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REVIEW

Correlates of immune protection against human rotaviruses: natural infection and vaccination

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Abstract

Species A rotaviruses are the leading viral cause of acute gastroenteritis in children under 5 years of age worldwide. Despite progress in the characterization of the pathogenesis and immunology of rotavirus-induced gastroenteritis, correlates of protection (CoPs) in the course of either natural infection or vaccine-induced immunity are not fully understood. There are numerous factors such as serological responses (IgA and IgG), the presence of maternal antibodies (Abs) in breast milk, changes in the intestinal microbiome, and rotavirus structural and non-structural proteins that contribute to the outcome of the CoP. Indeed, while an intestinal IgA response and its surrogate, the serum IgA level, are suggested as the principal CoPs for oral rotavirus vaccines, the IgG level is more likely to be a CoP for parenteral non-replicating rotavirus vaccines. Integrating clinical and immunological data will be instrumental in improving rotavirus vaccine efficacy, especially in low- and middle-income countries, where vaccine efficacy is significantly lower than in high-income countries. Further knowledge on CoPs against rotavirus disease will be helpful for next-generation vaccine development. Herein, available data and literature on interacting components and proposed CoPs against human rotavirus disease are reviewed, and limitations and gaps in our knowledge in this area are discussed.

Introduction

Species A rotaviruses, members of the family *Sedoreoviridae*, are the leading viral cause of acute gastroenteritis and are responsible for 128,500–215,000 deaths of children under 5 years old worldwide [103, 120, 165, 170]. Rotavirus particles consist of a triple-layered capsid including the core shell formed by virus protein 2 (VP2), which encloses the 11 segments of the double-stranded RNA (dsRNA) genome [62], the intermediate capsid (VP6), and the outer capsid (VP7), which is decorated with VP4 spikes protruding from its surface [62]. Based on the RNA sequences of VP7 (a glycoprotein or G-type antigen) and VP4 (a protease-sensitive protein or P-type antigen), rotaviruses are classified into various G and P genotypes. Neutralizing antibodies (nAbs) are induced by both VP7 and VP4 proteins, while non-neutralizing antibodies are elicited by other structural proteins (VP6, VP2) and non-structural protein 4 (NSP4) [42, 145, 161, 162]. Proteolysis of VP4 results in its cleavage into two subunits, VP5* and VP8*, the head of the VP4 spike, which interacts with host cell receptors and is required for virion attachment and thus rotavirus infection [154]. Transmission occurs mainly by the fecal-oral route, although spread by person-to-person contact, contaminated water, or fomites is also possible [52]. The virus is highly contagious, and almost all unvaccinated children experience at least one rotavirus infection during their first two years of life [98, 175]. Accordingly, rotavirus infection is one of the main causes of childhood morbidity and mortality globally [165].

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To date, no specific therapy for rotavirus-induced gastroenteritis is available, but the introduction of approved, safe, and effective live attenuated oral vaccines such as Rotarix and RotaTeq has had a great impact on the prevention and control of severe rotavirus-associated disease [13]. Moreover, Rotavac (Bharat Biotech) and Rotasiil (Hyderabad and Serum Institute of India) have exhibited an efficacy similar to that of RotaTeq and Rotarix in India [15] and have been prequalified by the World Health Organization (WHO). In 2009 [190], WHO recommended the inclusion of rotavirus vaccines in the national vaccination programs of all member countries. To date, 120 countries have included oral rotavirus vaccines (RotaTeq or Rotarix) in their national vaccination programs, and approximately 15 additional countries are planning to introduce them [1, 33]. Following the introduction of rotavirus vaccines, numerous high-income countries in the Americas, Europe, and Australia have reported a significant decline in hospitalizations and deaths of infants due to acute gastroenteritis [13, 23, 26]. However, this has not been the case in several low- and middle-income countries [56, 134, 165, 183], implying the need for improved next-generation vaccines [69] and/or a better understanding of the immune correlates of protection (CoPs) during the course of natural infection and vaccination. There are several reasons suggested for the observed lower efficacy/effectiveness of live attenuated rotavirus vaccines in low- and middle-income countries than in high-income countries. The most notable reasons include high titers of maternal antibodies (Abs) [56, 133, 174], impaired immune responses (due to malnutrition, environmental enteropathy, gut microbiota, and coinfections) [36, 56, 109, 135, 174], and differences in host receptor human histo-blood group antigens (HBGAs) [56, 121, 126].

