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REVIEW

Factors That Influence the Immune Response to Vaccination

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SUMMARY There is substantial variation between individuals in the immune response to vaccination. In this review, we provide an overview of the plethora of studies that have investigated factors that influence humoral and cellular vaccine responses in humans. These include intrinsic host factors (such as age, sex, genetics, and comorbidities), perinatal factors (such as gestational age, birth weight, feeding method, and maternal factors), and extrinsic factors (such as preexisting immunity, microbiota, infections, and antibiotics). Further, environmental factors (such as geographic location, season, family size, and toxins), behavioral factors (such as smoking, alcohol consumption, exercise, and sleep), and nutritional factors (such as body mass index, micronutrients, and enteropathy) also influence how individuals respond to vaccines. Moreover, vaccine factors (such as vaccine type, product, adjuvant, and dose) and administration factors (schedule, site, route, time of vaccination, and coadministered vaccines and other drugs) are also important. An understanding of all these factors and their impacts in the design of vaccine studies and decisions on vaccination schedules offers ways to improve vaccine immunogenicity and efficacy.

KEYWORDS antibodies, cellular, cytokines, humoral, immunization, immunoglobulin

INTRODUCTION

Vaccination is the most cost-effective life-saving medical intervention and is estimated to save at least 2.5 million lives each year (1, 2). Protection induced by vaccinations is mediated through a complex interplay between innate, humoral, and cell-mediated immunity (3, 4). Methods to quantify vaccine responses include measuring geometric mean antibody titers (GMTs), seroconversion rates (SCRs), seroprotection rates (SPRs), functional antibodies (by flow cytometric opsonophagocytosis assays), antibody avidity, B and T cell activation, lymphoproliferation, and cytokine responses. There is substantial variation between individuals in the immune response to vaccination, in both quantity and quality. For example, the antibody responses to yellow fever (YF) vaccination vary >10-fold between individuals (5), those to 7- and 13-valent conjugated pneumococcal (PCV7 and PCV13) and *Haemophilus influenzae* type b (Hib) vaccination up to 40-fold (6), and those to trivalent inactivated influenza vaccine (TIV) (7) and hepatitis B (HepB) vaccination >100-fold (6, 8). Similarly, cytokine responses to *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccination vary up to 10-fold (9). Other examples of differences in the quality of vaccine responses include a lower avidity of antibodies (10) or strength of cell-mediated immune responses (11) in neonates. These variations in vaccine responses have consequences for both protective efficacy and the duration of protection. Worryingly, a significant proportion of vaccine-preventable infections occur in vaccinated individuals (12). It is estimated that large numbers of vaccinated children are unprotected due to vaccine ineffectiveness, including 77 million from tuberculosis (TB) (following BCG vaccination), 19 million from measles, 18 million from poliomyelitis (following vaccination with inactivated polio vaccine [IPV]), and 10 million from pertussis and from pneumococcus (13).

In this review, we provide a general overview of factors that influence the immune response to vaccination (Fig. 1). A greater understanding of these factors offers opportunities to improve vaccine immunogenicity and efficacy.

FACTORS INFLUENCING VACCINE RESPONSES

Intrinsic Host Factors

Age. Age is an important factor that influences vaccine responses, especially in the extreme ages of life. Infants should receive immunizations as early as possible to minimize the time that they are susceptible to infections. However, neonates have a

