Review

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Future MICROBIOLOGY

Causes of impaired oral vaccine efficacy in developing countries

Edward PK Parker*,[1], Sasirekha Ramani[2], Benjamin A Lopman[3], James A Church[4], Miren Iturriza-Gómara[5], Andrew J Prendergast[4] & Nicholas C Grassly[1]

[1]Department of Infectious Disease Epidemiology, St Mary's Campus, Imperial College London, London, W2 1PG, UK
[2]Baylor College of Medicine, Houston, TX 77060, USA
[3]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA
[4]Centre for Paediatrics, Blizard Institute, Queen Mary University of London, London, E1 2AT, UK
[5]Centre for Global Vaccine Research, Institute of Infection & Global Health, University of Liverpool, Liverpool, L69 7BE, UK
* Author for correspondence: edward.parker@imperial.ac.uk

Oral vaccines are less immunogenic when given to infants in low-income compared with high-income countries, limiting their potential public health impact. Here, we review factors that might contribute to this phenomenon, including transplacental antibodies, breastfeeding, histo blood group antigens, enteric pathogens, malnutrition, microbiota dysbiosis and environmental enteropathy. We highlight several clear risk factors for vaccine failure, such as the inhibitory effect of enteroviruses on oral poliovirus vaccine. We also highlight the ambiguous and at times contradictory nature of the available evidence, which undoubtedly reflects the complex and interconnected nature of the factors involved. Mechanisms responsible for diminished immunogenicity may be specific to each oral vaccine. Interventions aiming to improve vaccine performance may need to reflect the diversity of these mechanisms.

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Enteric pathogens are a substantial threat to public health. This threat takes many forms, from the toxin-producing bacteria (e.g., *Vibrio cholerae*) and flagellated protozoa (e.g., *Giardia lamblia*) that colonize the mucosal surface of the small intestine to the enteroviruses that are capable of spreading via the bloodstream to the CNS, causing acute flaccid paralysis (e.g., poliovirus). Each year, enteric pathogens cause hundreds of millions of cases of diarrhea and approximately 800,000 deaths, the vast majority of which occur among children in low-income countries [1]. The most common causes of childhood diarrheal morbidity include rotavirus, *Cryptosporidium*, enterotoxigenic *Escherichia coli* and *Shigella* [2].

Vaccines against enteric pathogens are important tools for mitigating this disease burden. Oral vaccines offer several distinct benefits compared with parenteral vaccines. They can be produced in large quantities at relatively low cost, are easy to administer and have the capacity to induce local immunity in the intestinal mucosa, thereby protecting vaccinated individuals against subsequent infection and – by blocking onward transmission – enhancing herd immunity [3,4]. Currently licensed oral vaccines include live-attenuated poliovirus vaccines containing one, two or three serotypes, live-attenuated rotavirus vaccines (Rotarix®, RotaTeq®, Lanzhou lamb rotavirus vaccine [China only] and Rotavac® [India only]), live-attenuated cholera vaccine (CVD 103-HgR or Vaxchora™), inactivated cholera vaccines (Dukoral® and Shanchol®) and live-attenuated typhoid vaccine (Ty21a). Other oral vaccines are in development, including those against *Shigella*, enterotoxigenic *E. coli*, *Campylobacter* and *Clostridium difficile*, as well as several novel rotavirus vaccine candidates (including the human neonatal vaccine RV3-BB [5] and an oral bovine pentavalent vaccine [6]).

Yet oral vaccines have an Achilles' heel – their immunogenicity and efficacy is impaired in low-income countries that experience the greatest burden of enteric disease (Box 1). For example, Rotarix has a 1-year protective efficacy against severe rotavirus-associated gastroenteritis of >95% in European infants [7], but less than 50% in Malawi [8]. Similar deficits in immunogenicity and/or efficacy have been documented for live-attenuated oral cholera

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Box 1. Measures of oral vaccine response.

- **Immunogenicity:** ability to induce an immune response. Typical measures in vaccine trials include seroconversion (see below) and post-vaccination antibody concentration (often reported as antibody titers)
- **Seroconversion:** the appearance of pathogen-specific serum antibodies in a previously seronegative individual, or a significant rise in antibody concentration between pre- and post-vaccination samples
- **Shedding (post-vaccination):** the detection of vaccine components in stool samples collected after immunization. Post-vaccination shedding indicates replication of live-attenuated vaccines, and is generally correlated with immunogenicity
- **Vaccine efficacy:** the percentage reduction in disease in vaccinated compared with unvaccinated individuals under optimal conditions (e.g., clinical trials)
- **Vaccine effectiveness:** the ability of a vaccine to prevent outcomes of interest during routine use

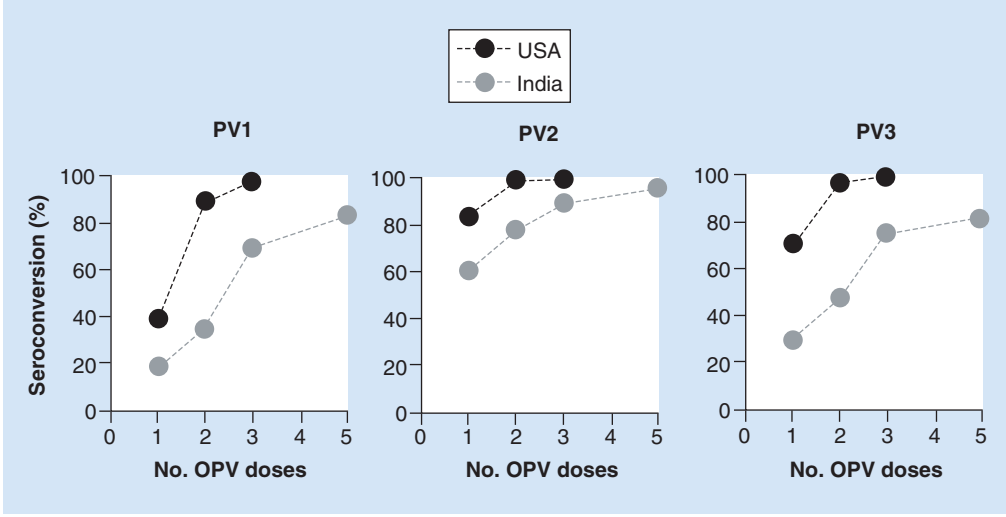

Figure 1. Impaired immunogenicity of oral poliovirus vaccine in India. Seroconversion rates for India are obtained from a report by John [194], which combines results from several trials of trivalent OPV performed in Vellore between 1969 and 1976. Immunogenicity data from the USA are obtained from a study by McBean *et al.* [195] in which three doses of trivalent OPV were administered to infants in Maryland at 2, 4 and 18 months of age. Seroprevalence estimates at 18 and 20 months of age are interpreted here as seroconversion.
OPV: Oral poliovirus vaccine; PV1: Type 1 poliovirus; PV2: Type 2 poliovirus; PV3: Type 3 poliovirus.

vaccines [9–11] and oral poliovirus vaccine (OPV) (Figure 1) [12]. Limited efficacy of OPV has contributed to the persistence of poliovirus transmission in several countries, delaying global eradication. Ty21a offers moderate efficacy against typhoid fever (reported at 48% over 3 years in a recent systematic review [13]), although there is no evidence to suggest that this is lower than protection offered to travelers from high-income, non-endemic countries [14,15]. One live-attenuated *Shigella* vaccine candidate was reactogenic and immunogenic when administered to North-American adults; however, when the same vaccine was tested in Bangladesh, it elicited no adverse reactions and failed to induce a serological response in any recipient [16,17]. Poor immunogenicity has also been observed for an oral-killed cholera vaccine among children in Nicaragua compared with Sweden [18]. Thus, poor vaccine immunogenicity and effectiveness have been observed for both killed- and live-oral vaccines targeting bacterial and viral pathogens. The same does not appear to be true of parenterally administered vaccines [19,20].

