



# Contribution of Maternal Immunity to Decreased Rotavirus Vaccine Performance in Low- and Middle-Income Countries

Katayi Mwila,<sup>a</sup> Roma Chilengi,<sup>a,c</sup> Michelo Simuyandi,<sup>a</sup> Sallie R. Permar,<sup>b</sup> Sylvia Becker-Dreps<sup>c</sup>

Centre for Infectious Disease Research in Zambia, Lusaka, Zambia<sup>a</sup>; Department of Pediatrics, Human Vaccine Institute, Duke University, Durham, North Carolina, USA<sup>b</sup>; Department of Family Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA<sup>c</sup>

**ABSTRACT** The role of maternal immunity, received by infants either transplacentally or orally from breast milk, in rotavirus vaccine (RV) performance is evaluated here. Breastfeeding withholding has no effect on vaccine responses, but higher levels of transplacental rotavirus-specific IgG antibody contribute to reduced vaccine seroconversion. The gaps in knowledge on the factors associated with low RV efficacy in low- and middle-income countries (LMIC) remain, and further research is needed to shed more light on these issues.

**KEYWORDS** immunization, low- and middle-income countries, maternal, rotavirus

Despite the progress seen with the global introduction of rotavirus vaccines (RV), diarrhea is still a leading cause of death in children under the age of 5 years, and a substantial proportion of disease cases are still attributable to rotavirus infection. The latest estimates show that approximately 215,000 children die each year from rotavirus-associated diarrhea, and approximately 56% of these deaths are in sub-Saharan Africa (1). The World Health Organization (WHO) recommended the introduction of oral RV into national immunization programs (2), and many countries have heeded this call. As of September 2016, the WHO lists 86 countries as having included RV in their national immunization programs, and 6 more are in the course of doing so in 2016 ([www.who.int/immunization/monitoring\\_surveillance/VaccineIntroStatus.pptx](http://www.who.int/immunization/monitoring_surveillance/VaccineIntroStatus.pptx)). Approximately 50% of the countries in Africa and Asia, over 80% of those in North America, South America, and Australia, and approximately 40% of those in Europe have introduced RV. Following RV introduction, there was a notable reduction in the number of deaths due to diarrhea (1). However, there is consistent evidence from clinical trials that RV have lower efficacies in low- and middle-income countries (LMIC): vaccine efficacies are 80 to 90% in high-income countries (HIC) and 40 to 60% in LMIC (3–8). Indeed, there is growing evidence from vaccine effectiveness studies emerging from the field that in real-life use, vaccine effectiveness is also consistently lower in LMIC (9–12).

In addition to the differences in observed vaccine efficacy and effectiveness, there are also marked differences in vaccine-elicited immunity as reported by various vaccine-elicited antibody titers following rotavirus immunization (13–18). A number of hypotheses have been put forward to explain the differences in efficacy and vaccine-elicited immunity between HIC and LMIC. The hypotheses include (i) maternal factors (such as interference from transplacental antibodies and antibody and nonantibody breast milk components [13, 19–23]), (ii) coadministration with the oral polio vaccine (24–27), (iii) concurrent infection with other enteric pathogens (28), (iv) micronutrient or protein-energy malnutrition (29–31), (v) effects of environmental enteropathy or

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Address correspondence to Roma Chilengi, [Roma.Chilengi@cidrz.org](mailto:Roma.Chilengi@cidrz.org), or Sylvia Becker-Dreps, [sbd@unc.edu](mailto:sbd@unc.edu).

dysbiosis of the gut microbiome (32–37), and (vi) host genetic factors (histo-blood group antigens [38, 39]). A better understanding of these factors which decrease the efficacy of RV in LMIC may help to inform interventions to improve efficacy and to further reduce the number of child deaths due to rotavirus disease. This review examines the correlations between maternal immune factors and RV responses and their potential effect on vaccine efficacy.