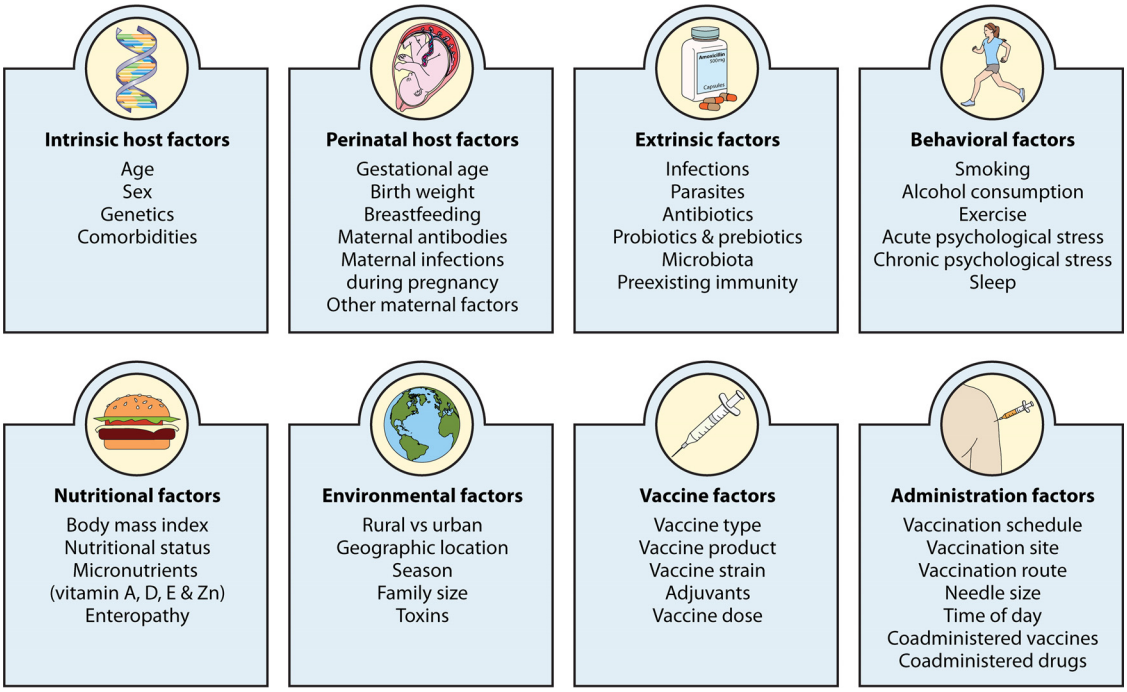

FIG 1 Factors that influence the immune response to vaccination.

lower level of antibody production and, moreover, passively acquired maternal antibodies interfere with vaccine responses (14; P. Zimmermann, K. Perrett, N. Messina, S. Donath, N. Ritz, F. R. M. van der Klis, and N. Curtis, submitted for publication). Additionally, cell-mediated immune responses are less strong, and the response to T-independent polysaccharide antigens is poor (11). Studies in the 1950s sought to establish the optimal age to start vaccination (15, 16). These studies showed, for example, that oral polio vaccine (OPV) given during the first week of life leads to adequate serum antibody responses in only 30% to 70% of infants but that, when it is given after 4 to 8 weeks of age, it leads to adequate responses in nearly all infants (15). Similarly, the diphtheria-tetanus-pertussis (DTP) vaccine is less effective when the first dose is given within the first week of life than when it is given at 6 months of age (16) (Table 1). Results of studies investigating the immunogenicity of BCG given at different ages are conflicting, with some studies showing better immunogenicity when the vaccine is given after the age of 2 months than when it is given at birth (17) and others reporting lower immunogenicity when the vaccine is given at 4 months than when it is given at birth (18). HepB vaccine given in the first year of life leads to lower long-term antibody responses than those obtained when it is given later in childhood: only 40% of adolescents who were HepB vaccinated at birth had antibody levels of $>$10 mIU/ml at the age of 15 years (19), and after a booster dose, antibodies rose above this protective level in only half of individuals (19, 20). However, importantly, in contrast to antibody levels, the number of memory B cells does not decrease over time (21), and hence booster doses of this vaccine are not necessary.

The most-studied vaccine in relation to the effect of age on vaccine responses, by far, is the measles vaccine (10, 22–48). A meta-analysis of 20 studies shows that the proportion of infants seroconverting after one dose of measles vaccination increases from 50% at 4 months of age to 85% at 8 months and that GMTs are lower in children who receive their first dose before 9 months of age than in those who receive their first dose at an older age (49). Additionally, antibodies wane significantly more quickly in infants who receive the first dose of measles vaccine before the age of 9 months (49), and antibodies have significantly lower avidity when the first dose of measles vaccine is given before the age of 6 months than when it is given at 9 to 12 months of age (10).

