovalent human–bovine reassortant G9P[10] | Yes [10] |
| Rotasiil | Serum Institute of India (India) | 2018 | Thermostable pentavalent human-bovine reassortant G1, G2, G3, G4, and G9 [12–14] | No* |

*No references indicating matAb does or does not interfere.
RV, rotavirus; WHO, World Health Organization.

https://doi.org/10.1371/journal.ppat.1009010.t001
These findings concur with studies of human cohorts in developing countries, such as Zambia and Vietnam, where babies of mothers with higher titers of anti-RV Abs in breast milk tend to have reduced responses to RV vaccines [9,20]. These observational studies demonstrate a consistent association between maternal humoral immunity, including both serum IgG and mucosal IgA, and infant responses to RV vaccines.

### Establishing a causal link between matAb interference and low RV vaccine efficacy in LMICs and defining mechanisms

While observational studies in animal and human populations have established a link between maternal immunity and infant vaccine efficacy, mechanistic studies demonstrating that matAb interference causes a reduction in RV vaccine efficacy are still needed. Previous studies have demonstrated an inverse correlation between serum and breast milk matAb titers and infant responses [9,27], but these studies do not isolate this effect to matAb alone. Further, there are several RV G/P serotypes in circulation [28], and maternal exposure to certain serotypes may impact the degree of matAb interference observed, depending on the level of cross-reactivity of matAbs between wild-type RV strains and attenuated vaccine viruses. There are many other potential immune factors conferred from mother to child that may inhibit infant vaccine responses. One study of Zambian children found that lactadherin, an antiviral glycoprotein present in breast milk, negatively associated with infant seroconversion after vaccination with Rotarix [29]. Additionally, genetic host factors, such as expression of histo-blood group antigens, a cellular receptor for RV, may also influence RV vaccine efficacy and susceptibility to disease [30–33]. Thus, studies in which matAb can be isolated as a variable are needed to establish a causal link to reduced RV vaccine efficacy. A major impediment to such studies is the difficulty in modeling human RV infection in animal models due to the limited host range of RVs [34].

Several mechanisms have been proposed for IgG-mediated matAb interference against different viruses, including neutralization of live-attenuated vaccines, epitope masking, cross-linking of B cell receptors (BCRs) and inhibitory Fcγ receptor IIB (FcγRIIB), vaccine antigen removal via antibody-mediated phagocytosis, and downstream inhibition of B cell differentiation into plasma or memory B cells (Fig 1) [24,35]. A study of maternal IgG-mediated interference to measles live-attenuated vaccination in the cotton rat model demonstrated that nonneutralizing monoclonal Abs mediated interference, while neutralizing monoclonal Abs did not [36]. This study also indicated that the fragment crystallizable (Fc) region is necessary to inhibit Ab responses to vaccination and that this inhibition is due to interaction with FcγRIIB [36]. However, studies in mice utilizing sheep red blood cells as a model antigen have supported epitope masking as a mechanism mediating this inhibition of B cell responses [37–39]. Notably, one study demonstrated that interference occurs in FcγR-deficient mice, demonstrating that BCR–FcγRIIB is not the sole mechanism of B cell inhibition in the presence of preexisting Ab [39]. Interestingly, RV Abs targeting the middle capsid layer (VP6), which have traditionally been considered nonneutralizing, are capable of intracellular neutralization, suggesting that the impact of such maternal Abs on neonatal vaccine efficacy may not be limited to Fc-mediated “nonneutralizing” effector functions [40]. In another recent study using influenza hemagglutinin as a model antigen, researchers found that matAbs do not impact germinal center formation but modulate which antigens are targeted by infant B cells and, in a dose-dependent manner, inhibit B cell differentiation of plasma and memory B cells through an undefined mechanism [35]. Together, these results suggest that multiple mechanisms may contribute to matAb-mediated inhibition of infant vaccine responses, possibly in an antigen-dependent manner.
Fig 1. matAb interference to infant RV vaccines [41]. (A) Placentally transferred IgG (red curve) begins reaching the infant as early as 8 weeks of gestation and peaks at term, approximately 40 weeks [22,42]. Maternally derived IgG wanes in the infant over 12 months after birth [24]. Breast-fed infants receive Abs, primarily IgA, through breast milk, which peaks in colostrum at a concentration of approximately 12 mg/mL and maintains approximately 1 mg/mL in mature milk (light blue curve) [23]. However, due to the volume of milk consumed by the infant, the absolute amount of matAb transferred via breast milk increases over time until the child can start getting energy from other kinds of food (dark blue curve) [43]. RV vaccination typically occurs in 2 to 3 doses when the infant is 2 to 6 months old, as indicated by the black arrows [44]. In breast-fed infants, both types of matAb are present at the time of RV vaccination. (B) RV vaccines are orally administered live-attenuated viruses, which rely on replication in infant enterocytes to elicit a robust immune response. Microfold (M) cells sample antigens from the gut lumen and present them to antigen-presenting cells, which stimulate the adaptive immune response in Peyer’s patches [45]. In the presence of matAbs, several mechanisms have been proposed for reduction of infant immune responses to RV vaccination, including (1) inhibition of vaccine virus replication in enterocytes by matAb neutralization; (2) removal of vaccine antigen by antibody-mediated phagocytosis; (3) inhibition of infant B cell activation by cross-linking BCRs with inhibitory FcγRIIB; (4) epitope masking, which inhibits infant Ab responses by hiding recognizable antigens from infant B cells, which may also shift B cell responses toward nonimmunodominant epitopes; and (5) impacting downstream differentiation of B cells into plasma cells or memory B cells [24,35]. Ab, antibody; BCR, B cell receptor; FcγRIIB, Fcγ receptor IIB; IgA, immunoglobulin A; IgG, immunoglobulin G; matAb, maternal antibody; RV, rotavirus.