By definition, a CoP is an immune response that is statistically correlated with protection against disease by vaccination (or natural infection) and might be either mechanistic (mCoP; which is causally responsible for the protection) or non-mechanistic (nCoP; which does not cause protection but correlates with other immune responses that are protective) [138]. In the case of rotavirus infection, CoPs are complex and can be affected by numerous factors. Currently, the rotavirus-specific immunoglobulin A (rotavirus-IgA) level is considered the standard for the assessment of vaccine/infection-induced immunity against rotavirus, while it is suggested to be a suboptimal nCoP marker in low- and middle-income countries [65, 142]. Indeed, maternal Abs, including IgG and IgA, which are thought to be responsible for the lower vaccine efficacy in low- and middle-income regions, might be factors that affect protection [104]. In addition, the presence of non-nAbs against VP2, VP6, NSP2, and NSP4, which are detected in most individual sera after rotavirus infection, are main antigenic targets other than VP4 and VP7 in immune responses and protection, but their clinical significance for protection is unclear [29, 44, 49, 131]. Moreover, the gut microbiome is also implicated in the pathogenesis of rotaviruses [57]. It has been shown that the microbiome diversity in rotavirus-infected children is lower than in healthy uninfected children [57]. The complexity and large number of factors contributing to protection against rotavirus infection present an important challenge, both for vaccination programs to control rotavirus infection in many (especially developing) countries and for next-generation vaccine development efforts. Herein, the clinical endpoints and the protective immune responses to natural infection or vaccination are reviewed, and limitations and gaps in our knowledge in this area are discussed.

Immune responses to natural rotavirus infection as potential CoPs

It has been suggested that immune responses to asymptomatic or symptomatic natural rotavirus infection do not provide sterilizing immunity but might protect the individual from moderate-to-severe disease and/or hospitalization for subsequent reinfections [64, 175]. Of note, the incidence of asymptomatic rotavirus infections in children between 6 and 24 months of age has been found to be 3-4 times higher than that of symptomatic infections. Interestingly however, both symptomatic and asymptomatic primary rotavirus infections confer a similar degree of protection against subsequent infections [175]. These observations highlight the crucial role of asymptomatic rotavirus infections in protection against disease and have implications for vaccine development.

The level of immunity generated by natural infection can be determined by observing a subsequent episode of rotavirus infection. One episode of rotavirus infection might provide > 70% protection against rotavirus-induced diarrhea, while after two subsequent infections (symptomatic or asymptomatic), complete protection for moderate-to-severe illness may be achieved [14, 18, 64, 93, 175, 186, 189]. In a cohort study of young children in India, the difference of the severity of diarrhea in the first and second infections was not found to be statistically significant, and protection against moderate or severe disease was only 79% after three subsequent infections [68]. Furthermore, a community cohort study of newborn children in Guinea-Bissau showed that a single infection conferred 66% protection against reinfection in the same epidemic, but only 34% protection against reinfection in subsequent epidemics [64]. The variability in protection after subsequent rotavirus infections could be attributed to differences in the subsequent inoculum size or differences in the level of immunity generated by natural infection in different population groups [44].

Numerous studies have shown that rotavirus-specific Abs can be used as immune markers following natural infection [40]. However, reports on Ab-based acquired homotypic and/or heterotypic immunity after natural rotavirus infection are complex and controversial. In this context, some studies have found homotypic Ab responses to be induced by initial exposure to a rotavirus and heterotypic Ab responses to be induced by subsequent exposures [38, 39, 55, 75, 129, 130, 147, 155, 163]. These findings suggest that homotypic immunity would be primed by Ab generation against homotypic epitopes on VP4 or VP7 proteins [74]. However, heterotypic protection might be boosted by generation of Abs against heterotypic (conserved) epitopes of VP4 or VP7 proteins [132] and also by non-nAbs directed against VP6, VP2, NSP2, and NSP4 [20, 125]. Accordingly, there are reports suggesting that serum titers of nAbs against rotavirus are correlated with either homotypic or heterotypic protection from viral disease [8]. However, due to the polyclonal nature and diversity of Abs raised against rotavirus proteins, the exact level (IU/mL) of serum Abs that can be considered protective is not known. In this context, the results of an early trial conducted in a Japanese orphanage indicated that nAb levels higher than 1:128 were protective against homotypic rotavirus gastroenteritis caused primarily by a G3 strain, while heterotypic responses against G1 and G4 strains were also produced [38]. Similarly, the results of a later study provided analogous data for homotypic protection, indicating that repeated infections with the same G type were less likely to occur [175], Accordingly, a case-control study in Bangladesh demonstrated that children with rotavirus-related diarrhea had considerably lower baseline homotypic and heterotypic nAb titers than age-matched controls, suggesting the importance of nAbs for protection against the disease [187]. Of note, results of similar studies on rotavirus-infected children with or without gastroenteritis indicated a correlation with pre-existing levels of IgA rather than IgG for protection against viral disease [84, 116]. In contrast, results of another study on Bangladeshi children suggested a correlation of IgG titers with protection against symptomatic and clinically significant rotavirus diarrhea [46]. Interestingly, the results of another study from Mexico [176] suggested the importance of both IgG and IgA as correlates of protection, showing that serum IgG titers of >6400 and IgA titers of >800 were associated with a lower risk of rotavirus infection. However, these titers were significantly higher than those reported in a study in the United States in which IgG titers of >800 and IgA titers of >200 were associated with a lower risk of rotavirus infection [130]. In parallel, results of a recent study on Indian children suggested the potential importance of sufficient pre-existing IgG and IgA Ab titers in serum for a reduced risk of rotavirus infection and found an increase in the titers of such Abs with age [141]. Therefore, ambiguous reports and controversial results pertaining to the type and titer of the Abs required for protection against rotavirus infection or disease indicate the need for better understanding of how they function as CoPs.