In addition to geographic variation, oral vaccine immunogenicity can vary by season and age at administration. OPV is less immunogenic when given during warm, humid months [21,22], while Rotarix was shown to have lower immunogenicity during the cool, dry season in Zambia [23]. Oral poliovirus and rotavirus vaccines may be less immunogenic when administered in early infancy (e.g., before 6 weeks of age) compared with later infancy, although the size of this effect is small [24–27] and may be reversed at older ages [28]. The immunogenicity of live-attenuated oral cholera and typhoid vaccines given to children does not appear to be strongly related to age, although it can be affected by pre-existing immunity from natural exposure to these pathogens [29,30]. By contrast, several studies of

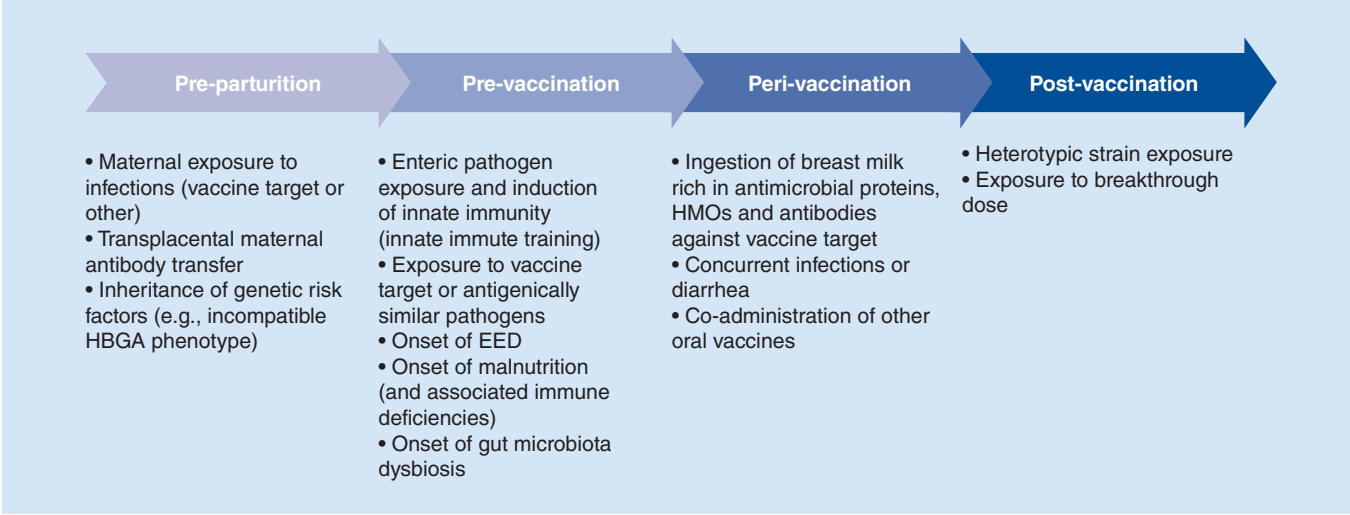

Figure 2. Oral vaccine failure: a timeline of contributing factors.
EED: Environmental enteric dysfunction; HBGA: Histo blood group antigen; HMO: Human milk oligosaccharide.

inactivated oral cholera vaccines have found lower immunogenicity and efficacy among young children (<5 years of age) compared with older children [31–34].

In each of these examples, deficits in oral vaccine performance have been observed within the context of trials in which the potency and cold-chain requirements of the administered vaccines were carefully maintained. Logistical failures therefore cannot fully account for poorer performance in the field, although in practice they may exacerbate the issue. What, then, explains the discrepancies in oral vaccine outcomes between high-income and low-income settings? In this review, we consider the biological mechanisms that might account for the geographic variation in oral vaccine performance. These mechanisms are varied, interconnected and play out across a timescale that begins before birth and ends well after immunization (Figures 2 & 3). Moreover, while the overall trend of impaired performance in developing countries appears to be common to almost all oral vaccines, the mechanisms responsible for this phenomenon may vary between vaccines. Where sufficient evidence is available, we will distinguish between risk factors for vaccine failure that are shared across oral vaccines and those that are specific to individual vaccines. We will also comment on whether these risk factors are consistent with the observed geographic and seasonal trends in vaccine immunogenicity.

Maternal risk factors

Transplacental antibodies

Newborn infants passively acquire serum antibodies from their mothers via the placenta at titers comparable to those in maternal serum [35,36]. These antibodies are predominantly of class IgG (IgA does not cross the placenta [37]) and decay with a half-life of approximately 28 days [38]. Maternally derived antibodies have been shown to interfere with both oral and parenteral vaccines [21,39], and are in this respect distinct from several of the mechanisms considered below. Precise mechanisms of interference remain uncertain, but may involve the masking of vaccine-derived antigens from B- and T-cell receptors [40].

An impaired immune response in infants with elevated titers of passively acquired antibodies has consistently been demonstrated in field trials of OPV [21,41–43], with the greatest inhibitory effect typically observed for serotype 3 [41,43]. Among infants in Brazil who received trivalent OPV at 0, 6, 10 and 14 weeks of age, type 3 seroconversion was observed in 70% of individuals who had a baseline homotypic antibody titer of less than 1:64, but only 29% of those with a baseline titer of at least 1:256 [21]. Diminished shedding of vaccine polioviruses after immunization (which correlates strongly with immunogenicity) has been observed among nonbreastfed newborn infants with elevated titers of passively acquired antibodies. This suggests that the inhibitory effect of maternal antibodies on OPV immunogenicity reflects in part a reduction in vaccine virus replication [44,45], possibly mediated by the passive transfer of maternal IgG across the intestinal epithelium (termed transudation) [40]. Passively acquired serum antibodies have also been linked with a reduction in the immunogenicity of oral rotavirus vaccines, including