https://doi.org/10.1371/journal.ppat.1009010.g001
RV vaccines are orally administered, so they may also be affected by Abs at the intestinal mucosa, primarily IgA delivered to the infant via breast milk. Notably, IgA-mediated interference may not follow the same mechanism(s) as IgG-mediated interference due to differences in Fc characteristics. Additionally, it is noteworthy that while breast milk contains mostly IgA Abs, breast milk IgG Abs are present and can be transported to the lamina propria and into circulation [46,47]. However, studies in multiple LMIC populations have shown that abstaining from breastfeeding for a period before and after RV vaccination does not change seroconversion rates [48–51]. The ineffectiveness of breastfeeding timing on RV vaccination may indicate that circulating, rather than breast milk, maternal IgG is the primary mediator of the interference. Further and more in-depth evaluation of Ab characteristics and the relative contribution of serum IgG and breast milk IgA would be informative for design and evaluation of strategies to overcome matAb interference.

Potential solutions for matAb interference to RV vaccines
Several strategies can help circumvent matAb interference, but each comes with its own risks. RV vaccination is associated with a slightly increased risk of intussusception, which is generally outweighed by the immense benefit of reduction in morbidity and mortality, but must be considered when evaluating alternative vaccination strategies [52]. For example, while increasing the vaccine antigen dose may overcome matAb interference [10], a matAb-exceeding dose could also lead to pathology due to excessive replication of live vaccine virus or an improper immune response. This approach was previously tested using a live-attenuated measles vaccine, which induced some protection in the presence of maternal IgG but also resulted in increased infant mortality, especially in girls, who tended to have less maternal IgG compared to boys [24,53–55]. Serology testing to quantitate preexisting Ab before vaccination is not feasible in LMICs, so it would not be possible to adjust the antigen dose based on matAb level, which would be an ideal compromise to improve the safety of this approach.

