



# How the gut microbiome regulates host immune responses to viral vaccines

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The co-evolution of the microbiota and immune system has forged a mutually beneficial relationship. This relationship allows the host to maintain the balance between active immunity to pathogens and vaccines and tolerance to self-antigens and food antigens. In children living in low-income and middle-income countries, undernourishment and repetitive gastrointestinal infections are associated with the failure of oral vaccines. Intestinal dysbiosis associated with these environmental influences, as well as some host-related factors, compromises immune responses and negatively impacts vaccine efficacy. To understand how immune responses to viral vaccines can be optimally modulated, mechanistic studies of the relationship between the microbiome, host genetics, viral infections and the development and function of the immune system are needed. We discuss the potential role of the microbiome in modulating vaccine responses in the context of a growing understanding of the relationship between the gastrointestinal microbiota, host related factors (including histo-blood group antigens) and resident immune cell populations.

## Addresses

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**Current Opinion in Virology** 2019, **37**:16–25

This review comes from a themed issue on **Viruses and the microbiome**

Edited by **Stephanie M Karst** and **Christiane E Wobus**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 1st June 2019

<https://doi.org/10.1016/j.coviro.2019.05.001>

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## Introduction

Numerous factors influence vaccine efficacy including nutrition, sex, age, genetics, and health status and these vary greatly between low-income and middle-income

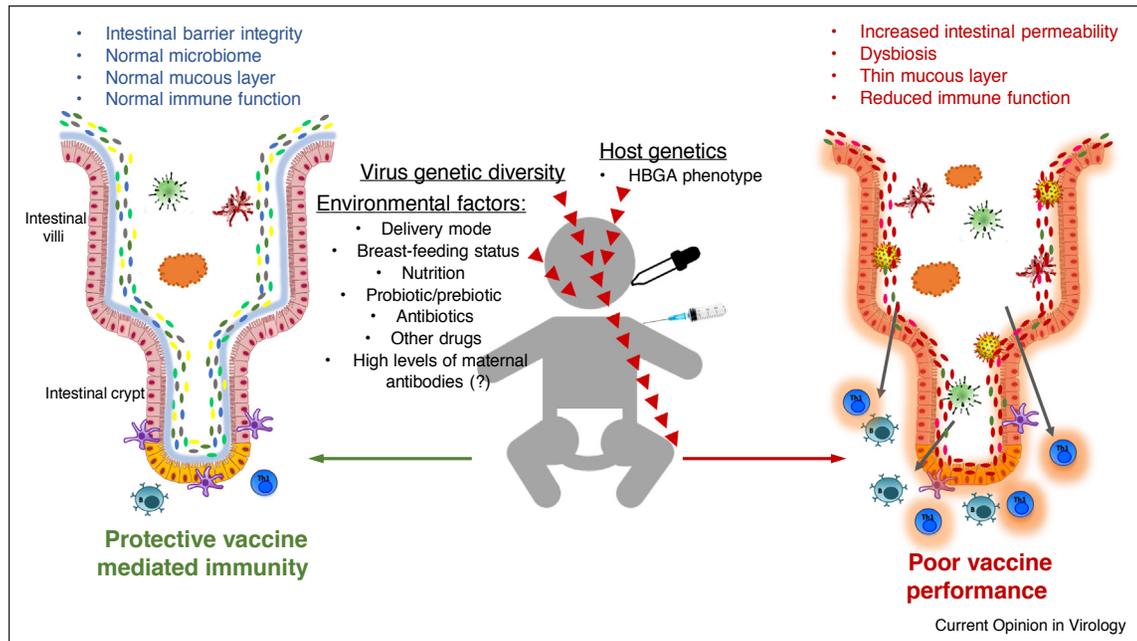
(LMIC) and high-income (HIC) countries as reviewed elsewhere [1<sup>\*\*</sup>]. Immune responses to oral cholera, poliovirus (PV) and rotavirus (RV) vaccines are significantly lower in children from LMICs than those of children from HICs [2]. For example, only 58% of Nicaraguan and 46% of Bangladeshi children respond to oral RV vaccine while the efficacy of the vaccine in Finland is over 98% [3–5]. The poor immune responsiveness to vaccination characteristic for LMICs is multifactorial and is associated with host-associated (genetics and commensal microbiota), pathogen-associated (genetic diversity) and environmental factors [6–8,9<sup>\*\*</sup>,10,11<sup>\*</sup>] (Figure 1).