### **NATURAL ROTAVIRUS INFECTION AND SUBSEQUENT PROTECTION**

Rotavirus has a triple-layered capsid composed of structural proteins (VP2, VP6, and VP7) and protruding spikes that mediate cell binding (VP4); the capsid surrounds the viral RNA-dependent RNA polymerase (VP1), the capping enzyme (VP3), and the viral genome, composed of 11 segments of double-stranded RNA (dsRNA). Rotaviruses occur in at least 8 different species (groups A to H) (40), but only group A to C and H rotaviruses can infect humans, and the majority of cases of human rotavirus disease (acute gastroenteritis) are caused by viruses of group A. Rotaviruses are further classified into G and P subtypes (according to antigenicity and the sequences of VP7 and VP4, respectively), among which rotaviruses of the subtypes G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and, more recently, G12P[8] cause approximately 90% of all cases of human rotavirus infection and disease (41). A classic cohort study by Velázquez et al. (42) showed that it takes two or more consecutive rotavirus infections before protection from rotavirus-associated disease is achieved.

Rotavirus infections can be blocked by maternal antibodies acquired passively from the placenta and from breast milk. Cord blood has been shown to contain rotavirus-specific IgG, but not other antibody isotypes (43), and concentrations of rotavirus-specific IgG in maternal serum are strongly correlated with concentrations of IgG in infant serum (44). Breastfeeding may protect against naturally occurring rotavirus infection, with protection mediated by rotavirus-specific IgA produced through the gut-mammary gland axis and by the nonspecific glycoproteins lactoferrin and lactadherin (45–48). In fact, it is hypothesized that maternally acquired rotavirus-specific antibodies may bind to the RV strains and thereby block the infant's active response to immunization (49). However, evidence for the protective effect of breastfeeding against rotavirus infection is mixed, with work by Glass et al. (50) and Wobudeya et al. (51) suggesting that breastfeeding does not protect against rotavirus gastroenteritis.

### **VACCINES CURRENTLY AVAILABLE FOR ROTAVIRUS CONTROL**

At present, there are two licensed RV endorsed by the WHO (2): monovalent RV (Rotarix), a live attenuated vaccine derived from a human G1P[8] strain, and pentavalent RV (Rotateq), composed of five human-bovine reassortants expressing G1-G4 VP7s and a P[8] VP4 from a human rotavirus parent strain (4, 5). A third available vaccine is a monovalent live attenuated vaccine (Rotavac) consisting of a human G9P[11] strain, which is currently licensed for use only in India (52). All three are oral vaccines, with the first dose recommended for administration at 6 weeks of age. Oral vaccines are noted for their ease of interference, and it is for this reason that the effect of breast milk on RV is of interest.

### **IN VITRO STUDIES OF POTENTIAL IMMUNE FACTORS THAT BLUNT INFANT ROTAVIRUS VACCINE RESPONSES**

Moon and colleagues assessed breast milk immune factors and their impacts on RV variants *in vitro* (19). Breast milk samples tested in vaccine microneutralization assays revealed that women from India had higher vaccine virus neutralization titers to all three RV than those of women from the United States. Plaque reduction assays were carried out on Indian and U.S. breast milk samples with high neutralizing titers and showed that samples from Indian women caused larger reductions in vaccine titers, corresponding to their neutralizing activity levels (19). Further, the breast milk samples from Indian women had the highest rotavirus-specific IgA titers among samples from women from India and three other countries (United States, Vietnam, and South Korea),

with up to 4-fold differences in median titers. Trang et al. (53) investigated the differences in rotavirus-specific IgA titers in breast milk samples from women from rural and urban settings. They showed that women from rural areas had higher levels of rotavirus-specific IgA in breast milk than those of their urban counterparts.

Nonspecific immune factors in breast milk, including glycoproteins and mucins, may also influence vaccine efficacy and effectiveness by inhibiting the replication of rotavirus (45, 46, 54, 55). Lactoferrin and lactadherin have been shown to reduce rotavirus vaccine strain infectivity in microneutralization assays, and similar results were also seen in plaque reduction assays (20). These results strengthened the hypothesis that non-antibody breast milk components play a role in RV efficacy and effectiveness. By investigating this hypothesis, Moon et al. showed that women from LMIC (India and South Africa) had higher lactoferrin and lactadherin levels than their counterparts from an HIC (United States) (20). Breast milk samples from other LMIC in Africa, Latin America, and Asia should be tested for lactoferrin and lactadherin levels before broader conclusions can be reached.