Another alternative strategy is changing the timing of vaccination to wait until matAb levels in the infant wane. The measles vaccine follows this strategy as administration after 9 months of age demonstrated reduction of matAb interference [56]. However, later vaccination can also pose a significant risk because it leaves the infant more vulnerable during the period before vaccination when matAb levels are low, which is an important consideration in LMICs with greater RV exposure [19]. However, passive immunotherapy of a breast milk–targeted antibody delivered to the mother may keep mucosal matAb at a protective level until vaccination at a later age. Thus, additional studies are needed to determine the age when RV-specific matAbs have waned enough to achieve successful vaccination without increasing mortality due to RV exposure prior to vaccination. However, the risk of intussusception after RV vaccination increases with infant age, so vaccinating later may not be a viable strategy [57,58]. Notably, a trial in Indonesia of the RV3-BB vaccine formulation (G3P[7], not currently endorsed by WHO) demonstrated better efficacy when the 3-dose series was administered earlier in life, starting at birth (75%) rather than at 8 weeks old (51%) [59]. This suggests that better efficacy can be achieved by vaccinating earlier in life and may circumvent the additional intussusception risk associated with RV vaccination in older infants.

Vaccine formulation other than oral exposure to live-attenuated virus is another potential alternative. For example, a recombinant, truncated VP4 protein was more immunogenic than live-attenuated formulations and was not inhibited in the presence of matAb in a mouse model [26]. However, the efficacy of nonreplicating RV vaccines needs to be further validated with challenge studies using human RV strains. Additionally, a nonreplicating vaccine formulation does not guarantee better infant vaccine response. For example, in a gnotobiotic piglet
model of human RV disease, boosting an oral live-attenuated vaccine with RV-like particles resulted in suppression of effector and memory B cell responses [60]. Furthermore, there are several protein vaccines whose efficacies are affected by matAb interference, including tetanus and hepatitis B vaccines [24].

Another potential alternative to oral live-attenuated RV vaccines is a viral-vectored vaccine designed for long-term antigen expression. Continuous expression of antigen through vectored expression, administered early to release antigen for a longer period, could stimulate the infant immune system after matAbs drop to a noninterfering level [24,61]. However, gene therapy approaches are held to a higher safety standard due to the potential of vector integration into the genome [62], and further investigation is needed to determine if such an approach would be effective in the context of RV vaccination. While there are several possible approaches, further investigation is needed to determine if their ability to overcome matAb interference outweighs the risks to the infant.

Prospects for overcoming matAb interference to infant RV vaccination

Effective RV vaccines currently exist, but efficacy of these vaccines is significantly reduced in LMICs. While many factors likely contribute to this reduction in efficacy, matAb interference is clearly associated with reduced vaccine efficacy, but further study is needed to isolate matAb interference as a contributing factor and fully establish a causal link. Mechanisms of matAb interference to orally administered RV vaccines may differ from those observed in other vaccines due to the importance of mucosal immunity and the potential for breast milk Abs to contribute to interference. Defining the mechanisms of matAb interference in this context will greatly inform alternative vaccination strategies to avoid or overcome matAb interference. Several alternative vaccination strategies have been proposed to reduce matAb interference, but these require further testing to determine the relative safety. Thus, more research into mechanisms of RV vaccine matAb interference and the safety and efficacy of alternative vaccination strategies is needed to ultimately achieve improved RV vaccine efficacy in LMICs and further reduce mortality from the leading diarrheal disease worldwide.