The diverse communities of microbes that colonize the gut and other body surfaces (microbiome) have coevolved with their host species in a symbiotic relationship [12<sup>\*</sup>]. The microbiome as a whole or its individual members play important roles in the development and functionality of the immune system [13<sup>\*</sup>]. Colonization occurs mostly during birth and soon after, and the microbiome becomes mature by ~2 years of age. Until then, the microbial composition is highly variable and can be easily perturbed by various environmental exposures [14<sup>\*\*</sup>,15<sup>\*</sup>].

The environmental influences of early life that affect the microbiome and can therefore alter vaccine efficacy include diet, delivery method (vaginal versus caesarean section), and hygiene (clean versus unsanitary environment) [16–18]. Additionally, breastfeeding is known to modulate vaccine responses in infants via altering the microbiome composition and maternal antibody interference with the development of the active (post-vaccine) immune response [19]. High levels of neutralizing antibodies (Ab) in the breast milk of mothers from LMICs were shown to correlate with lower seroconversion rates in their children, suggestive of maternal Ab interference with the ‘take’ of oral RV vaccines. However, restriction of breastfeeding did not enhance the IgA immune response to oral RV vaccines in children [20<sup>\*</sup>,21].

A combination of gut microbiome alterations associated with negative health effects is known as intestinal or enteric dysbiosis. The latter is often accompanied by environmental enteric dysfunction (EED, environmental enteropathy) representing structural and functional disorder of the small intestine that is frequently seen in children from the LMICs or patients with chronic inflammatory diseases. Thus, differences in the efficacy of oral RV and PV as well as other vaccines observed in LMICs

Figure 1



A schematic illustration of how the microbiota may influence vaccine responses. There are interconnections between the intestinal microbiota and the immune response. This mutualistic relationship is bidirectional with intestinal microbiota influencing immune system development and functions, and the immune system modulating microbial diversity and controlling its anatomical constraint. Effective vaccines should be capable of eliciting protective immune responses against the viral agents administered, whereas microbiota composition and diversity modulate the immune response to vaccines directly and indirectly (via regulating gut barrier function).

can result from enteric dysbiosis and EED [1<sup>\*\*</sup>,22,23]. In agreement with these observations, celiac disease patients have decreased seroconversion to hepatitis B vaccine [24<sup>\*</sup>]. Also, chronic infections with many viruses including human cytomegalovirus and human immunodeficiency virus induce immune suppression decreasing the effectiveness of many vaccines [25]. However studies on the interactions between the resident virome and host immune function are scarce [26,27]. Collectively, these observations emphasize that ‘healthy’ gut microbiome is the key element that maintains intestinal homeostasis critical for optimal vaccine performance.

### Influence of the intestinal microbiome composition on vaccine responses

Since the gut microbiota is intimately linked with immune system development, it is likely that immune responses to all vaccines are modulated by distinct microbial profiles [28]. Systemically immunized GF and antibiotic treated conventional mice showed decreased serum Ab and T-cell responses compared to the age-matched conventional animals [29<sup>\*\*</sup>]. The introduction of the normal microbiota to the GF mice improved their immune responsiveness following immunization [29<sup>\*\*</sup>]. In addition, the nasal microbiota also contributes to immune responses to live influenza vaccine, by modifying antiviral IgA Ab production [30]. However, comprehensive studies that directly evaluate how the gut microbiota,

as a whole or the individual major microbial taxa, influence immune responses to vaccines are limited.

In a recent study, transplantation of dysbiotic microbiota from stunted Nicaraguan infants decreased numbers of intestinal and systemic effector T cells that coincided with decreased protection against human RV (HRV) challenge in vaccinated human microbiota-associated (HMA) piglets [31]. Numerically decreased IgA and IgG Ab responses were also observed in the dysbiotic HMA piglets further emphasizing the suboptimal HRV vaccine performance associated with intestinal dysbiosis. Importantly this study emphasizes that dysbiotic microbiome is the primary factor associated with the decreased immune responses, because unlike in infant donors, EED was not evident in the HMA piglets. Further, these results and our previous data [32] suggest that specific pathological microbial signatures can be maintained after dysbiosis was induced and can even be transferrable to another host, negatively affecting their immunity. The latter indicates that maternal dysbiosis can be transferred to infants and leading to health and developmental setbacks in early life.