It has been shown that passive transmission of IgA and nAbs via breast milk can inhibit rotavirus infection [19, 32, 61, 123, 124, 152, 167]. Therefore, breastfeeding may protect against rotavirus infection not only by the nonspecific action of glycoproteins such as lactoferrin and lactadherin [160] but also by rotavirus-specific IgA that is produced via the gut-mammary gland axis [127]. Previous studies showed a rural/urban residency gradient of rotavirus-specific Abs [45, 127]. In this context, it has been shown that the level of IgA against rotavirus in breast milk from Bangladeshi mothers (whose exposure to rotaviruses is considerably higher) was higher than that from Swedish mothers. Considering the higher efficacy of rotavirus vaccination in Sweden than in Bangladesh, this observation might suggest a reverse relation of rotavirus-specific IgA in breast milk to rotavirus vaccination efficacy in breastfed children [127]. A similar study conducted in a rural community in Bangladesh showed that exclusive breastfeeding might temporarily protect infants and postpone severe rotavirus diarrhea, but there was no overall protection during the first two years of life [45]. In agreement with this, in a study in India, it was shown that IgA titers in the breast milk of mothers whose infants were infected with rotavirus within the first 5 days of life were significantly lower than in that of those whose infants were uninfected during the same time period [89]. However, contrary to the above reports, in a Mexican study, there was no difference in the titers of breast milk Abs between breastfed infants infected with rotavirus and those who remained unaffected during the first year of life [22]. Accordingly, a study undertaken in Vietnam showed that, while the level of total IgA was significantly higher in mothers living in a rural region than those in an urban region, urban mothers had significantly higher rotavirus-specific IgA Ab titers than rural mothers [168]. Although maternal anti-rotavirus Abs protect neonates and unvaccinated infants during the period of immune system maturation and can be protective during this time of high risk for experiencing severe rotavirus disease, further studies are required to determine its importance and contributing role in protection against rotavirus disease. Despite extensive investigations on the protective role of rotavirus-specific Abs [40], studies and data on the protective role of the T-cell immune responses in the course of natural rotavirus infection or vaccination are limited [101, 115]. Studies in animal models have indicated a crucial role of T cells in replication-inhibited clearance of infection and generation of protection-associated Abs [55, 118, 119]. Induction of both $CD4^+$ and $CD8^+$ T cell responses in rotavirus infection has been documented, albeit at much lower levels compared to

other viral infections [88, 114]. A recent systemic review showed that although rotavirus-specific T cells are generally present at low frequency, their reactivity is broadened with increasing age in children [101]. In addition, $CD4^+$ and $CD8^+$ T cell responses in rotavirus infection are heterotypic and more transient, but they can occur in the absence of detectable antibody responses through repeated exposure [101]. Therefore, it is necessary to fully understand the protective role of rotavirus-specific T-cell responses in the course of natural infection or vaccination [111]. A summary of studies on potential CoPs against natural rotavirus infection is shown in Table 1.

Immune responses to rotavirus vaccination as potential CoPs

For most of the vaccines that have been approved for human use, such as those against hepatitis A and B, rabies, poliovirus, measles, anthrax, diphtheria, and tetanus, the humoral (antibody) response, which is usually measured by neutralization assay or ELISA, is the most important CoP [85, 139]. Of note, for many established enteric vaccines (such as those for hepatitis A, Vi typhoid, and poliovirus infections), humoral responses are considered CoPs, although they may not correlate well with protective efficacy or relevant gut immune responses [85, 139]. Likewise, in the case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), strain-specific neutralizing Abs are the principal CoPs, and their titers correlate directly with protection against infection [58, 70]. However, it has also been shown that T cell responses and Fc effector Abs are also important players

Table 1 Summary of studies describing potential CoPs in natural rotavirus infection

Location	Seroconversion %	Mediator of protection against infection and/or disease	Refs.
United States	67	IF antibody and nAb*[a]	[93]
Japan	Not reported	Homotypic nAb[b]	[38]
Denmark	73 (IgA) and 100 (IgG)	Serum IgA	[84]
United States	66	Serum IgG and jejunal NA	[187]
United States	67	Serum nAb against VP4 and VP7 (homotypic and heterotypic)	[74]
Bangladesh	Not reported	Serum IgG	[46]
Bangladesh	Not reported	Heterotypic NA	[188]
Japan	Not reported	Homotypic NA	[39]
United States	83 (Fecal IgA)	Fecal IgA	[116]
United States	91 (IgA), 88 (IgG), and 79 (NA)	Serum IgA[c], IgG[d] and NA (homotypic)	[130]
United States	36 and 77 (IgA)[h] 45 and 96 (IgG)	Serum IgA and IgG	[129]
Venezuela	92 (IgA)	Homotypic NA	[147]
Mexico	77[c]	Serum IgA and IgG	[176]
Nicaragua	> 55	Colostrum IgA	[61]
Mexico	77	Serum IgA[e] and IgG[f]	[177]
Guinea-Bissau	70	Not reported	[64]
India	Not reported	Serum IgA and IgG[g]	[141]
Bangladesh	49	Serum IgA and IgG	[110]