References

1. Burnett E, Jonestelle r CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality From Diarrhea. J Infect Dis J Infect Dis [Internet]. 2017 [cited 2020 Jun 12]; 215:1666–72. Available from: https://doi.org/10.1093/infdis/jix186 PMID: 28430997
2. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD, Agocs M, Serhan F, et al. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013. Clin Infect Dis [Internet]. 2016 [cited 2020 Jun 20]; 62:S96–105. Available from: https://academic.oup.com/cid/article-abstract/62/suppl_2/S96/2478843. https://doi.org/10.1093/cid/civ1013 PMID: 27059362
3. WHO | Rotavirus [Internet]. [cited 2020 May 15]. Available from: https://www.who.int/immunization/diseases/rotavirus/en/.
4. Clark A, van Zandvoort K, Flasche S, Sanderson C, Bines J, Tate J et al. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. Lancet Infect Dis. 2019 Jul 1; 19(7):717–727. https://doi.org/10.1016/S1473-3099(19)30126-4 PMID: 31178289
5. Soares-Weis er K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2019 Oct; 28:2019(10).
6. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SAC et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006 May 1; 354(1):11–22. https://doi.org/10.1056/NEJMoa052434 PMID: 16394298
7. Keating GM. Rotavirus vaccine (RotaTeq). Vol. 8, Pediatric Drugs. Springer; 2006. p. 197–202. https://doi.org/10.2165/00148581-200608030-00008 PMID: 16774301
8. Becker-Dreps S, Viches S, Velasquez D, Moon S-S, Hudgens MG, Zambrana LE, et al. Rotavirus-specific IgG Antibodies From Mothers’ Serum May Inhibit Infant Immune Responses to the Pentavalent
20. Trang NV, Braeckman T, Lernout T, Hau VTB, Anh LTK, Luan LT et al. Prevalence of rotavirus antibodies in breast milk and inhibitory effects to rotavirus vaccines. Hum Vaccines Immunother. 2014 Dec 1; 10(12):3681–3687. https://doi.org/10.4161/vim.28594599. PMID: 28594599

19. Chilengi R, Simuyandi M, Beach L, Mwila K, Becker-Dreps S, Emperador DM, et al. Association of Maternal Immunity with Rotavirus Vaccine Immunogenicity in Zambian Infants. Weaver EA, editor. PLoS One [Internet]. 2016 Mar 14 [cited 2020 May 15]; 11(3):e0150100. Available from: https://doi.org/10.1371/journal.pone.0150100 PMID: 26974432

18. Julian TR. Environmental transmission of diarrhoeal pathogens in low and middle income countries [Internet]. Vol. 18, Environmental Science: Processes and Impacts Royal Society of Chemistry; 2016. p. 944–55. Available from: https://pubmed.ncbi.nlm.nih.gov/27384220/.

17. Van De Perre P. Transfer of antibody via mother's milk. In: Vaccine. Elsevier BV; 2003. p. 3374–6. https://doi.org/10.1016/s0264-410x(03)00336-0 PMID: 12850343

16. Niewiesk S. Maternal antibodies: Clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Vol. 5, Frontiers in Immunology. Frontiers Media S.A.; 2014. p. 446.

15. Velasquez DE, Parashar U, Jiang B. Decreased performance of live attenuated, oral rotavirus vaccines in low-income settings: causes and contributing factors. Vol. 17, Expert Review of Vaccines. Taylor and Francis Ltd; 2018. p. 145–61. https://doi.org/10.1080/14760584.2018.1418665 PMID: 29252042

14. Rathi N, Desai S, Kawade A, Venkatramanan P, Kundu R, Lalwani SK et al. A Phase III open-label, randomized, active controlled clinical study to assess safety, immunogenicity and lot-to-lot consistency of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 2018 Dec 18; 36 (52):7943–7949. https://doi.org/10.1016/j.vaccine.2018.11.006 PMID: 30420116

13. Naik SP, Zade JK, Sabale RN, Pisal SS, Menon R, Bankar SG et al. Stability of heat stable, live attenuated Rotavirus Vaccine. Pediatr Infect Dis J [Internet]. 2015 Jan [cited 2020 Jun 20]; 34(1):115–6. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006454-20150100-00031. https://doi.org/10.1097/INF.0000000000000481 PMID: 25741808

12. Kulkarni PS, Desai S, Tewari T, Kawade A, Goyal N, Garg BS et al. A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 2017 Oct 27; 39(45):6228–6237. https://doi.org/10.1016/j.vaccine.2017.09.014 PMID: 28967523

11. Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: A randomised, double-blind, placebo-controlled trial. Lancet. 2014 Jun 21; 383(9935):2136–2143. https://doi.org/10.1016/S0140-6736(13)62630-6 PMID: 24629994

10. Appaiahgari MB, Glass R, Singh S, Taneja S, Rongsen-Chandola T, Bhandari N et al. Transplacental rotavirus IgG interferes with immune response to live oral rotavirus vaccine ORV-116E in Indian infants. Vaccine. 2014 Feb 3; 32(6):651–656. https://doi.org/10.1016/j.vaccine.2013.12.017 PMID: 24374502