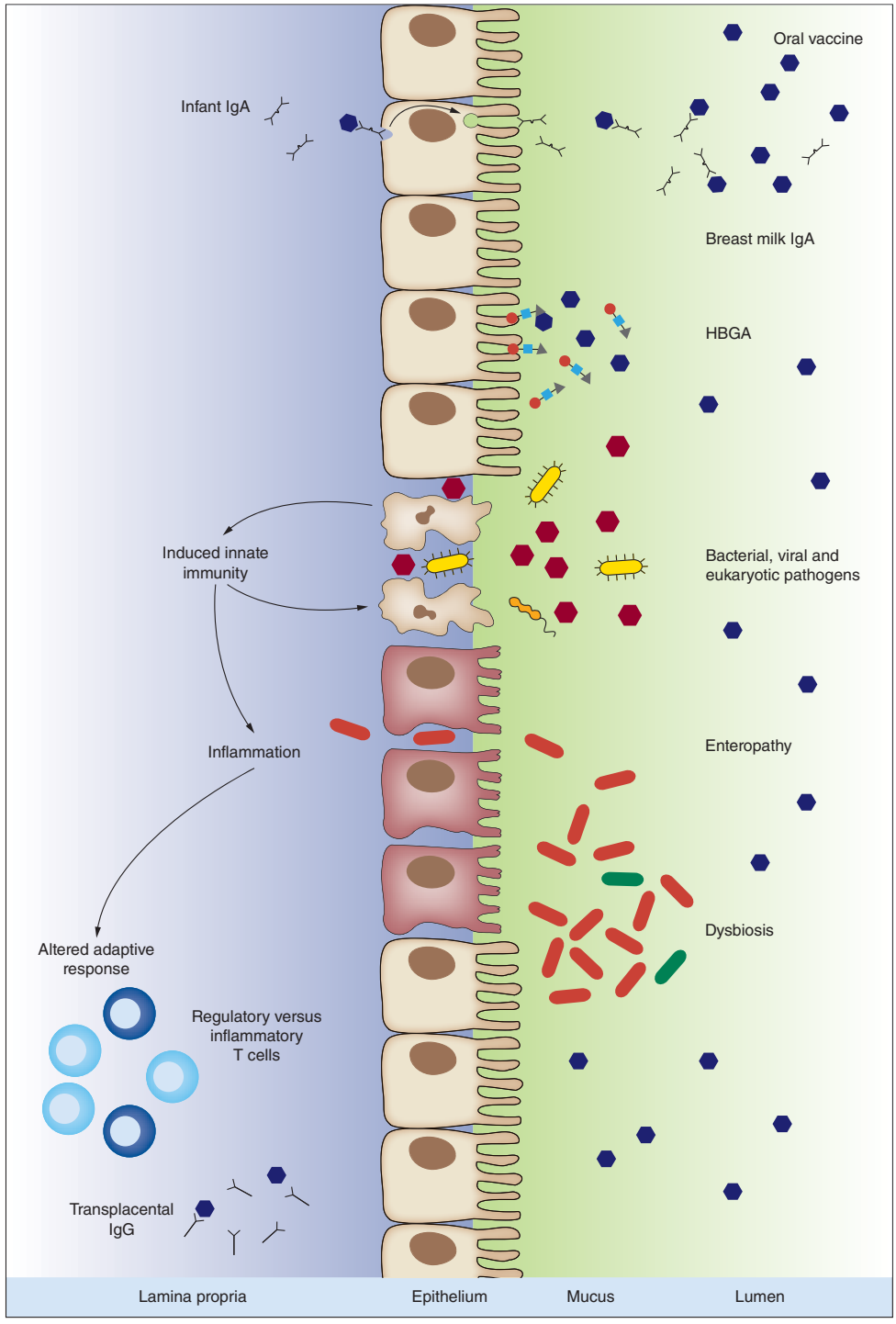

Figure 3. Potential mechanisms underlying variation in oral vaccine efficacy. Upon arrival at the gastrointestinal epithelium, multiple factors may impact the ability of an oral vaccine to replicate and/or cause a protective immune response. Breast milk IgA may neutralize the vaccine, as may infant IgA induced by prior exposure to the infection being targeted. HBGAs act as binding sites for many enteric infections. Their precise structure as well as their presence in mucosal secretions are genetically determined and vary among individuals. The presence of enteric pathogens at the time of immunization may activate innate immune pathways that inhibit the immunogenicity of oral vaccines. Repeated pathogen exposure may also give rise to enteropathy – a subclinical condition associated with increased gut permeability and the induction of a pro-inflammatory state that may inhibit oral vaccine immunogenicity. The bacterial microbiota is crucial both to the development of the intestinal immune system and the replication of enteric viruses. Perturbations of the microbiota (or dysbiosis) may therefore have an inhibitory effect on oral vaccines. Pathogen exposure, enteropathy and microbiota dysbiosis may also alter the adaptive response to oral vaccines; for example, by inducing regulatory T cells that promote a state of mucosal tolerance. Finally, transplacental IgG in infant serum has been shown to interfere with both oral and parenteral vaccines.
HBGA: Histo blood group antigen.

Rotarix [36], RotaTeq [46] and Rotavac [47]. An increase in seroconversion rates by up to 25% has been observed following the administration of Rotarix at 10 and 14 weeks of age as opposed to the standard schedule of 6 and 10 weeks (when maternal antibodies will have had less time to decay) [48]. However, a recent study of Rotavac in north India concluded that maternal antibodies explained less than 10% of variation in post-vaccination antibody levels [49]. Oral cholera and typhoid vaccines are not licensed in infants and studies demonstrating inhibition by transplacental antibodies are therefore lacking.

The degree to which trends in maternal antibodies contribute to the geographic, age-related and seasonal patterns of OPV and rotavirus vaccine performance is less certain. Maternal exposure to natural infection, and consequent boosting of serum antibody titers, will be greatest in places and at times of year that transmission is most efficient, enhancing the potential influence of passively acquired antibodies in young infants. These trends generally appear to correlate with observed patterns of OPV and rotavirus vaccine immunogenicity, although cross-sectional surveys of poliovirus- and rotavirus-specific maternal antibody titers in different sites using standardized methods are currently lacking [50,51]. It is also worth noting that maternal infection with malaria or HIV is associated with a reduction in the transfer of antibodies across the placenta [52]. As such, the effect of maternal antibodies on vaccine immunogenicity may be diminished in populations with a high burden of these infections.

Breastfeeding

Breast milk has the capacity to directly inhibit replication of vaccine strains in the gut owing to the presence of neutralizing antibodies (predominantly of class IgA), antimicrobial proteins such as lactadherin and lactoferrin, and human milk oligosaccharides that bind enteric viruses, potentially blocking cell entry [53,54]. This may, in turn, contribute to geographic and seasonal variation in oral vaccine performance. Rotavirus-specific IgA and neutralizing antibody titers tend to be significantly higher in breast milk obtained from mothers in low-income countries (e.g., India and Bangladesh) compared with mothers from high-income countries (e.g., the USA and Sweden) and in the rotavirus high season compared with the low season [23,55,56]. Similarly, higher levels of lactoferrin and lactadherin have been observed in breast milk obtained from Indian and South-African women compared with North-American women [57], although these innate immune factors did not correlate with RotaTeq immunogenicity in a recent study in Nicaragua [58]. In the case of poliovirus, significantly higher IgA titers were documented in breast milk samples from unvaccinated women from Pakistan compared with vaccinated women from Japan or Sweden in the early 1990s [59], and it is likely that similar discrepancies between endemic and nonendemic settings persist today. Antibodies against cholera toxin and lipopolysaccharide are also common among mothers in low-income countries [60].