### **OBSERVATIONAL CLINICAL STUDIES OF MATERNAL IMMUNITY AND ROTAVIRUS VACCINE RESPONSES**

Several observational studies have examined the association between breastfeeding and RV immunogenicity. A case-control study in Germany performed by Adlhoch and colleagues found that children who were exclusively breastfed were less likely to seroconvert (56). In Zambia, higher maternal breast milk IgA titers prior to immunization were associated with a lower frequency of infant seroconversion in response to the monovalent RV. In that study, there was a statistically significant decrease in the percentage of children who seroconverted from the lowest to the highest cumulative breast milk IgA quartile, with seroconversion rates of 71%, 54%, 51%, and 46% (13). Yet a study conducted in Nicaragua did not find an association between rotavirus-specific IgA titers in breast milk on the day of infant immunization and the immunogenicity of the pentavalent RV (22). Further, they did not find an association between the innate antiviral factors in breast milk, including lactoferrin, lactadherin, and tenascin-C, and RV responses (57).

One observational study from Nicaragua found a significant association between high maternal rotavirus-specific IgG titers in serum and the failure to seroconvert in response to the pentavalent RV in infants (22). Similar results were seen in a South African cohort, in which higher levels of prevaccination IgG and IgA were associated with lower immunogenicity of the monovalent RV (23).

### **CLINICAL TRIALS OF ROTAVIRUS VACCINE EFFICACY IN BREASTFED AND NONBREASTFED INFANTS AND INTERVENTIONS TO IMPROVE ROTAVIRUS VACCINE EFFICACY**

Two approaches were used to assess the effect of breastfeeding on infant RV efficacy in clinical trials. The first involved comparisons of RV efficacies in breastfed and bottle-fed infants (58–62). These studies were undertaken predominantly in HIC and found no statistically significant difference in seroconversion frequency between children who were fed formula and those who were breastfed, although numbers of seroconverters tended to be slightly higher for formula-fed children. No such studies have been performed in LMIC, likely because of the high prevalence of breastfeeding as opposed to bottle feeding.

The second area of investigation was withholding of breast milk feeding at the time of vaccination. Clinical trials of breastfeeding withholding at the time of monovalent RV administration have been performed in South Africa, India, and Pakistan (63–66). In these settings, lactating women and their infants were recruited and randomly allocated to groups for withholding of breastfeeding for 1 h (South Africa and Pakistan) or 30 min (India) prior to and after vaccination, while control groups breastfed normally. Despite high compliance of the mothers, none of these studies reported differences in seroconversion rates between infants who had breast milk withheld prior to vaccination and those who did not.

While the clinical trials described above seem to refute the hypothesis that breast milk immunity interferes with RV seroconversion, some additional factors should be considered. The clinical trials that reported no differences in breastfed and formula-fed infants were conducted in HIC, so further investigation of the differences in seroconversion between breastfed and formula-fed infants in LMIC is warranted. Another important consideration is that antibodies or other immune factors may persist in the infant's gastrointestinal tract for longer periods than that during which breastfeeding was withheld in the studies. Research has shown that the infant gastric half-emptying time is between 47 and 56 min (67–69); this means that despite withholding of breast feeding before immunization in the reported trials, the vaccine still may have come into contact with breast milk in the stomach, or perhaps more distally, in the intestines, and therefore may have been neutralized before an immune response could be produced. Addressing this question through studies that withhold breastfeeding would require longer withholding periods that may not be feasible or ethical. To avoid interference of oral RV by breast milk, one potential option may be a shift to parenteral RV in LMIC (70–75).