9. Chilengi R, Simuyandi M, Beach L, Mwila K, Becker-Dreps S, Emperador DM, et al. Association of Maternal Immunity with Rotavirus Vaccine Immunogenicity in Zambian Infants. Weaver EA, editor. PLoS One [Internet]. 2016 Mar 14 [cited 2020 May 15]; 11(3):e0150100. Available from: https://doi.org/10.1371/journal.pone.0150100 PMID: 26974432

8. Clifford HD, Hayden CM, Khoo SK, Naniche D, Mandomando IM, Zhang G, et al. Genetic variants in the IL-4/IL-13 pathway influence measles vaccine responses and vaccine failure in children from mozambique. Viral Immunol [Internet]. 2017 Sep 1 [cited 2020 Sep 15]; 30(7):472–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28594599/. https://doi.org/10.1089/vim.2017.0014 PMID: 28594599

7. Van De Perre P. Transfer of antibody via mother's milk. In: Vaccine. Elsevier BV; 2003. p. 3374–6. https://doi.org/10.1016/s0264-410x(03)00336-0 PMID: 12850343

6. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Vol. 2012. Clin Dev Immunol:2012. https://doi.org/10.1155/2012/985646 PMID: 22235228

5. Chan J, Ninwati H, Triasis R, Bogdanovic-Sakran N, Soenarto Y, Hakimi M et al. Maternal antibodies to rotavirus: Could they interfere with live rotavirus vaccines in developing countries? Vaccine. 2011 Feb 1; 29(6):1242–1247. https://doi.org/10.1016/j.vaccine.2010.11.087 PMID: 21147127

4. Niewiesk S. Maternal antibodies: Clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Vol. 5, Frontiers in Immunology. Frontiers Media S.A.; 2014. p. 446.

3. Van De Perre P. Transfer of antibody via mother's milk. In: Vaccine. Elsevier BV; 2003. p. 3374–6. https://doi.org/10.1016/s0264-410x(03)00336-0 PMID: 12850343

2. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Vol. 2012. Clin Dev Immunol:2012. https://doi.org/10.1155/2012/985646 PMID: 22235228

1. Van De Perre P. Transfer of antibody via mother's milk. In: Vaccine. Elsevier BV; 2003. p. 3374–6. https://doi.org/10.1016/s0264-410x(03)00336-0 PMID: 12850343
26. Yang H, Luo G, Zeng Y, Li Y, Yu S, Zhao B et al. The distinct impact of maternal antibodies on the immunogenicity of live and recombinant rotavirus vaccines. Vaccine. 2019 Jul 9; 37(30):4061–4067. https://doi.org/10.1016/j.vaccine.2019.05.086 PMID: 31182323

27. Mwila K, Chilengi R, Simuyandi M, Permar SR, Becker-Dreps S. Contribution of maternal immunity to decreased rotavirus vaccine performance in low- and middle-income countries. Vol. 24, Clinical and Vaccine Immunology. American Society for Microbiology; 2017.

28. Estes MK, Kapikian AZ. Rotaviruses. In: Knipe DM, Howley PM, editors. Fields Virology, volume 2. 5th ed. Lippincott Williams and Wilkins; 2007. p. 1917–74.

29. Mwila-Kazimbaya K, Garcia MP, Bosomprah S, Laban NM, Chisenga CC, Permar SR, et al. Effect of innate antiviral glycoproteins in breast milk on seroconversion to rotavirus vaccine (Rotarix) in children in Lusaka, Zambia. Iturriza-Gómara M, editor. PLoS One [Internet]. 2017 Dec 28 [cited 2020 May 16]; 12(12):e0189351. Available from: https://dx.plos.org/10.1371/journal.pone.0189351. https://doi.org/10.1371/journal.pone.0189351 PMID: 29284036

30. Ramani S, Giri S. Influence of histo blood group antigen expression on susceptibility to enteric viruses and vaccines. Vol. 32, Current Opinion in Infectious Diseases. Lippincott Williams and Wilkins; 2019. p. 445–52. https://doi.org/10.1097/QCO.0000000000000571 PMID: 31335438