Findings regarding the overall impact of breastfeeding on oral vaccine performance are notable for their lack of consistency. The effects of breastfeeding are confounded with those of transplacental antibodies owing to the close correlation between antibody titers in maternal breast milk and serum [45]. Nonetheless, several studies have documented a reduction in the shedding of vaccine polioviruses in breastfed versus non-breastfed neonates immunized shortly after birth [44,61], and this discrepancy appears to persist across a range of maternal serum antibody titers [45]. Later in infancy, the picture is more ambiguous – while an increase in the duration of breastfeeding was associated with a lower seroconversion rate (significant for serotype 3) following four doses of trivalent OPV among infants in Brazil, breastfeeding status had no effect on seroconversion rates during studies in Uganda [62] and India [63]. To confuse matters further, several studies have documented an improvement in OPV immunogenicity among breastfed infants [43,64,65].

Studies of oral rotavirus vaccines have similarly failed to establish a clear inhibitory or beneficial effect of breastfeeding on vaccine performance. While several trials have observed a reduction in immunogenicity among breastfed infants [66,67], the effect has typically been modest. Recent trials of Rotarix in South Africa, India and Pakistan did not document a significant improvement in seroconversion rate in conjunction with the temporary withholding of breastfeeding immediately before and after vaccination [49,68,69]. Indeed, in the latter study Rotarix immunogenicity was significantly higher among infants who were breastfed at the time of immunization [69]. In the case of inactivated oral cholera vaccine (Dukoral), withholding breastfeeding for 3 h prior to immunization was associated with a modest increase in immunogenicity (based on vibriocidal antibody titers), although this was only apparent in a subgroup analysis of older children (10–18 months of age) and was not seen for antibodies against cholera toxin [70].

It is possible that the conflicting findings of these studies reflect contradictory influences of breastfeeding on vaccine immunogenicity. On the one hand, IgA and innate immune factors may inhibit the replication of live-

attenuated oral vaccines – an effect that is likely to be particularly potent in newborns given the elevated titers of antibodies in colostrum. However, breastfeeding may also prevent enteric infections [71], promote the maturation of the infant immune system [72] and buffer vaccine viruses from gastric acid [67], which together may alleviate or indeed reverse the inhibitory effects of breast milk IgA.

Genetic risk factors

Although unable to account for seasonal fluctuations in oral vaccine response, a role for genetic variation in shaping the immune response to oral vaccines is supported by a study of 207 twin pairs in the Gambia who received multiple doses of OPV [73]. By comparing within-pair correlations in antibody titers between monozygotic and dizygotic twins, approximately 60% of the variation in OPV response was attributed to heritable factors.

Histo blood group antigens

Among the potential genetic sources of variation in oral vaccine outcome, histo blood group antigens (HBGAs) are important candidates. HBGAs are ABH and Lewis glycans present on the surface of epithelial cells and in mucosal secretions. HBGA synthesis occurs via the sequential addition of monosaccharides to precursor disaccharides through the expression of genetically encoded glycosyltransferases such as *FUT2* (secretor gene) and *FUT3* (Lewis gene). Individuals with functional *FUT2* are referred to as secretor-positive because HBGAs can be found in mucosal secretions; those with functional *FUT3* are referred to as Lewis-positive. The fucosyltransferases are nonfunctional in individuals with mutations in *FUT2* and *FUT3*, and such individuals are referred to as secretor-negative (or nonsecretors) and Lewis-negative, respectively.

A number of enteric pathogens and pathogen-derived toxins use HBGAs as attachment factors. These interactions, in turn, may give rise to marked associations between HBGA phenotype and enteric pathogen susceptibility [74]. For individual pathogens, HBGA interactions are often strain/genotype-specific. For example, secretors are significantly more susceptible than nonsecretors to norovirus genotype GII.4, but the same is not true of other norovirus genotypes such as GII.3 [75]. Rotaviruses are classified into G and P types based on the composition of the outer capsid proteins VP7 and VP4, respectively. Binding to HBGA occurs through the VP8* domain of protein VP4 [76,77]. To date, 47 VP4 (P) genotypes have been identified, of which P[4], P[6] and P[8] are most common. A recent systematic review based on studies in France, Vietnam, the USA and Burkina Faso documented a 27-fold increase in susceptibility to P[8] rotavirus in secretors versus nonsecretors, but showed no association between secretor status and susceptibility to P[4] or P[6] genotypes [75]. In Burkina Faso, no Lewis-negative secretors (expressing H type 1 antigen) were infected with P[8] strains, despite making up 25% of the study population [78], suggesting that the infectivity of P[8] strains may be dependent on both secretor and Lewis status. However, population-specific differences may exist; for example, P[8] infections were detected in both secretors and nonsecretors during a study in Tunisia [79].

In addition to being among the globally dominant rotavirus genotypes, P[8] strains are a component of Rotarix and RotaTeq. It is therefore plausible that genotype-specific HBGA binding patterns may contribute to geographic differences in vaccine efficacy. While nonsecretors make up just 20% of Caucasians, this phenotype may reach a prevalence of 30–50% in parts of Bangladesh, India and Pakistan [80–82], where the immunogenicity and efficacy of oral rotavirus vaccines is poor. Similarly, the Lewis-negative phenotype is significantly more common in parts of Africa (reaching >30% in some populations) than in Caucasians (4–6%) [83]. Thus, an impaired replicative capacity of P[8] strains combined with the high prevalence of P[6] genotypes in Lewis-negative individuals, as reported in Burkina Faso [78], would be consistent with observed discrepancies in rotavirus vaccine efficacy.

A key challenge for the coming years will be to determine the extent to which host genetic determinants of rotavirus diarrhea susceptibility apply to attenuated vaccine strains. Notably, during a recent study in Pakistan, Rotarix immunogenicity was associated with secretor status and ABO blood group – seroconversion was seen in 19% of nonsecretors, 30% of secretors with non-O blood groups and 51% of secretors with blood group O [84]. How this poorer immunogenicity impacts clinical protection is not yet clear and may be complex. For example, while nonsecretors may be less likely to respond to vaccination, they will also be less susceptible to natural infection with certain genotypes.

The effect of HBGAs on OPV immunogenicity has not been studied, although blood group O has been linked with an increased occurrence of paralytic poliomyelitis [85]. HBGA phenotype also appears to influence susceptibility to bacterial enteropathogens [86,87], including *V. cholerae* [88,89]. Nonsecretors are more likely to suffer from severe cholera than secretors [90]. Somewhat paradoxically, individuals with blood group O are less likely to be

colonized by *V. cholerae* [89], but are more likely, upon colonization, to develop severe symptoms [88,89]. The extent to which HBGA phenotype influences cholera vaccine response remains uncertain. Several studies have documented increased immunogenicity or protective efficacy following administration of CVD 103-HgR to individuals with O versus non-O blood groups [11,91–93], though a recent study in North-American adults failed to replicate these findings [94]. Meanwhile, trials of oral-killed whole-cell vaccines have yielded conflicting results when comparing immunogenicity or efficacy according to ABO blood type, including observations of either improved or impaired response in individuals with blood group O (vs non-O) [32,95,96], or no difference according to blood group [97,98]. It is worth noting that regions in which oral cholera vaccine candidates have underperformed (e.g., Thailand and Indonesia) do not differ markedly in blood group O frequency from those in which a robust vaccine response is seen (e.g., North America) [11,99]. Nonetheless, HBGA phenotype (including Lewis and secretor status) should continue to be a consideration during cholera vaccine trials.