*nAb: neutralizing antibody

[a]Adult volunteer study

[b]NA titer >1:128

[c]A serologic response (77 percent), of which 52% were first and 48% repeated infections

[d]IgA titer >1:200

[e]IgG titer >1:800

[f]IgA titer >1:800

[g]IgG titer >1:6400

[h]The prevalence of protective serum IgA and IgG titers increased from 36% and 45% before season 1 to 77% and 96% after season 2 ($P < 0.02$ and 0.001).

that can affect the efficacy of vaccines against SARS-CoV-2 infection [58, 67, 96]. It should be noted that vaccine-induced Abs might either act directly by neutralizing the infectious agent or be a marker for the presence of a robust T-cell response that protects against pathogenesis through distinct immunological mechanisms [21]. Therefore, despite the value of vaccine-induced neutralizing Abs as CoPs, for development of effective and durable vaccines against rotaviruses, other factors might need to be considered. Indeed, rotavirus vaccines represent one of the most complex challenges for the definition of CoPs. Vaccination has already impacted the global burden and epidemiology of rotavirus disease in a positive way, with great success in high-income countries, but the same is not true for low-income societies [24]. Infants typically receive two oral doses of Rotarix (GSK, UK) or three oral doses of RotaTeq (Merck, USA) in their first 6 months of life. In addition, two other live attenuated oral rotavirus vaccines, Rotavac (Bharat Biotech) and Rotasiil (Hyderabad and Serum Institute of India), have also been prequalified by WHO and licensed in several countries. Moreover, several monovalent rotavirus vaccines, such as Rotavin-M1 (PolyVac) [151, 166], Lanzhou lamb rotavirus (LLR) [192], and neonatal rotavirus vaccine (RV3-BB) [16], are licensed nationally in Vietnam, China, and Australia, respectively. Furthermore, several non-replicating rotavirus vaccines, including recombinant or inactivated vaccines, have shown promising results in preclinical or clinical studies. Identifying relevant CoPs for these vaccines would permit us to predict both the risk of clinical disease and vaccination efficacy [8]. Since the introduction of rotavirus vaccines, the intestinal IgA response and its surrogate, the serum IgA level, have been considered the principal CoPs. In this context, various human trials conducted in several countries around the world with different economic, cultural, sanitary, and nutritional conditions have used anti-rotavirus-IgA levels to examine the efficacy of rotavirus vaccines, especially for Rotarix and RotaTeq. Vaccine-induced anti-rotavirus IgA levels (> 20 U/mL) are an important predictor of protection against rotavirus infection and are associated with vaccine efficacy [11, 44, 65, 137, 169]. In some trials, type-specific neutralizing Ab titers have also been reported [9, 44, 156, 178]. A review of clinical trial data for the Rotarix and RotaTeq vaccines [137] showed that a geometric mean concentration (GMC) of anti-rotavirus IgA below 90 was associated with a decline in vaccine efficacy. Indeed, efficacy during first 2 years of life was significantly lower in countries with an IgA GMC < 90 than in countries with a GMC > 90. This suggests that IgA titers might be an important immune correlate protecting children from rotavirus diarrhea [137]. However, rotavirus-specific post-immunization serum IgA titers and seroconversion were more strongly associated with protection from rotavirus diarrhea in high-income (low child-mortality) countries than in low- and middle-income (high child-mortality) countries. In this context, it was shown that rotavirus-specific post-immunization serum IgA titers were not an optimal correlate of protection in many low- and middle-income (high child-mortality) countries such as Bangladesh [110]. Similar studies have shown that low serum rotavirus-specific IgA is associated with increased rotavirus load in vaccinated Malawian children with acute gastroenteritis and is also associated with an increased risk of clinical rotavirus vaccine failure [12, 140]. It has been shown that the kinetics of fecal Rotarix RNA shedding as well as the IgA responses in immunized twins after the first and second vaccine doses were similar, suggesting that rotavirus vaccine viral replication in the intestine and the host immune response are similar in twin siblings [60]. Generally, the documentation of factors that are related to protection will facilitate the improvement of rotavirus vaccines strategies. A summary of studies on potential CoPs related to vaccination is presented in Table 2.

Live attenuated rotavirus vaccines

WHO-prequalified rotavirus vaccines

The results of clinical trials and systemic reviews on all four licensed rotavirus vaccines [6, 9, 13, 82, 102, 197] have indicated low vaccine efficacy and effectiveness in low- and middle-income countries (29–77% within the first/second year after vaccination) compared to that of higher-income countries, where the efficacy was 85–98% for preventing severe rotavirus disease by immunization with RotaTeq or Rotarix [6, 15, 59, 95, 102, 108, 122, 144, 150, 159, 164, 177, 179, 180]. The results of the clinical trials in India and Niger for the Rotasiil vaccine demonstrated an efficacy of 36% and 67%, respectively, against severe rotavirus gastroenteritis [86, 99]. The results of a phase III efficacy trial of the Rotavac vaccine in India indicated an efficacy of 55% against severe rotavirus disease, with overall protection up to two years of age [15]. Similar results were reported for the same vaccine in infants in Zambia [41]. Reports on post-licensure vaccine effectiveness data indicated 84-86% (13 studies), 75-77% (8 studies), and 57-63% effectiveness for Rotarix in countries with low, medium, and high childhood mortality rates, respectively. For the RotaTeq vaccine, effectiveness was reported to be 84-90% (20 studies) and 45-66% in countries with low and high child mortality rates, respectively [25, 91]. Although efficacy data from clinical trials are available for Rotavac and Rotasiil, no post-licensure vaccine effectiveness data have been reported for these vaccines.