31. Lee B, Dickson DM, DeCamp AC, Ross Colgate E, Diehl SA, Uddin MI, et al. Histo–Blood group antigen phenotype determines susceptibility to genotype-specific rotavirus infections and impacts measures of rotavirus vaccine efficacy. In: Journal of Infectious Diseases [Internet]. Oxford University Press; 2018 [cited 2020 Oct 18]. p. 1399–407. Available from: https://pubmed.ncbi.nlm.nih.gov/29390150/. https://doi.org/10.1093/infdis/jiy054 PMID: 29390150

32. Huang P, Xia M, Tan M, Zhong W, Wei C, Wang L et al. Spike Protein VP8* of Human Rotavirus Recognizes Histo-Blood Group Antigens in a Type-Specific Manner. J Virol. 2010 May 1; 86(9):4833–4843. https://doi.org/10.1128/JVI.01512-09 PMID: 20245472

33. Gozalbo-Rovira R, Ciges-Tomas JR, Vila-Vinent S, Buesa J, Santiso-Bellón C, Monedero V, et al. Unraveling the role of the secretor antigen in human rotavirus attachment to histo-blood group antigens. Rey FA, editor. PLoS Pathog [Internet]. 2019 Jun 21 [cited 2020 Jun 16]; 15(6):e1007865. Available from: https://doi.org/10.1371/journal.ppat.1007865 PMID: 31232617

34. Gray J, Desselberger U, Ciarlet M, Conner ME. Evaluation of Rotavirus Vaccines in Small Animal Models. In: Rotaviruses. Humana Press; 2003. p. 147–87.

35. Vono M, Eberhardt CS, Auderset F, Andersen P, Lambert P-H, Correspondence C-AS. Maternal Antibodies Inhibit Neonatal and Infant Responses to Vaccination by Shaping the Early-Life B Cell Reertoire within Germinal Centers. Cell Reports [Internet]. 2019 [cited 2020 Aug 17]; 28:1773–1784.e5. Available from: https://doi.org/10.1016/j.celrep.2019.07.047 PMID: 31412246

36. Kim D, Huey D, Oglesbee M, Niewiesk S. Insights into the regulatory mechanism controlling the inhibition of vaccine-induced seroconversion by maternal antibodies. Blood [Internet]. 2011 Jun 9 [cited 2020 Jul 1]; 117(23):6143–51. Available from: https://ashpublications.org/blood/article-pdf/117/23/6143/1340052/zh802311006143.pdf. https://doi.org/10.1182/blood-2010-11-320317 PMID: 21357766

37. Heyman B, Wigzell H. Immunoregulation by monoclonal sheep erythrocyte-specific IgG antibodies: suppression is correlated to level of antigen binding and not to isotype. J Immunol. 1984; 132(3).

38. Getahun A, Heyman B. Studies on the Mechanism by Which Antigen-Specific IgG Suppresses Primary Antibody Responses: Evidence for Epitope Masking and Decreased Localization of Antibigen in the Spleen. Scand J Immunol [Internet]. 2009 Sep 1 [cited 2020 Jul 1]; 70(3):277–87. Available from: https://doi.org/10.1111/j.1365-3083.2009.02298.x PMID: 19703017

39. Karlsson MCI, Wernerson S, De Stahl TD, Gustavsson S, Heyman B. Efficient IgG-mediated suppression of primary antibody responses in Fcγ receptor-deficient mice. Proc Natl Acad Sci U S A [Internet]. 1999 Mar 2 [cited 2020 Jul 1]; 96(5):2244–9. Available from: www.pnas.org, https://doi.org/10.1073/pnas.96.5.2244 PMID: 10051626

40. Caddy SL, Vaysburd M, Wing M, Foss S, Andersen JT, O’Connell K, et al. Intracellular neutralisation of rotavirus by VP6-specific IgG. PLoS Pathog [Internet]. 2020 Aug 1 [cited 2020 Sep 10]; 16(8): e1008732. Available from: https://pubmed.ncbi.nlm.nih.gov/32750093/.