TABLE 1 Results with regard to age from studies investigating intrinsic host factors that influence vaccine responses[a]

	Vaccine: measurement [reference(s)]		
Type of response	**Effective when given at birth**	**Lower vaccine responses in neonates and young infants**	**Lower vaccine responses in elderly people**
Humoral responses	aP: GMTs (52, 53) HepB: SPRs (55) OPV: SPRs (15)	Diphtheria: SPRs (16) OPV: SPRs (15) Tetanus: SPRs (16) wP: SPRs (16)	Diphtheria: SPRs (60) HepA: GMTs (61, 63, 65, 142), SCRs (63, 76), SPRs (61, 62, 65, 142) HepB: GMTs (61, 69, 71, 73, 75, 77), SCRs (70, 71, 75, 80, 110), SPRs (61, 62, 66–69, 72–75, 77–79, 81) PPV23: GMTs (82–84) TBE: GMTs (88) Tetanus: GMTs (88), SPRs (60, 89) TIV: GMTs (87)
Cellular responses	BCG: Th1, Th2, Treg responses (18)	BCG: CD4 T cell response (17)	TIV: Th cell and cytotoxic T cell responses (86), lymphoproliferative responses (87)
Cytokine responses	BCG: IL-6 and IL-17 production (18)		TIV: IL-2 (85), IL-10 (87), and IFN-γ (87) production

[a]AGGs, agglutinogens; aP, acellular pertussis; BCG, bacillus Calmette-Guérin; CD, cluster of differentiation; FHA, filamentous hemagglutinin; GMTs, geometric mean antibody titers; HepA, hepatitis A; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; HLA, human leukocyte antigen; HSV, herpes simplex virus; MHC, major histocompatibility complex; IFN, interferon; IL, interleukin; IPV, inactivated polio vaccine; MCV, meningococcal conjugate vaccine; MPV, meningococcal polysaccharide vaccine; OCV, oral cholera vaccine; OPV, oral polio vaccine; ORV, oral rotavirus vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; PRN, pertactin; PRR, pattern recognition receptor; PT, pertussis toxin; SCRs, seroconversion rates; SPRs, seroprotection rates; TBE, tick-borne encephalitis; TGF, transforming growth factor; Th, T helper; TIV, trivalent inactivated influenza vaccine; TLR, Toll-like receptor; TNF, tumor necrosis factor; Treg, T regulatory cell; wP, whole-cell pertussis.

A recent large study summarizing randomized controlled trials (RCTs) shows that children who receive their first measles vaccine before the age of 12 months have lower SCRs and geometric mean concentrations (GMCs) than those of children who receive their first measles vaccine after the age of 15 months (50). Lower antibody concentrations persist after the second dose of measles vaccine (49, 50). In contrast, age at first measles vaccination does not influence cellular responses: no differences in *in vitro* T cell proliferation in response to measles virus were observed after starting vaccination at 4, 6, 9, or 12 months (30, 37, 38, 51).

Despite the fact that many vaccines have lower immunogenicity in neonates, it has been shown that for acellular pertussis (aP) (52, 53), BCG (54), HepB (55), and OPV (15) vaccines, vaccination can be effective in the neonatal age group when adjuvants and formulations are adapted to the function of the early immune system (56) (Table 1). The early neonatal immune system shows suboptimal interaction between antigen-presenting cells and T cells, leading to impairment of CD4 and CD8 T cell function and a polarization toward T helper type 2 (Th2) cells (57) and toward induction of memory B cells rather than antibody-secreting plasma cells (58, 59). T cells largely remain unaffected by passively acquired maternal antibodies.

In addition to those in early life, vaccine responses are also diminished in the elderly, who also have more rapid waning of antibodies. Elderly people have lower antibody responses to diphtheria (60), hepatitis A (HepA) (61–65), HepB (61, 62, 66–81), pneumococcal polysaccharide vaccine (PPV23) (82–84), TIV (85–87), tick-borne encephalitis (TBE) (88), and tetanus (60, 88, 89) vaccination (Table 1). After vaccination with TIV, elderly people also have lower cellular vaccine responses (85–87, 90). In contrast, one study reports higher antibody responses to TIV vaccination in elderly people, with a higher avidity of antibodies and slower antibody dissociation (91). Aging is accompanied by a shift toward anti-inflammatory interleukin-10 (IL-10), which is associated with a decline in CD8 T cells responsible for clearing influenza virus. Hence, adjuvants in TIV that stimulate inflammatory cytokines and suppress the IL-10 response would potentially enhance protection in this age group (92).