As discussed above, rotavirus-specific IgA Abs are used to monitor vaccine effectiveness at the population level. Studies relating rotavirus IgA seroconversion to

Table 2 Summary of studies describing potential CoPs for rotavirus vaccines

	Vaccine	Location	% Vaccine efficacy	% Anti-rotavirus seroconversion** (95% CI)	Anti-rotavirus IgA or IgG, Serum nAb, GMT*** (95% CI) U/ml	Ref
World Health Organization prequalified	Rotarix	Europe	90.4	86 (83–88)	197 (175–222)	181
		Latin American	80	61 (53–68)	66 (49–87)	169
		Japan	91	85 (68–95)	217 (109–428)	95
		South Africa	32	57 (44–68)	59 (37–93)	112
		Malawi	34	47 (30–64)	51 (26–102)	53
		Hong Kong	95	97 (86–99)	314 (215–460)	108
	Rotateq	Ghana	55	78 (67–87)	23 (15–37)	9
		Kenya	63	73 (60–84)	30 (18–51)	164
		Mali	17	82 (70–91)	31 (18–51)	159
		Bangladesh	42	78 (66–87)	29 (18–45)	156
		Vietnam	63	97 (89–99)	158 (107–234)	198
		Europe, the United States, and Latin America	-	95 (91–97)	-	181
		China	95	-	82 (66–102)	122
	ROTASIIL	India	36	46 (43–50)	19 (17–21)	144
		Nigeria	67	-	-	86
	ROTAVAC	India	55	35 (29–41)	20 (17–23)	15, 59
		Zambia	-	33 (24–42)	-	41
	ROTAVAC-5D		-	40 (32–49)	-	
Nationally licensed	RV3-BB	Indonesia	94, 75^	-	185 (78–437)	153
	RV3-BB	New Zealand	-	-	74, 63[&]	16
	RV3-BB	Malawi	-	-	52, 67, 59[#]	192
	BRV-TV	India	-	-	28 (24–32)	151
	ROTAVIN	Vietnam	-	188 (64–75)	48 (40–57)	166
	ROTAVIN-M1		-	87 (55–72)	35 (27–44)	
Non-replicating, parenteral	P2-VP8*	South Africa	-	99–100[#] 20–34^	≥4-fold increase from baseline[#,^] ≥2·7-fold increase from[$] baseline	79

*Serum nAb: serum neutralizing antibody; **seroconversion: ≥ 20 u/ml or threefold rise; ***GMT = geometric mean titre; [#]IgG; ^IgA; [$]nAbs

^Vaccine efficacy of three doses of RV3-BB vaccine administered on a neonatal schedule against severe rotavirus gastroenteritis was 94% at 12 months and 75% at 18 months of age.

[#]Serum IgA seroconversion was observed in 52% of participants 4 weeks after administration of three doses of RV3-BB administered on the neonatal schedule. At 18 weeks, cumulative IgA seroconversion was also detected in 67% of participants in the neonatal schedule group compared with 59% of participants in the infant schedule group.

[&]A serum IgA response was detected in 74% and 63% of RV3-BB recipients in the infant and neonatal schedule group, respectively.

protection have indicated that, in high-income countries, including Europe, Japan, Hong Kong, China, and Australia, high levels of vaccination effectiveness for both Rotarix and RotaTeq, with long-lasting (until two years of age) protection (both homotypic and heterotypic) have been documented. More recently, it was shown that for infants vaccinated with Rotarix in high-income countries, seroconversion might serve as a perfect CoP, correlating with 96% reduction in the risk of rotavirus gastroenteritis compared to infants showing no seroconversion [11]. However, lower and more variable levels of protection (about 30-60%) and reduction in the duration of protection have been reported in low- and middle-income countries, including South Africa, Malawi, Ghana, Kenya, and Mali, for the same vaccines [9, 15, 41, 53, 86, 99, 112]. In clinical studies, anti-rotavirus IgA is a valuable indicator of protection against rotavirus gastroenteritis. In particular, oral rotavirus vaccines replicate in the gut, and a mucosal IgA response (or its surrogate, serum IgA) can

be considered an imperfect CoP. Although, it is not considered a true clinical endpoint and does not accurately predict specific levels of protective immunity, it is still a practical and informative measure of an infant's risk of rotavirus gastroenteritis after vaccination.