41. Created with Biorender.com.

42. Fouda GG, Martinez DR, Swamy GK, Permar SR. The Impact of IgG transplacental transfer on early life immunity. Immunohorizons. 2018 Jan 1; 2(1):14–25. Available from: https://pubmed.ncbi.nlm.nih.gov/29457151/.

43. World Health Organization. Infant and young child feeding Model Chapter for textbooks for medical students and allied health professionals. 2009. Available from: www.who.int/nutrition/publications/infantfeeding/9789241597494/en/

44. Birth-18 Years Immunization Schedule | CDC [Internet], [cited 2020 Jul 1]. Available from: https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.
45. Ding S, Song Y, Brulois KF, Pan J, Co JY, Ren L, et al. Retinoic Acid and Lymphotixin Signaling Promote Differentiation of Human Intestinal M Cells. Gastroenterology [Internet]. 2020 Jul 1 [cited 2020 Sep 10]; 159(1):214–226.e1. Available from: https://pubmed.ncbi.nlm.nih.gov/32247021/. https://doi.org/10.1053/j.gastro.2020.03.053 PMID: 32247021

46. Tuaillon E, Valea D, Beccourt P, Al Tabaa Y, Meda N, Bollore K, et al. Human Milk-Derived B Cells: A Highly Activated Switched Memory Cell Population Primed to Secret Thrombin. J Immunol [Internet]. 2009 Jun 1 [cited 2020 Sep 15]; 182(11):7155–62. Available from: https://pubmed.ncbi.nlm.nih.gov/19454712/. https://doi.org/10.4049/jimmunol.0803107 PMID: 19454712

47. Pyzika M, Rath T, Lencer W, Baker K, Blumberg RS. FcRn: The Architect Behind the Immune and Non-immune Functions of IgG and Albumin. J Immunol [Internet]. 2015 May 15 [cited 2020 Sep 15]; 194(10):4595–603. Available from: /pmc/articles/PMC4451002/?report = abstract. https://doi.org/10.4049/jimmunol.1403014 PMID: 25934922

48. Jiang B, Jones S, Groome MJ, Velasquez D, Moon S-S, Parashar UD, et al. Effect of breastfeeding on immunogenicity of oral live-attenuated human rotavirus vaccine: a randomized trial in HIV-uninfected infants in Soweto, South Africa. Vol. 92, Bulletin of the World Health Organization. 2014. p. 238–45. https://doi.org/10.2471/BLT.13.128066 PMID: 24700991

49. Moon S, Wang Y, Shane AL, Nguyen T, Ray P, Dennehy P et al. Inhibitory effect of breast milk on infectivity of live oral rotavirus vaccines. Pediatr Infect Dis J. 2010; 29(10):919–923. https://doi.org/10.1097/INF.0b013e3181e232ea PMID: 20442687

50. Rongsen-Chandola T, Strand TA, Goyal N, Flem E, Rathore SS, Arya A et al. Effect of withholding breastfeeding on the immune response to a live oral rotavirus vaccine in North Indian infants. Vaccine. 2014; 32(S1).

51. Groome MJ, Moon SS, Velasquez D, Jones S, Koen A, van Niekerk N, et al. Effect of breastfeeding on immunogenicity of oral live-attenuated human rotavirus vaccine: a randomized trial in HIV-uninfected infants in Soweto, South Africa. Bull World Health Organ [Internet]. 2014 [cited 2020 Sep 7]; 92(4):238–45. Available from: /pmc/articles/PMC3967577/?report = abstract. https://doi.org/10.2471/BLT.13.128066 PMID: 24700991

52. Yih WK, Lieu TA, Kuldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception Risk after Rotavirus Vaccination in U.S. Infants. N Engl J Med [Internet]. 2014 Feb 6 [cited 2020 Sep 7]; 370(6):503–12. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1303164. PMID: 24422676