Further, *Lactobacillus rhamnosus* strain GG (LGG), in a dose-dependent manner, enhanced innate, cytokine, and cellular T cell responses in HMA piglets vaccinated with HRV vaccine [33]. However, the enhanced immune

responses did not translate into increased Ab levels [34]. These findings are in contrast to a previous study from the same group that demonstrated that LGG supplementation enhanced HRV Ab responses in GF piglets [35], which emphasizes the importance of evaluating probiotics in the context of the microbiome.

In another study from the Netherlands, higher levels of RV shedding were observed in adults receiving antibiotic treatment before vaccination against RV compared with controls receiving no antibiotic treatment [36\*\*]. This suggests that a dysbiotic microbiome (with decreased abundance of different bacterial taxa or with altered composition) alters the replication of the attenuated RV vaccine. Further, the altered RV replication was not associated with changes in RV-specific IgA Ab levels, suggesting that it could have resulted from direct RV–microbiota interactions [36\*\*].

### Impact of nutritional status on the microbiota and vaccine effectiveness

Most frequently, diet is the primary factor that defines the diversity and functions of the gut microbiota and epigenetically re-programs the host metabolism [15,37–39]. While balanced fiber-rich diets maintain a healthy microbiota [15\*,37], disturbances in the nutritional status (especially in children) impair immune responses and compromise gut barrier integrity [40]. Specifically, protein deprivation leads to intestinal dysbiosis, epithelial breaches, altered metabolism, EED, and immune deficiencies in malnourished children [41,42], which in turn promotes opportunistic infections [43]. Clinical studies show that childhood malnutrition is associated with lower seroconversion rates of oral vaccines [45,46] and contributes to almost half of all deaths of children under five years old [42]. Therapeutic food interventions have reduced mortality in children with severe acute malnutrition, but persistent immaturity of the gut microbiota and the associated incomplete restoration of healthy growth and metabolism remains a major problem [14\*\*]. Vaccinated protein-deficient pigs had lower protection rates against human RV diarrhea and significantly increased fecal virus shedding titers compared with their protein-sufficient counterparts, which coincided with suppression of multiple innate and adaptive immune responses [44]. These results confirm the negative effects of protein-calorie malnutrition (PCM) on immune responses to HRV and on vaccine efficacy, which were exacerbated in the HMA versus GF pigs. In this study, PCM decreased the Firmicutes-to-Bacteroides ratios post-challenge, which coincided with increased abundance of *Proteus* in the gut, while decreased levels of *Turicibacter* were observed in spleen and ileum [44]. While *Proteus* species are mostly associated with pro-inflammatory responses, playing roles in the pathogenesis of many gastrointestinal disorders, including Crohn's disease [45], the relative abundance of *Turicibacter* species

correlates with adequate immune function in mice [46,47].

Additionally, undernourishment is often associated with specific micronutrient deficiencies and deficiencies in key microbiota-derived metabolites. For example, vitamin A deficiency (VAD) affects millions of children in LMICs [48] and leads to significantly impaired mucosal immunity and oral vaccine efficacy [49,50]. Our studies in neonatal GF pigs demonstrated that the protective efficacy of human monovalent and pentavalent RV vaccines and immunoregulatory responses were compromised by VAD [51,52]. Vitamin A derivative, retinoic acid (RA), is required for activation of gut dendritic cells and for imprinting gut homing receptors (CCR9 and  $\alpha 4\beta 7$ ) on vaccine induced B and T cells [53–56]. Currently, little direct evidence is available on the interactions between the intestinal commensals and vitamin A—both key regulators of intestinal health. In a recent study, VAD induced substantial alterations of the bacterial community structure and meta-transcriptome [57]. *Bacteroides vulgatus* was identified as a prominent responder to vitamin A status with increased abundance in VAD [57]. VAD was shown to be associated with altered bile acid metabolism *in vivo*, suggesting that retinol and bile acid metabolites may interact altering microbial communities in the gut [57]. Additionally, growing evidence suggests that the gut microbiota, through its effects on bile acids [58], short chain fatty acids (SCFA) and cholesterol metabolism in the gut lumen, can in turn affect intake and metabolism of all fat-soluble vitamins, including vitamin A [59].