Nationally licensed rotavirus vaccines

A study of vaccination with one dose of rhesus rotavirus-tetravalent vaccine (RRV-TV, licensed as RotaShield) showed that anti-rotavirus-IgA seroconversion was associated with protection from infection, but not from gastroenteritis. After three doses, the titer of anti-rotavirus IgA was found to have a significant association with protection against acute gastroenteritis, but no specific titer was reported as a CoP for this vaccine [43]. Another study compared serum anti-rotavirus IgA levels as a marker of protection in both RRV-TV (RotaShield)-vaccinated and naturally infected children. The results of that study indicated that a serum anti-rotavirus IgA level >1:800 correlated with 68% protection in children who had been infected previously, but this was not a reliable CoP for those immunized with the RRV-TV vaccine [73]. In parallel, results of a meta-analysis on the same vaccine indicated that levels of anti-rotavirus IgA ≥ 20 U/mL were moderately correlated with a lower risk of gastroenteritis in vaccinated children [37].

The effect of maternal Abs (either acquired transplacentally or from breast milk) were also studied extensively, but no inhibitory or beneficial effect on rotavirus vaccination efficacy ('vaccine uptake') could be documented [5, 77, 149]. It has been shown that, in the presence of maternal Abs and breast milk, neonatal P[6] strains such as RV3 (G3P[6]) replicate efficiently in the gut of the infected infant without causing any disease symptoms [30]. Based on this finding, this naturally attenuated human neonatal strain (G3P[6]) was used to develop the RV3-BB vaccine. The RV3-BB vaccine has been shown to be immunogenic and well tolerated when the first dose is given within 0–5 days after birth (neonatal schedule) or when the first dose is administered at 6-8 weeks of age (routine infant schedule) [16, 18]. The efficacy of RV3-BB when administered in three doses on a neonatal schedule (birth, 6 weeks, and 10 weeks) was shown to be 94% at 12 months and 75% at 18 months of age in a high-child-mortality setting in Indonesia [17, 153]. In a similar study in Malawi, 4 and 18 weeks after administration of three doses of RV3-BB on a neonatal schedule (birth, 6 weeks, and 10 weeks), cumulative serum IgA seroconversion was observed in 52% and 67% of participants, respectively, compared to 59% of these on an infant schedule (6, 10, and 14 weeks) [191]. Furthermore, recent studies in Indonesia and New Zealand [34, 54] have shown that maternal rotavirus Abs in breast milk appear to have a minimal impact on RV3-BB vaccine uptake when administered with a short delay in breast-feeding in settings with a high rotavirus disease burden. Anti-rotavirus IgA levels in colostrum or breast milk and levels of placental IgG and serum nAbs did not show any impact on the serum IgA response or stool excretion after three doses of RV3-BB vaccine using either a neonatal or infant schedule [34, 54]. Interestingly, immunization with three doses of RV3-BB vaccine in Indonesia resulted in an efficacy of 94% for neonates (0 to 5 days, 8, and 14 weeks of age) and 75% for infants (8 weeks, 14, and 18 weeks of age), suggesting that this vaccine is appropriate for use in a birth dose vaccination schedule [17]. Strategies including changes in vaccine scheduling, administration of probiotics, antibiotics, or immunomodulatory drugs, and development of novel vaccine formulations may further improve rotavirus vaccine performance [69]. However, it remains to be seen whether improved immune responses will translate into improved CoPs.

Non-replicating rotavirus vaccines

P2-VP8*-based recombinant rotavirus vaccines (RecVs)

It has been shown that protection against rotavirus infection can be mediated by nAbs that target epitopes on the VP7, VP5*, and VP8* proteins [125, 163]. Therefore, these proteins are candidate antigens for the development of improved, next-generation, broadly effective rotavirus vaccines [107, 125]. In this context, the results of a recent study showed that VP8* fused with the P2 epitope of tetanus toxin (so-called P2-VP8*; a non-replicating, parenteral vaccine) was capable of inducing anti-rotavirus nAbs with homotypic protection characteristics [66], i.e., they were protective only against the rotavirus genotypes included in the vaccine formulation. More recently, to cope with this shortcoming and to induce significant heterotypic immunity, a trivalent P2-VP8*-P[8]/P[6]/P[4] vaccine was developed (numbers in brackets indicate the included genotypes) [76, 117]. The results of human trials in South African adults, children, and infants showed that this vaccine induced high levels of anti-P2-VP8* IgG and nAbs against three different P-type antigens [78, 79]. However, the proportion of infants with an anti-P2-VP8 IgA seroresponse to each P-type antigen was only between 20% and 34% [79]. It remains to be seen whether Abs to the trivalent P2-VP8 subunit vaccine are capable of protecting children against infection and diarrhea from increasingly variable homologous and heterologous rotavirus strains. More recently, several mRNA-based P2-VP8 vaccines have been developed and evaluated in mice, guinea pigs, and gnotobiotic pigs [33]. Induction of high levels of anti-P[8] IgG and virus-neutralizing antibodies against both homotypic P[8] and heterotypic P[4] and P[6]

rotavirus strains was observed in the vaccinated animals [33]. It should be noted that almost all human rotavirus G types have been detected in combination with P[8], P[4], or P[6] specificity. Therefore single or multivalent formulations with two or more of the P[8], P[4], and P[6] VP8* proteins (VP8*-P[8]/P[4]/P[6]) might provide pan-antigenic coverage of almost all G (VP7) types and confer cross-neutralizing protection against the most common rotavirus genotypes.