53. Martins C, Bale C, Garly ML, Rodrigues A, Lisse IM, Andersen A et al. Girls may have lower levels of maternal measles antibodies and higher risk of subclinical measles infection before the age of measles vaccination. Vaccine. 2009 Aug 20; 27(38):5220–5225. https://doi.org/10.1016/j.vaccine.2009.06.076 PMID: 19596409

54. Whittle H, O'Neill K, Marsh V, Aaby P, Hanlon P, Hanlon L et al. Trial of high-dose Edmonston-Zagreb measles vaccine in the Gambia: antibody response and side-effects. Lancet. 1988 Oct 8; 332(8615):81–84. https://doi.org/10.1016/s0140-6736(88)92781-x PMID: 2902264

55. Garenne M, Leroy O, Beau JP, Sene I. Child mortality after high-titre measles vaccine: prospective study in Senegal. Lancet. 1991 Oct 12; 338(8772):903–907. https://doi.org/10.1016/0140-6736(91)91771-l PMID: 2902264

56. Rongsen-Chandola T, Strand TA, Goyal N, Flem E, Rathore SS, Arya A et al. Effect of withholding breastfeeding on the immune response to a live oral rotavirus vaccine in North Indian infants. Vaccine. 2014; 32(S1).

57. Koch J, Harter T, Von Kries R, Wichmann O. Invaginationsrisiko nach Impfung gegen Rotaviren: Systematisches Review und Metaanalyse. Dtsch Arztebl Int [Internet] 2017 Apr 1; 114(10):4595–603. Available from: /pmc/articles/PMC4451002/?report = abstract. https://doi.org/10.4049/jimmunol.1403014 PMID: 25934922

58. Koch J, Harter T, Von Kries R, Wichmann O. Invaginationsrisiko nach Impfung gegen Rotaviren: Systematisches Review und Metaanalyse. Dtsch Arztebl Int [Internet] 2017 Apr 1; 114(10):4595–603. Available from: /pmc/articles/PMC4451002/?report = abstract. https://doi.org/10.4049/jimmunol.1403014 PMID: 25934922

59. Yung CF, Chong CY, Thoon KC. Age at First Rotavirus Vaccination and Risk of Intussusception in Infants: A Public Health Modeling Analysis. Drug Saf [Internet]. 2016 Aug 1 [cited 2020 Jul 22]; 114(15):255–62. Available from: https://pubmed.ncbi.nlm.nih.gov/28468712/.

60. Yung CF, Chong CY, Thoon KC. Age at First Rotavirus Vaccination and Risk of Intussusception in Infants: A Public Health Modeling Analysis. Drug Saf [Internet]. 2016 Aug 1 [cited 2020 Jul 22]; 114(15):255–62. Available from: https://pubmed.ncbi.nlm.nih.gov/28468712/.

61. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human neonatal rotavirus vaccine (RV3-BB) to target rotavirus from birth. N Engl J Med [Internet]. 2018 Feb 22 [cited 2020 Sep 10]; 378(8):719–30. Available from: https://pubmed.ncbi.nlm.nih.gov/29466164/. https://doi.org/10.1056/NEJMoa1706804 PMID: 29466164

62. Nguyen TV, Yuan L, Azevedo MSP, Jeong K. Il, Gonzalez AM, Iosef C, et al. High titers of circulating maternal antibodies suppress effector and memory B-cell responses induced by an attenuated rotavirus priming and rotavirus-like particle-immunostimulating complex boosting vaccine regimen. Clin Vaccine Immunol. 2006 Apr; 13(4):475–485. https://doi.org/10.1128/CVI.13.4.475-485.2006 PMID: 16603615
61. Zhou X, Wang D, Xiong J, Zhang P, Li Y, She R. Protection of chickens, with or without maternal antibodies, against IBDV infection by a recombinant IBDV-VP2 protein. Vaccine. 2010 May 21; 28 (23):3990–3996. https://doi.org/10.1016/j.vaccine.2010.03.021 PMID: 20338216

62. Gruntman AM, Flotte TR. The rapidly evolving state of gene therapy. FASEB J [Internet]. 2018 Apr 29 [cited 2020 Jun 16]; 32(4):1733–40. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1096/fj. 201700982R. PMID: 31282760