Further, microbiota-associated intestinal inflammation can alter RA levels [60\*] affecting the balance between immunoregulatory and inflammatory T cells, emphasizing that the interactions between gut microbiota and vitamin A are bidirectional in nature. Zinc is another micronutrient that is often deficient in low income settings and affects the efficiency of oral vaccines. Mice on a zinc-deficient diet had decreased Th1 and IgG responses to a Hepatitis B vaccine [61]. While zinc deficiency is linked with poor vaccine responses and can modify the composition of the microbiota [62], direct competition between intestinal bacteria and the host for zinc may explain why oral supplementation of zinc does not compensate for its deficiency.

Collectively, these recent studies suggest that while nutrient imbalance and dysbiotic microbiome induce negative effects on host health, immunity and intestinal barrier, their synergistic interactions are implicated in the pathogenesis of severe childhood PCM.

### Microbial interactions with resident immune cells

The significance of the microbial–immune interactions is best exemplified by the fact that the immune system of

germ-free (GF) mice and pigs is anatomically and functionally immature [63,64\*\*,65,66\*\*], while colonization of the GF animals with commensal microbiota or even individual probiotic species corrects these defects [67\*,68,69\*\*,70–72]. Further, individual commensal microorganisms and their metabolites induce maturation of the intestinal and systemic immune systems [71,73] and modulate cellular signaling as summarized by Valdez *et al.* [1\*\*]. Besides induction of immune maturation, microbiota regulates the state of hypo-responsiveness against commensals, self-antigens, and food antigens [72,74\*].

Immune cells are equipped with various innate immune receptors [including Toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)] to recognize and interact with microbial cells. Our recent study comparing TLR expression profiles in GF and conventional newborn and young pigs demonstrated that exposure to commensal microbiota has a greater influence on TLR mRNA expression than age [75]. TLRs on epithelial and dendritic cells (that can extend their dendrites through the epithelial layer) come into direct contact with luminal microorganisms [76]. These TLR–microbial interactions induce production of anti-microbial peptides and secretory (polymeric) IgA by epithelial and immune cells, respectively [77,78]. Binding of anti-microbial peptides and IgA to the mucus layer that separates commensal bacteria from the apical surface of intestinal epithelial cells (IECs) constrains the topography, composition, and functions of commensal bacteria, thereby preventing inflammatory reactions [79].

Intestinal dysbiosis associated with inadequate diets, antibiotic use, and enteric pathogens cause local inflammation, altering intestinal barrier function. This results in aberrant interactions between immune cells and microbes, which triggers systemic inflammation and autoimmunity, as reported in type 1 diabetes [80]. Further, numerous mouse models deficient in TLRs/NLRs and/or their signaling adaptor proteins (such as MyD88) develop intestinal dysbiosis [81] which leads to the development of various diseases [82]. The latter illustrates the role of genetic factors in dysbiosis development. Often transfer of this ‘dysbiotic microbiota’ into naïve hosts is sufficient to induce disease and reproduce its pathogenesis [32,83,84\*\*]. Therefore, this complex two-way communication plays a critical role in intestinal health and disease.

Finally, although it is recognized that the gut microbiota composition influences systemic immunity, the exact mechanisms of how the gut bacteria exert the immunomodulatory effects at systemic immune sites remain largely unknown [85]. Two alternative theories postulate that these effects can be achieved either via secretion and systemic circulation of microbiota-derived soluble factors

[86] or via migration of the activated lamina propria lymphocytes into the periphery [87].

### Relationships between gastrointestinal microbiota, RV vaccines and histo-blood group antigens

ABO/H and Lewis family antigens are recognized as receptors by numerous pathogens, including, noroviruses (NoVs), RVs, and coronaviruses [88–94] and the severity of RV disease is reportedly higher in children with blood group A [95]. Several recent studies demonstrated that host histo-blood group antigen (HBGA) phenotypes impact incidence of all-cause diarrhea [96] and the efficacy of oral RV vaccines by altering susceptibility to RV in unvaccinated children [97]. Lewis A phenotype was shown to be a restriction factor for RotaTeq and Rotarix vaccine-take [98].