Another relevant genetic factor for future consideration is maternal secretor status. This significantly impacts the quantity and quality of oligosaccharides found in breast milk [100], potentially modifying any direct or indirect effects of breastfeeding on oral vaccine efficacy. Ultimately, the HBGA status of a mother–infant pair may play a role in shaping infant microbiota composition [101,102], mucosal immune development and pathogen receptor expression (in breast milk, mucus and on intestinal epithelial cells), thereby influencing both pathogen susceptibility and oral vaccine outcomes. However, further work is required to disentangle these pathways.

Other genetic associations

Genetic risk factors for oral vaccine failure may extend beyond HBGAs. Candidate gene and genome-wide association studies have helped to uncover genetic variants that influence the performance of vaccines targeting measles, rubella and hepatitis B, among others [103,104]. Variants within the *HLA* locus (encoding the major histocompatibility complex proteins involved in antigen presentation) have typically been among the top associations identified. A recent genome-wide association study among infants in Bangladesh identified several single-nucleotide polymorphisms that may contribute to variation in OPV response, including those associated with histone modification [105]. However, there is no reason to suspect that geographic variation in oral vaccine response is correlated with the distribution of these genetic polymorphisms. Analogous studies are presently lacking for oral vaccines other than OPV.

Malnutrition & micronutrient deficiencies

Malnutrition is common in the world's poorest countries, and may contribute to more than half of deaths among children under 5 years of age [106]. It appears in various forms, including impaired growth (e.g., stunting) and deficiencies in specific micronutrients (e.g., zinc, iron and vitamin A). Several abnormalities in immune function have been linked with malnutrition, including deficits in secretory IgA, complement production, gut barrier function and T-cell memory maintenance, among others [107]. In spite of these immunological deficits, a consistent link between malnutrition and oral vaccine performance has not been found [108,109]. A recent study among infants in Bangladesh documented significantly lower serotype 3 poliovirus antibody titers in conjunction with underweight (weight-for-age Z score ≤ 2) after at least three doses of OPV [65]. However, other studies in India, Nigeria and Pakistan have not observed an association between malnutrition and OPV immunogenicity [110–112]. Similarly, supplementation with vitamin A did not significantly impact OPV seroconversion rates during trials in Bangladesh, Indonesia and Ghana [113–115], while the receipt of zinc supplements (which are known to have a significant therapeutic effect during the treatment of acute gastroenteritis [116]) had no effect on OPV seroconversion during a recent placebo-controlled trial in Pakistan [117].

Data regarding the potential impact of malnutrition on oral vaccines other than OPV are limited [108]. During a trial of CVD 103-HgR in Bangladesh, supplementation with zinc (but not vitamin A) significantly boosted vibriocidal antibody response [118]. Low levels of serum zinc have also been associated with rotavirus risk in Bangladesh [119], though supplementation with zinc did not improve Rotarix immunogenicity during a study in India [120]. Overall, while it remains plausible that malnutrition and micronutrient deficiencies may contribute to the impaired performance of oral vaccines in low-income countries, particularly given their geographic and seasonal patterns of occurrence, we currently lack robust data to support this notion [121]. It is also worth noting that enteric infections and environmental enteropathy are strongly associated with malnutrition [122,123], and may in turn be worsened by its onset. These factors may have a greater impact on oral vaccine performance than malnutrition itself, although teasing apart such effects is likely to prove challenging (see below).

Environmental exposures

Enteric infections

Enteric infections have long been recognized as a major cause of morbidity and mortality among young infants, and this burden is greatest in the developing countries where oral vaccines are least immunogenic [2,124]. Enteric infections present at the time of vaccination or in the period leading up to vaccination might impede oral vaccines in several ways. Interference with live-attenuated viral vaccines by viral pathogens may arise via competition for cell entry or receptor binding, or (after entry) for cellular factors required during transcription, replication and assembly – a notion supported by the interference that occurs among the three vaccine poliovirus serotypes when co-administered [12]. Interference might also arise via the induction of nonspecific innate immunity. In particular, type I, II and III interferons induced by viral or bacterial pathogens may inhibit vaccine virus replication and immunogenicity through a number of mechanisms including direct antiviral activity, innate immune cell activation and regulation of adaptive immune responses [125,126]. Other immunomodulatory effects may be pertinent, such as the suppression of Th1 cytokine production by intestinal helminths [127,128], the promotion of mucosal tolerance via the induction of regulatory T cells or the functional reprogramming of innate immune cells that protects against subsequent colonization (trained immunity) [129].

The inhibitory effect of non-polio enteroviruses (NPEVs) on OPV is perhaps the most robust association to be demonstrated between a group of enteric pathogens and an oral vaccine. NPEVs show both geographic and seasonal patterns of incidence that coincide with impaired immunogenicity of OPV [22]. In a systematic review of OPV trials dating back to 1959, the presence of NPEVs at the time of vaccination (detected in stool samples in the absence of symptoms) was consistently associated with a reduction in the odds of seroconversion per dose of OPV, though it remains unclear whether this inhibitory effect varies among enterovirus species [130]. The association between the presence of NPEVs and OPV immunogenicity has since been confirmed by studies in south India [28] and Bangladesh [131] that used sensitive PCR-based methods for the detection of multiple enteric pathogens, including enteroviruses, at the time of OPV administration. In the latter study, enterovirus quantity at 10 weeks of age was also negatively correlated with the immunogenicity and efficacy of Rotarix (administered at 10 and 17 weeks) – an effect that was not observed for any other viral, bacterial or eukaryotic pathogen, or for Sabin polioviruses [131]. Thus, the negative repercussions of enterovirus exposure for oral vaccines may extend beyond OPV.

Given that OPV and oral rotavirus vaccines are regularly co-administered as part of routine immunization programs, the potential interference between these attenuated viruses has garnered considerable interest. Rotavirus replication *in vitro* is impaired by the presence of an enterovirus, but the converse is not true [132]. Consistent with this, vaccine co-administration does not appear to inhibit the immunogenicity of OPV [133]. The situation for rotavirus vaccines may be more complex – while the first dose of either Rotarix or RotaTeq has generally proven to be less immunogenic when administered with OPV than without, after a full course antibody titers are similar in these groups [134]. Nonetheless, among infants in Bangladesh who received Rotarix at 6 and 10 weeks of age, concomitant OPV administration during at least one of these doses was associated with a reduction in rotavirus seroconversion rate (47%) compared with staggered vaccine administration ($\geq$1 day apart) at both doses (63%) [135]. Thus, it is possible that the continued use of OPV in developing countries (as opposed to the IPV-only schedules generally adopted in high-income countries) contributes to the geographic discrepancies observed in rotavirus vaccine performance.