There are ongoing prime/boost vaccination studies using oral and parenteral non-replicating rotavirus vaccines. In this context, immunization with one dose of the oral Rotarix vaccine (prime) followed by one dose (boost) of the trivalent nanoparticle vaccine (S-VP8*P [8]/P[4]/P[6] nanoparticles consisting of the S domain of norovirus VP1 and rotavirus VP8*) was shown to be capable of eliciting high titers of virus-specific neutralizing IgG and IgA Abs [33, 83].

It should be noted that oral vaccines replicate in the gut and induce an intestinal mucosal IgA response. Therefore, it is logical to consider that non-replicating parenteral rotavirus vaccines might use other pathways of protection and thus have different CoPs than their live oral vaccine counterparts. Of particular note, it has been shown that some of the IgA Abs in serum contain a secretory component that might be derived from the intestine via "spillover". This observation might account for the correlation of rotavirus-specific IgA levels in serum with protection from disease [7]. For parenteral vaccines, however, IgG rather than IgA might be a suitable marker of immunogenicity and a CoP. In this context, it has been shown that transplacental-derived IgG protects infants from rotavirus disease and interferes with live oral rotavirus vaccine uptake, while hyperimmune serum protects non-human primates against rotavirus challenge [133]. Serum IgG has also been shown to protect against viral infections in the lung and intestinal lumen due to its ability to cross epithelial barriers by receptor-mediated transcytosis [31, 143]. Future studies might clarify the role of neutralizing Abs and key immunogen(s) responsible for broad and durable protection.

VP6-based RecVs

It has been suggested that Abs targeting the VP6 protein of the middle capsid layer might play a significant role in protection from rotavirus infection by inhibiting virus replication [29, 162]. VP6-specific Abs (which are elicited at high titers in the course of natural infection/vaccination) are capable of protecting rotavirus-infected mice via passive transfer [27, 63], while immunization with VP6-based vaccines also induces or enhances protective immunity [71, 105]. Recently, parenteral and/or mucosal immunization of mice with a VP6 oligomeric subunit preparation was shown to provide partial protection against rotavirus challenge [172]. In addition to being highly immunogenic, VP6 has several other useful characteristics that could allow it to be used in adjuvants, immunological carriers, and drug-delivery vehicles and also as a scaffold for production of valuable nano-biomaterials [158]. Moreover, VP6-specific llama-derived nanobodies have been shown to have extensive cross-neutralizing activity that protects neonatal mice from rotavirus-associated diarrhea [28, 113]. Similarly, orally administered rotavirus VP6-specific nanobodies have been shown to be effective against rotavirus-induced diarrhea in neonatal pigs [172]. These findings highlight the potential value of broadly neutralizing VP6-specific nanobodies as a treatment that might complement or be used as an alternative to the current strain-specific rotavirus vaccines [172]. It has been shown that Abs elicited against VP6 during natural infection of mice and humans are of the IgA and IgG isotypes [94] and that natural infection and vaccination induce similar levels of serum IgA Abs [106]. However, results of a more recent study indicated that neutralization by VP6-specific IgG was far more effective than neutralization by VP6-specific IgA [29]. These results suggest that rotavirus VP6 Abs may play an important role as a potential CoP and suggest that VP6 might be useful as a vaccine antigen.

VP6-NSP4-based RecVs

The rotavirus nonstructural glycoprotein 4 (NSP4) is a viral enterotoxin that plays important roles in rotavirus pathogenesis. There is a high seroconversion rate for induction of anti-NSP4 Abs following natural rotavirus infection, with a heterotypic response detectable in 48% of people infected [181]. These observations suggest that anti-NSP4 Abs might be CoPs in rotavirus-induced diarrhea. Abs raised against NSP4 are broadly reactive and might prevent diarrhea caused by various rotavirus genotypes [145, 181, 193]. Therefore, despite being a relatively weak immunogen, NSP4 has been used in several studies as a target Ag for development of rotavirus vaccines [2, 193]. Recently, it was reported that a combination of recombinant rotavirus VP6 nanospheres (VP6S) and NSP4 proteins formulated in aluminum hydroxide adjuvant elicited higher levels of anti-NSP4 Abs in mice than NSP4 alone [4]. Thus, it appears that the immunogenicity of NSP4 can be enhanced by cost-effective strategies for the purpose of developing NAP4-based rotavirus subunit vaccines.