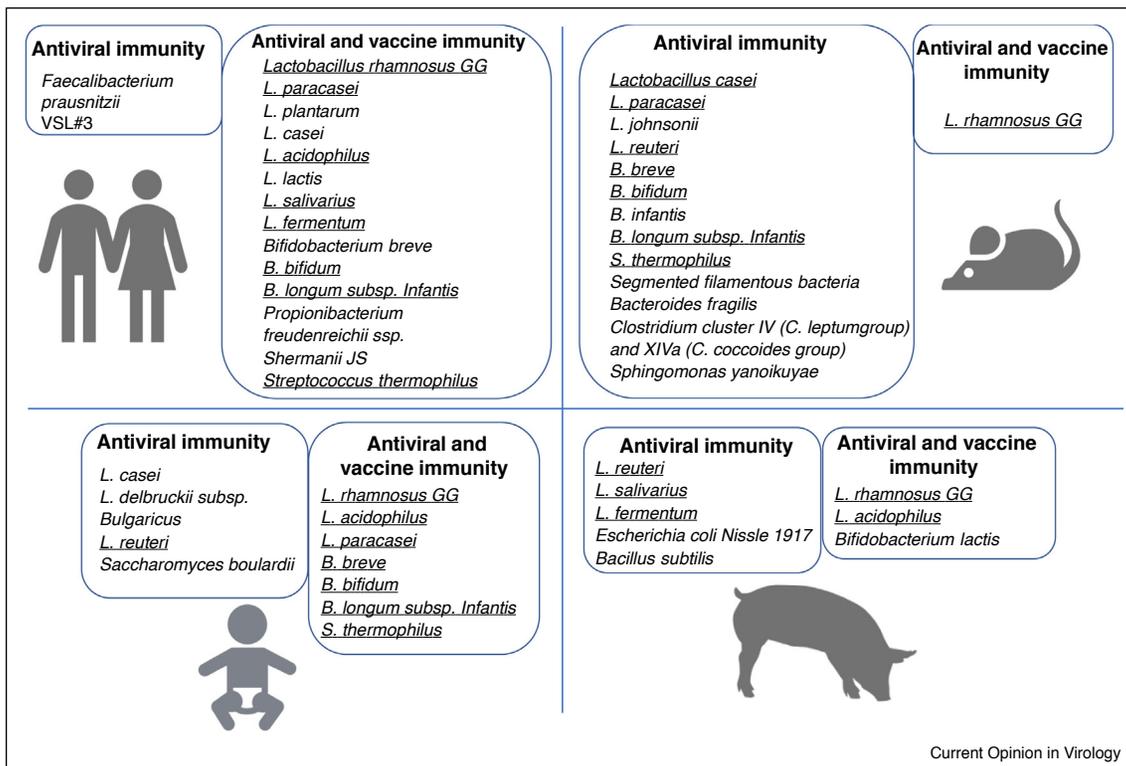
The polymorphic HBGAs, including the ABO/H, secretor and Lewis families, are found on red blood cells, mucosal epithelia [99] and in biologic fluids (saliva, intestinal contents, milk, and blood) of secretor individuals [100]. The nonsecretor homozygous genotype in fucosyltransferase 2 (FUT2; occurring due to natural polymorphisms) is associated with resistance to NoV genogroup II and *Helicobacter pylori* infections that vary with ethnicities [101,102]. Distinct HBGA phenotypes also result in variable binding specificities of innate immune factors such as the galectins [103] or differential profiles of circulating natural Abs [104]. Different HBGAs are also observed in animals, including pigs that express A and H antigens (that share high identity with those of humans), which may facilitate zoonotic and reverse zoonotic infections [105]. Further, certain lactobacilli were shown to bind HBGAs [106,107] while some enteric bacteria [108] produce HBGA-like substances suggesting that such bacteria can directly bind some enteric viruses [108]. Collectively, these data suggest that commensal and pathogenic microorganisms have evolved that exploit human and animal HBGAs as cellular receptors.