Aside from the clear inhibitory potential of enteroviruses (either NPEVs or OPV), the relationship between other enteric pathogens and oral vaccine outcome remains equivocal. Concurrent diarrhea has consistently been linked with a reduction in the immunogenicity of OPV [21,130,136]. Several studies have also highlighted the potential inhibitory effect of bacterial or eukaryotic pathogens on OPV, often in the absence of gastrointestinal symptoms [131,137,138]. However, a 3-day course of azithromycin (a broad-spectrum macrolide antibiotic) did not alter the immunogenicity of a subsequent dose of type 3 monovalent OPV among 6–11 month-old infants in India despite reducing the prevalence of bacterial pathogens (including *Campylobacter*, *Salmonella* and several pathotypes of *E. coli*) [28].

Studies concerning the association between enteric infections and oral cholera vaccine outcome have generally focused on specific pathogens. An inhibitory association between *Helicobacter pylori* colonization and CVD 103-HgR response has been reported among Chilean children <5 years of age, but not in children aged 5–9 years [93]. Notably, this species is rarely documented among children <1 year of age, and is therefore unlikely to influence the immunogenicity of oral vaccines administered in early infancy [28,131]. During a placebo-controlled trial among

6–13 year-old children in Ecuador who were infected with *Ascaris lumbricoides*, two doses of albendazole (an anthelmintic) prompted a modest improvement in immunogenicity following a subsequent dose of CVD 103-HgR [92], though seroconversion rates in albendazole-treated children (~30%) still fell considerably short of those observed in North-American adults (>90%) [139]. A subsequent trial in Ecuadorian teenagers revealed that *A. lumbricoides* inhibits Th1 cytokine responses (including IL-2 and IFN-γ) to CVD 103-HgR, and that albendazole treatment prior to vaccination partly reverses these effects [128]. However, deworming did not yield similar benefits for the immunogenicity of inactivated cholera vaccine among children in Bangladesh or Gabon [140,141].

Maternal helminth exposure may also be pertinent to infant vaccination outcomes. During a recent study in Ecuador in which OPV and Rotarix were administered according to routine schedules, infants exhibited higher plasma IgA levels for rotavirus and poliovirus if their mothers were infected with helminths in the last trimester of pregnancy [142]. Mechanisms underlying these effects are unclear, but may involve the transfer of helminth-induced cytokines (e.g., IL-10) across the placenta or in breast milk.

The commensal microbiota

The potential influence of the intestinal microbiota on oral vaccine response is not restricted to enteric pathogens. Colonization of the intestinal tract with commensal bacteria begins at birth [143]. The ensuing cross-talk between the bacterial microbiota and mucosal immune cells is critical to the development of the intestinal immune system, as evidenced by the gross deficits in immune function seen in germ-free mice [144]. Specific bacterial taxa may promote the expansion of particular immune cell subsets; for example, segmented filamentous bacteria trigger the accumulation of Th17 cells in the small intestine [145]. In addition to these effects on the developing immune system, the bacterial microbiota appears to facilitate the uptake and replication of a number of enteric viruses [146]. Depletion of commensal bacteria by antibiotics inhibits poliovirus replication and pathogenesis in mice [147], although this was not seen in human infants given therapeutic doses of azithromycin [28]. It has also been observed *in vitro* that poliovirus infectivity is enhanced by exposure to bacterial surface polysaccharides such as lipopolysaccharide and peptidoglycan [147], possibly via the effect of these polysaccharides on virion stability and receptor attachment [148]. Analogous effects have been reported for rotavirus, which exhibits reduced infectivity and pathogenicity (but greater immunogenicity) in antibiotic-treated mice [149].

While the intestinal microbiota plays a critical role in the development of the infant intestinal immune system, it is less clear whether variation in microbiota composition underlies variation in vaccine outcomes. The composition of the bacterial microbiota displays considerable variation by geographic setting [150–152], lifestyle [153] and season [154]. As such, the ecological landscape into which an oral vaccine is introduced is likely to vary considerably between infants in high- and low-income countries. To date, several observational studies have been performed in developing countries to examine the association between microbiota composition and oral vaccine response. OPV immunogenicity was positively correlated with the abundance of Actinobacteria (particularly the genus *Bifidobacterium*) among infants in Bangladesh [155]. In rural Ghana, Rotarix immunogenicity was associated with a lower abundance of Bacteroidetes and a greater abundance of Bacilli (specifically *Streptococcus bovis*) at 6 weeks of age, while infants who seroconverted exhibited an overall microbiota profile more similar to that of Dutch infants compared with nonresponders [156]. However, no comparable discrepancies in pre-vaccination microbiota composition were observed according to rotavirus or poliovirus seroconversion status among infants in India who received Rotarix and OPV at 6 and 10 weeks of age [157]. Thus, a consistent link between microbiota composition and oral vaccine performance has not yet been identified, and there is limited evidence to suggest that vaccine failure is associated with overt perturbations in the microbiota (or 'dysbiosis').

In addition to observational studies of microbiota composition, several trials have examined whether augmenting the infant microbiota with probiotic supplements has the capacity to improve oral vaccine outcomes. To date, the potential benefits of this approach remain equivocal, as reviewed elsewhere [158]. However, the administration of daily supplements of *Lactobacillus rhamnosus* GG provoked a modest improvement in Rotarix immunogenicity during a placebo-controlled trial in India [120]. As our understanding of the infant microbiota develops, microbiota-directed therapies may offer novel ways of boosting oral vaccine efficacy.

Additional studies exploring the relationship between commensal bacteria and oral vaccine response are likely to accumulate swiftly over the coming years. The potential impact of viral and eukaryotic components of the intestinal microbiota on oral vaccine outcome also merits further exploration (e.g., via shotgun sequencing of the metagenome), as does the metabolic output of the gut microbiota (the metabolome). Ultimately, potential associations will need to be validated using animal or *in vitro* organoid models. For example, gnotobiotic animals

with a humanized gut microbiota have been used to test causal relationships between microbiota composition and disease states such as kwashiorkor [159] and inflammatory bowel disease [160]. This approach was recently applied to the phenomenon of oral vaccine failure by inoculating 24 newborn pigs with the fecal microbiota of a RotaTeq nonresponder with a high enteropathy score or a RotaTeq responder with a low enteropathy score (both from a study in Nicaragua) [161]. Although this approach failed to induce the manifestations of enteropathy (described below), pigs in the latter group exhibited stronger rotavirus-specific T-cell responses in the ileum, spleen and blood, and a reduction in the incidence of viral shedding and diarrhea after rotavirus challenge.

Environmental enteric dysfunction

Environmental enteric dysfunction (EED) – also referred to as 'environmental enteropathy' – is a subclinical disorder characterized by the flattening of intestinal villi, nutrient malabsorption, intestinal inflammation (including an influx of inflammatory cells into the lamina propria) and increased gut permeability [162,163]. These manifestations may begin to appear soon after birth: during a study in India, the majority of infants displayed some degree of villous blunting within the first 30 days of life [164]. The precise etiology of EED is unclear; however, it appears to be associated with poor environmental conditions, and in a murine model, inadequate diet and repeated microbial exposure were sufficient to promote the features of EED [165].