Transplacentally acquired rotavirus-specific IgG represents one of the proposed factors for reduced infant vaccine efficacy (21, 22), as shown for other pediatric vaccines, such as measles, tetanus, and pneumococcal vaccines (76). The clinical trial of ORV-116E (Rotavac; Bharat Biotech) found that transplacentally acquired rotavirus-specific IgG interfered with seroconversion but that this effect could be overcome by an increase of the vaccine dose (21). Transplacental rotavirus-specific IgG titers are likely higher in LMIC than in HIC, based on differences observed in breast milk (19, 48), possibly due to repeated exposure of mothers to enteric pathogens in LMIC. This work suggests that a higher dose of RV or additional booster doses of RV at a time when transplacental IgG has waned may improve vaccine immunogenicity in LMIC.

### **HIV INFECTION/EXPOSURE AND ITS IMPLICATIONS FOR ROTAVIRUS VACCINE EFFICACY**

Due to the high prevalence of HIV infection in many LMIC, trials have been conducted to assess the efficacy of RV in HIV-positive and HIV-negative children. In these studies, the HIV status of children did not affect their ability to mount an immune response to the vaccine, and no significant adverse reactions have been reported (77–79). A review by Filteau (80) also brings to light the fact that HIV is responsible for significant immune dysfunction, including a reduced ability of HIV-positive pregnant mothers to transfer transplacental antibodies to infants (81, 82). While this may leave children at greater risk for a large number of infections, there may be an unanticipated benefit in the context of vaccines. We postulate here that in LMIC, where maternal antibodies have been noted to potentially interfere with RV seroconversion in infants, the lower level of functional maternal antibodies may in turn render HIV-exposed but -uninfected children more likely to seroconvert, if transplacental antibodies do indeed interfere with vaccine responses. This effect was found in one case-control study conducted in South Africa (83), in which vaccine effectiveness trended higher in HIV-exposed but -uninfected children than in HIV-unexposed children, especially for the 6-week dose, but additional research is needed to formulate a more conclusive association, as this observation was not statistically significant.

### **CONCLUSIONS**

In this review, we summarized reports on associations between immune factors in breast milk as well as transplacental antibodies and infant RV efficacy. We reviewed reports on *in vitro* studies that have shown that both antibody and nonantibody components of breast milk may have an effect on the infectivity of RV strains and therefore may partially contribute to blocking of the immune response of infants. Our review of observational trials showed a general association of higher breast milk rotavirus-specific IgA and transplacentally acquired rotavirus-specific IgG titers with failed seroconversion, while in clinical trials that withheld breast milk at the time of

vaccination it appeared that there was no significant effect on seroconversion of infants. Lastly, we hypothesize that immune dysfunction due to maternal HIV infection may be associated with higher RV effectiveness.

If the association of maternal immunity and vaccine interference is strengthened in LMIC, there are a number of strategies that may improve the infant vaccine response in areas of high rotavirus burden. First, an increase in vaccine dosage is one strategy worth considering to help overcome interference from maternal immune factors. Second, following the successful strategy applied to the measles vaccine, a modified RV schedule or additional doses of vaccine when maternal antibody has waned may improve vaccine responsiveness. In fact, studies of the monovalent RV from Ghana, South Africa, and Bangladesh all suggest a benefit of this strategy (84–86). These studies showed benefits in immunogenicity of delaying the first dose of RV from 6 until 10 weeks of life and adding a third dose of RV either at 14 weeks or at 9 months of age. However, the benefits of these alternative schedules need to be weighed carefully against decreased protection in early infancy, prior to receipt of the first RV dose, as well as potential impacts to vaccine coverage that may result with a change in schedule. Finally, learning from the polio vaccine experience, the switch to a parenteral route would overcome the hypothesized interference by breast milk immune factors (87, 88). While some inactivated parenteral RV candidates have shown promise in animal studies (70, 89), the research and development costs to bring these vaccines to human clinical trials would be substantial. Improving RV efficacy through alterations in dosing, schedule, or administration route may have a major impact on global infant diarrheal disease and its associated mortality.

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