Further, recent data showed that healthy subjects with different HBGA possessed distinct profiles of fecal microbiota [109\*,110]. The nonsecretor status was also linked to the gut microbiome alterations in patients with inflammatory bowel disease [111]. These provide examples of the influence of host genetics on the intestinal microbiome composition and suggests that HBGA-mediated modulation of the intestinal microbiome may contribute to the observed variations in the vaccine efficacy. Thus, future vaccine trials should account for HBGA status or offer optimized multivalent vaccines that can perform equally well in hosts with different HBGAs.

### Probiotic impacts on vaccine responses

As discussed above, live, oral vaccines, including RV and PV vaccines, have historically underperformed in the

Figure 2



Probiotic and commensal bacteria that possess immunomodulatory/antiviral [1\*\*,71,73] and vaccine adjuvant [112,113,120,121,128\*] properties as demonstrated in human clinical trials and animal experiments in pigs and mice. Bacterial species that were shown to possess immunomodulatory properties in two or more species are underlined.

LMICs. Alterations in the intestinal microbiota are currently being recognized as a leading factor associated with vaccine failures, and their effects are being evaluated in human clinical trials. Supplementation with specific strains of probiotics has been shown to have modulatory effects on intestinal and systemic immune responses in animal models providing the basis for studies with vaccines in humans [72,73,112,113] (Figure 2). However, most clinical studies conducted in children and adults generated results that varied by age, antigen, type of Ab response, and probiotic strain [19]. The mechanisms that influence vaccine performance include direct or indirect immunomodulatory actions of probiotics that have yet to be fully evaluated experimentally. Direct effects include alteration of the pathogen-associated molecular patterns presented to the gut-associated lymphoid tissue. Indirect effects can be mediated by changes to the gut microbiota and immunoactive microbial metabolites such as SCFA [114]. Probiotics also affect the functions of IECs through modulation of tight junctions, increasing mucin and defensin production, inducing antimicrobial and heat shock protein production, interfering with pathogenic organisms, and modulating signaling pathways and cell survival [115–118]. Certain probiotic strains have been shown to enhance Ab responses to oral vaccines against

RV [35,119–121], *Salmonella* [122], PV [123], and *Vibrio cholerae* [124] in human volunteers, and this effect was observed after a short period (1–5 weeks) of probiotic treatment. The positive effect of probiotics on immune responses was also seen in parenterally administered vaccines against diphtheria, tetanus, *Haemophilus influenzae* type B, and hepatitis B [125–127] in infants after a six-month period. However, no mechanistic explanations for the observed effects or detailed microbiome analysis were available from these studies.

### Concluding remarks and outstanding questions

Despite extensive research and plentiful novel data, there still is a need for improved understanding of the role of microbiota in the immune responses to vaccines. To establish causal relationships between the composition of microbiota and responses to oral and parenteral vaccines, additional clinical and experimental studies are needed. Large-scale studies correlating the effects of diets, probiotics, and antibiotics with pre-vaccine microbial diversity and post-vaccine immune responses will identify environment and microbiota-driven effects. Adoptive transfer of the dysbiotic microbiomes to GF animals would define the function and reversibility of the

microbiome alterations. While most studies conducted thus far have been limited to general changes in microbial profiles, a detailed analysis of the role of a particular bacterial species or community and their correlation with vaccine responses is lacking. The lack of clearly defined 'healthy' baseline microbiome makes it challenging to identify optimal and suboptimal microbiome composition for viral vaccines. To further improve post-vaccine responses, new adjuvants based on particular microbiota-derived immune-modulating molecules or bioactive micronutrients should be evaluated. The ever-expanding knowledge on how the microbiota is altered by the host and environmental factors and the downstream effects of these alterations need to be considered in the design of future vaccines.

### Conflict of interest statement

Nothing declared.

### Acknowledgements

This work was partially supported by grants from the NIAID at NIH (grant # R01 A1099451) and Bill and Melinda Gates Foundation (OPP117461), as well as federal funds appropriated to the Ohio Agricultural Research and Development Center (OARDC) of The Ohio State University. Salaries and research support were provided by state and federal funds provided to the OARDC, The Ohio State University.

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