VLP-based vaccines

Virus-like particles (VLPs) have been investigated as rotavirus vaccine candidates in several studies [128, 157, 194]. Several VLP vaccine candidates based on the combination of VP2, VP4, VP6, and VP7, produced either in baculovirus-infected insect cells (Baylor College of

Medicine) or using plant-based platforms (Mitsubishi Tanabe Pharma) have been developed [48, 50, 51, 90, 100]. In preclinical studies, these vaccine candidates induced production of a broad range of heterotypic and homotypic nAbs without any significant toxicity in animal models. Accordingly, a plant-based VLP vaccine (Ro-VLP) is currently being tested in a human clinical trial. The results show that intramuscular administration of this Ro-VLP vaccine to infants elicited a stronger IgG than IgA response in serum, and nAbs against rotavirus were elicited that protected vaccinated infants from disease [100]. Moreover, it has been shown that intramuscular administration of a live or inactivated rotavirus vaccine in an animal model (rabbits) is capable of inducing intestinal rotavirus-specific IgG and protecting rabbits from rotavirus infection [47]. In further support of a protective role of IgG, it has been shown that intravenous injection of sera with high rotavirus-specific IgG titers to non-human primates resulted in the transport of IgGs to the intestinal lumen to inhibit rotavirus infection [188]. These findings suggest that both parenteral immunization with rotavirus VLP vaccines and administration of oral rotavirus vaccines have the potential to contribute to protection against rotavirus infection through transudation or permeation of Abs (IgG) into the intestinal lumen.

Inactivated rotavirus vaccines

Although inactivated rotavirus vaccines (IRVs) can be safe and effective for prevention of rotavirus infection in children, no approved and licensed vaccines are available to date. The Centers for Disease Control and Prevention (CDC) of the United States recently developed a heat-inactivated whole-virus vaccine consisting of human rotavirus G1P[8] strain CDC-9. Pre-clinical studies showed that intramuscular administration of IRV CDC is able to induce IgG, IgA, and homotypic and heterotypic nAbs in serum and protection against rotavirus infection and acute gastroenteritis in animal models [173, 184, 185]. In addition, parenteral administration of this inactivated vaccine was also shown to induce mucosal immunity by promoting expression of the gut homing receptor LPAM-1 (integrin α4β7) on T and B cells in the spleen and intestinal mesenteric lymph nodes of vaccinated mice [146]. In support of this, it has also been shown that circulating T and B cells in children with rotavirus gastroenteritis express LPAM-1, while LPAM-1-expressing B cells secrete rotavirus-specific Abs [72, 87, 148]. However, no defined CoPs for LPAM-1 expression after either natural rotavirus infection or oral and parenteral rotavirus vaccination have been suggested.

Gut microbiome and CoPs against rotavirus infection

An antiviral effect of probiotics against rotavirus infection via mechanisms such as immune enhancement or modulation of intestinal microbiota (probiotic-related reductions in rotavirus gastroenteritis) has been proposed [3, 97]. Rotavirus-induced gastroenteritis has been shown to decrease the intestinal microbial diversity and composition, while recovery is associated with a return of the intestinal flora to that of the non-infected state [35, 171]. The significant role of the gut microbiome in immune responses that indirectly affect CoPs against rotavirus infection has mainly been demonstrated in rotavirus-infected/vaccinated animal models, such as gnotobiotic (Gn) piglets. Several clinical studies have suggested that the gut microbiota plays a role in the variation of rotavirus vaccine efficacy observed in different parts of the world. Although vaccine efficacy usually correlates with anti-rotavirus IgA levels, anti-rotavirus IgA is an imperfect CoP and may not necessarily reflect protection against clinically relevant disease. Furthermore, intestinal commensals such as *Lactobacillus rhamnosus* GG (LGG), *L acidophilus*, *L. reuteri*, and *Bifidobacterium lactis* Bb12 (Bb12), which regulate gut immunity, significantly enhance rotavirus vaccine immunogenicity and reduce the severity of gastroenteritis and the amount of viral shedding [10, 80, 92, 136, 182, 195, 196]. These observations support further exploration of microbiome manipulation as a way of improving rotavirus vaccine efficacy [81]. Since gut microbiota might indirectly affect the CoPs in rotavirus infection/vaccination, understanding the influence of the diversity and composition of the microbiome on gut immunity might lead to new treatments or vaccination approaches [97].

Conclusion

Although natural infection and rotavirus vaccination both induce anti-rotavirus immune responses, the mechanisms by which these immune responses contribute to long-term protection against rotavirus infection is not fully understood. In general, levels of rotavirus IgA and homotypic and heterotypic nAbs in serum, elicited by natural infection might protect children from later infections and thus might be considered CoPs in the context of natural infection. Since oral rotavirus vaccination failures seem to be correlated with lower anti-rotavirus IgA levels in serum, the level of IgA induced by vaccination might also be considered a CoP in the context of vaccination. Moreover, the significant role of IgGs that transudate into the intestinal lumen and inhibit virus infection has also been highlighted by studies of parenteral rotavirus vaccines. In the case of oral rotavirus

vaccines, differences in the gut microbiota have been found to be associated with rotavirus immunogenicity, and specific taxa of bacteria have been associated with a boosted rotavirus vaccine response. Accordingly, total circulating Abs and homotypic and heterotypic nAbs are associated, but not completely correlated, with protection. This implies a potential role of other immune mechanisms such as cross-reactive T cells in protection against rotavirus infection. Some predictors of protection may not be directly involved in the control or clearance of infection. Therefore, further studies on the molecular immunology of rotavirus vaccination and infection are needed to understand the interactions between the arms of the immune system and viral antigens and to fill the knowledge gap regarding correlates of protection against rotavirus infection.

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Data availability The data used to support the findings of this study are included in the article.

Declarations

Conflict of interest The authors declare that there is no conflict of interests.

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