Owing to its pervasive nature in developing countries and the changes in intestinal immune function with which it is likely associated, EED has been hypothesized to play a key role in shaping geographic trends in oral vaccine performance [162,166,167]. Specific inhibitory effects might include the induction of a hostile pro-inflammatory state in the small intestine, the increased production of short-chain fatty acids or other immunomodulatory molecules that are inhibitory to oral vaccines, and the dampening of immune responses due to alterations in regulatory T-cell or dendritic-cell function [168].

In addition to its occurrence in developing countries, EED can also show seasonal variation, consistent with patterns of OPV immunogenicity [169]. However, a key difficulty faced by studies attempting to elucidate the impact of EED on oral vaccine outcome has been how best to measure and define the condition. Owing to the invasive nature of intestinal biopsies, studies of EED have tended to rely on serum and fecal biomarkers, such as those indicative of small bowel bacterial overgrowth (e.g., hydrogen breath test), gut inflammation (e.g., fecal calprotectin and myeloperoxidase), microbial translocation (e.g., serum EndoCab) and mucosal permeability (e.g., lactulose/mannitol test). To date, the study of these biomarkers has failed to yield any consistent associations between EED and oral vaccine performance [28,98,170–173], as discussed in detail elsewhere [Church *et al.*, In Preparation].

The relative importance of EED in shaping the immune response to oral vaccines thus remains uncertain. It is possible that the ubiquitous nature of EED in developing countries is partly responsible for this. Indeed, in several of the studies that have examined the potential association between EED and oral vaccine outcome, the majority of infants displayed elevated levels for at least one inflammatory biomarker compared with those observed in high-income countries, and it would therefore be possible to classify nearly all vaccine recipients as having some degree of EED [28,171]. In such populations, EED may contribute to oral vaccine failure despite the absence of consistent correlations between individual biomarkers and vaccine outcome. Such homogeneity within study populations presents a considerable challenge to identifying whether individual-level EED or specific biomarkers are associated with vaccine response.

Transmission intensity & strain diversity of the infectious agent

Pre-vaccination exposure

The transmission intensity of enteric pathogens varies considerably by region. If natural exposure precedes vaccination, this may induce systemic and/or local immunity that impairs vaccine immunogenicity. In the case of rotavirus, exposure to natural infection in the neonatal period is common in settings with a high transmission intensity, and appears to be greatest at times of year associated with impaired vaccine immunogenicity [23]. In a review of Rotarix trials, baseline rotavirus-specific IgA seropositivity (indicative of prior virus exposure) was rare in studies performed in Europe and North America but was observed in up to 26% of participants in higher-burden settings [174]. A reduction in vaccine immunogenicity among infants positive for rotavirus-specific IgA was recently observed during studies of Rotarix conducted in Zambia [23], Bangladesh [135] and South Africa [36], but not in India [175]. Pre-vaccination exposure seems to have a similar effect on the immunogenicity of oral cholera vaccines, including both live-attenuated [11,93,176] and inactivated vaccines [96,177,178]. Together, these findings suggest that the induc-

tion of immunity following a previous encounter with a pathogen may contribute to the impaired immunogenicity of oral vaccines in high-transmission settings. Although potentially relevant in the past, pre-vaccination exposure is unlikely to influence OPV outcomes today given that individuals in endemic settings are typically immunized at birth and regularly thereafter (and thus prior to potential wild-type virus exposure).

Post-vaccination exposure

The nature of post-vaccination exposure to the targeted pathogen may also be pertinent to geographic variation in the protective efficacy of oral vaccines. Oral rotavirus vaccines confer homotypic and heterotypic protection against a wide variety of rotavirus genotypes [179,180]. However, as demonstrated in a range of settings, this protection appears to be lower against fully heterotypic strains (i.e., differing from the vaccine at both G and P epitopes) [181,182]. Such exposures may be more frequent in low-income countries, where the circulation of unusual rotavirus strains is more common [183,184].

In addition to strain diversity, variation in transmission intensity may be a relevant factor. Following a trial of Ty21a in Indonesia, the authors suggested that an increase in the infectious inoculum ("*more frequent inoculations of greater numbers of bacteria*") in this high-transmission setting may have contributed to the lower efficacy observed in comparison to earlier trials in Chile and Egypt [185]. Similarly, an increase in infectious load following extensive flooding was implicated during a large outbreak of paralytic poliomyelitis within a highly immunized population in South Africa between 1987 and 1988 [186]. These hypotheses rest on the assumption that for a given level of vaccine-induced immunity there can be a 'breakthrough dose' that is capable of causing infection. In support of this idea, increasing the viral titer of OPV has been shown to increase the likelihood of infection among previously vaccinated individuals [187,188]. Comparable data for cholera and rotavirus infection are lacking.

Conclusion & future perspective

Deficits in the immunogenicity of oral vaccines targeting poliovirus, rotavirus and several other enteric pathogens have consistently been documented in settings where they might have the greatest benefit. Despite considerable effort, we are yet to fully determine the biological mechanisms responsible for this phenomenon, let alone how best to circumvent it.

In Figure 4, we provide a qualitative synthesis of the literature on oral vaccine failure. Effect sizes are a notable omission from this table, and several associations would benefit from a dedicated systematic review and meta-analysis. Nonetheless, a number of conclusions can be drawn. Several risk factors for oral vaccine failure appear to have a consistent effect across multiple viral or bacterial vaccines, including passively acquired maternal antibodies and prior natural exposure to the vaccine target. Other risk factors may be unique to specific vaccines; for example, while co-administration with OPV may impair the response to live-attenuated oral rotavirus vaccines, OPV is robust to the effects of co-administration. Meanwhile, concurrent viral pathogens clearly inhibit OPV, and the same may be true of oral rotavirus vaccine. Finally, a consistent effect has not been forthcoming for risk factors such as EED and dysbiosis of the bacterial microbiota, perhaps owing to the ubiquitous nature of these conditions in settings associated with oral vaccine failure. It is also important to highlight that the mechanisms considered in this review do not occur in isolation. Consider, for example, the interconnected nature of enteric pathogen exposure, EED, bacterial microbiota composition and malnutrition, among others. Although we have discussed the evidence behind individual risk factors for oral vaccine failure separately, in reality these factors may combine to induce a state of immune hyporesponsiveness.

The impaired performance of oral vaccines does not negate their benefits. Indeed, a partially effective vaccine in a high-burden setting may prevent many more cases than a completely effective vaccine in a low-burden setting. In countries such as Botswana and Zambia, the delivery of rotavirus vaccines in routine immunization programs has been accompanied by 20–30% declines in diarrhea-related hospitalizations and deaths [189,190], and the continued roll-out of rotavirus vaccines elsewhere is likely to bring about comparable benefits to public health.

Yet in spite of these benefits, the issue of impaired vaccine performance in resource-poor settings lingers on. Overcoming this problem may require the development of novel vaccine formulations or interventions to improve the immune response to existing vaccines, such as changes in scheduling, the delivery of additional doses (e.g., a birth dose of rotavirus vaccine), increases in vaccine titer, or administration of immunomodulatory drugs or anti- or pro-biotics. So far, such interventions have had mixed results and none have offered a clear advantage that has translated into policy (with perhaps the exception of increasing the number of vaccine doses administered for OPV). A systematic review of these interventions is beyond the scope of this manuscript, but is currently underway [191].

Risk factor	Poliovirus (live)	Rotavirus (live)	Cholera (live)	Cholera (killed)	Ref.
Pre-parturition					
Receipt of elevated transplacental antibody titers against vaccine target	●●	●●	○	○	[21], [36], [42], [43], [46], [47]
Inheritance of incompatible HBGA genotype	○	●	●●●	●●●†	[11], [32], [84], [91], [92], [94–98]
Pre-vaccination					
Exposure to vaccine target	NA	●●●	●●	●●	[11], [23], [32], [36], [93], [96], [135], [175], [176], [178]
Onset of environmental enteric dysfunction	●●●●	●●●	●	●●●	[28], [98], [170–173]
Development of inhibitory bacterial microbiota composition	●●	●●	○	○	[155–157]
Malnutrition	●●●	●●	○	●	[65], [98], [108], [135], [171], [196]
Peri-vaccination					
Breastfeeding	●●●●●	●●●●‡	○	●	[43–45], [49], [61–70], [197]
Concurrent oral vaccine administration	●●	●●●●	●	○	[67], [133–135], [198–201]
Concurrent enteric pathogens (viral)	●●●§	●●	○	○	[130], [131], [157], [202]
Concurrent enteric pathogens (non-viral)	●●●	●	●●●	●	[28], [92], [93], [128], [131], [137], [138], [140],
Post-vaccination					
Heterotypic strain exposure	NA	●●●●	NA	NA	[8], [181], [182], [201], [203], [204]

●: Inhibitory effect; ●: No effect ●: Beneficial effect; ○: Data lacking. Designations are based on a qualitative, non-systematic synthesis of the current literature. Unless otherwise specified, one circle of a given color signifies the observation of a trend in 1–2 studies, while two circles signify the observation of a trend in ≥3 studies or within a literature review. For example, ●●●● indicates that an inhibitory effect has been observed in ≥3 studies, no effect has been observed in 1–2 studies, and a beneficial effect has been observed in up to two studies.

†The direction of the observed association between ABO phenotype and oral killed cholera vaccine outcome has been inconsistent, as described in the main text.

‡ Studies demonstrating an inhibitory effect of breastfeeding on oral rotavirus vaccines (n ≥ 3) are outnumbered by those demonstrating no such effect.

§ Although ≥3 studies have document no association between concurrent viruses and OPV response, the balance of evidence supports an inhibitory effect of these infections.

HBGA: Histo blood group antigen; NA: Not applicable.

Figure 4. Summary of evidence regarding mechanisms of oral vaccine failure.

Notably, in the case of rotavirus, serum IgA is typically measured during studies of vaccine immunogenicity, but is an imperfect correlate of protection [192]. The identification of new correlates of protection may precipitate an improved understanding of the factors that shape vaccine performance.

We are in the midst of a period of profound change in the use of oral vaccines. OPV has formed the foundation of global efforts to eradicate poliomyelitis and has taught us much regarding the mechanisms that shape oral vaccine efficacy. However, it must eventually be phased out from all immunization activities to prevent the emergence of vaccine-derived polioviruses [193] – a process that began with the replacement of trivalent with bivalent OPV (lacking serotype 2) in April 2016. It appears likely that polio eradication will be achieved in spite of the impaired immunogenicity of OPV. On the other hand, the global roll-out of oral rotavirus vaccine continues, and the impaired performance of rotavirus vaccines in resource-poor settings is likely to gain ever-greater prominence as immunization efforts expand. Improving our understanding of the determinants of oral vaccine immunogenicity

Executive summary

Poor immunogenicity & efficacy of oral vaccines in low-income countries

- Oral vaccines against rotavirus, poliovirus, cholera and typhoid are currently licensed.
- They are easy to administer and induce protective mucosal immunity against infection and disease.
- However, they have consistently proven to be less immunogenic and efficacious in low-income countries, limiting their effectiveness and impact. The reasons for this phenomenon have not been fully elucidated.

Potential explanations & underlying mechanisms

- In infancy, transplacental or breast milk antibodies specific to the vaccine may interfere with immunogenicity. IgA in breast milk may neutralize vaccine virus or limit colonization by bacterial vaccine strains, while transplacental IgG in infant serum can interfere with both oral and parenteral vaccine immunogenicity through mechanisms that remain unclear.
- Histo blood group antigens in breast milk and epithelial cell secretions can bind vaccine virus, potentially facilitating or blocking replication and immunogenicity.
- Other human genetic polymorphisms associated with oral vaccine immunogenicity have not been clearly identified.
- Intestinal infection with bacterial, viral and eukaryotic pathogens may induce an innate immune response that inhibits replication of the vaccine strain and suppresses a systemic immune response. Their significance remains unclear, although enterovirus infections have been clearly shown to reduce oral poliovirus vaccine immunogenicity.
- Environmental enteropathy is found in infants in low-income countries as a result of frequent exposure to intestinal pathogens and is characterized by intestinal inflammation, increased permeability and microbial translocation. These may contribute to oral vaccine failure, but biomarkers of enteropathy have not shown consistent associations with oral vaccine immunogenicity.
- Malnutrition and micronutrient deficiencies occur in populations where oral vaccine immunogenicity is diminished, but measures of malnutrition and growth of infants do not appear to be directly associated with immunogenicity.
- Pre-vaccination exposure to the pathogen or the size of the infectious challenge dose post vaccination may limit vaccine effectiveness in low-income countries, but evidence in support of this hypothesis is limited.

Interventions

- Insights from studies of the mechanisms responsible for poor oral vaccine immunogenicity have so far failed to yield effective interventions to improve immunogenicity or better-designed vaccines.
- Increases in the number of doses of vaccine given have in some cases led to improvements in immunogenicity and efficacy (e.g., oral poliovirus vaccine).
- Withholding breastfeeding has not significantly improved the immunogenicity of oral poliovirus, rotavirus or cholera vaccines.
- Treatment of enteropathy and supplementation with micronutrients or probiotics have not consistently resulted in improvements in oral vaccine immunogenicity.

Conclusion

- Oral vaccines are among the more cost-effective health interventions, but their impact is not fully realized because of diminished immunogenicity and efficacy in the populations that need them most.
- We remain uncertain about the mechanisms responsible for diminished immunogenicity, although new studies and technologies are providing unprecedented insights. Some mechanisms may be general, applying to all oral vaccines, while others may apply only to specific vaccines.
- Intervention studies aimed at improving oral vaccine immunogenicity need to account for vaccine-specific mechanisms. Such trials are needed in order to move beyond studies of association only.

will be key to maximizing the impact of licensed oral vaccines as well as stimulating development of this route of immunization in the context of a crowded parenteral schedule.

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