Notably, the influence of age on vaccine responses is not seen just at the extremes of age. For example, antibody responses to TIV are higher in children of 2 to 4 years of

age than in younger children (93), and GMTs after meningococcal conjugate vaccine (MCV-C) vaccination are higher in children over the age of 10 years than in younger children (94). The findings of studies that investigated the influence of age on vaccine responses are summarized in Table 1.

Sex. The findings across studies and meta-analyses investigating the effect of sex on vaccine responses are largely consistent (Table 2). Females have higher antibody responses to dengue (95), HepA (61–65, 96–104), HepB (61, 62, 66–78, 80, 100, 101, 105–117), Hib (118), IPV (119), rabies (120–122), smallpox (123), and TIV (124–134) vaccination, while males have higher antibody responses to diphtheria (135–138), MCV-A (139), PCV7 (140), PPV23 (83, 122, 140–144), and tetanus (88, 89, 119) vaccination. Additionally, females also have higher cellular responses to a herpes simplex virus (HSV) vaccine that is not currently used (145). Only a few studies report opposite findings, with higher antibody responses to diphtheria (60, 146), PCV13 (118), and tetanus (60, 147) vaccination in females, higher antibody responses to TIV (91) vaccination in males, or no difference between sexes in antibody responses to rabies (148) vaccination (Table 2).

Notably, even though females have an overall tendency to have higher antibody responses, faster waning of antibodies has been shown following HepA (103) and PPV23 (83, 144) vaccination.

Studies investigating sex differences in response to the measles-mumps-rubella (MMR) vaccine report less consistent findings. Some studies report higher GMTs or SPRs after measles (149), mumps (150), and rubella (151) vaccination and higher cytokine responses after measles (152) vaccination in females, while other studies report transiently higher GMTs and lymphoproliferative responses after rubella (153) vaccination and higher SCRs after measles (154) vaccination in males or no sex differences in GMTs after mumps (155) and rubella (156) vaccination or cytokine responses after rubella (156) vaccination (Table 2).

Reported sex differences in antibody responses to YF vaccine vary depending on the vaccine used (157–159). Interestingly, 3 to 10 days after YF vaccination, expression of 660 genes changes in women, while only 67 genes are expressed differently in men (160). Many of these differentially expressed genes are involved in the early innate immune response (160).

Genetics. Different ethnic groups living in the same location have varied responses to vaccination (64, 89, 161–166) and decline of antibodies (89), indicating a genetic influence on vaccine responses. Studies of twins estimate the degree of heritability to be 36 to 90% for humoral responses (167–173) and 39 to 90% for cellular responses, depending on the specific vaccine (167, 169) (Table 3).

One mechanism identified with variations in humoral (150, 174–190) and cellular (145, 150, 186, 191) vaccine responses is polymorphism in major histocompatibility complex (MHC) genes (summarized in Table 3). Further genetic factors are polymorphisms in pattern recognition receptors (PRRs), such as Toll-like receptor (TLR) or RIG-like receptor (RLR) genes (192–195) (Table 3). In addition, many single-nucleotide polymorphisms (SNPs) in other genes, for example, those coding for cytokines or cytokine, viral, or vitamin receptors, are also associated with variations in vaccine responses (182, 190, 192, 193, 196–211) (Table 3). Further, different expression levels of genes also influence vaccine responses. For example, individuals with increased expression of genes involved in early interferon signaling, antigen processing, and antigen presentation have higher antibody responses to TIV (194, 212).

Blood group antigens are important receptors or coreceptors for microorganisms. Additionally, they can also modify the innate immune response to infection (213). It is therefore likely that blood group antigens influence responses to vaccination. It has been suggested that a cholera subunit-killed oral vaccine is less efficient in individuals with blood group O (214, 215). In contrast, the oral cholera vaccine (OCV) has been reported to induce higher antibody concentrations in individuals with blood group O (216). This has not, however, been a consistent finding (217).

Comorbidities. Numerous studies have investigated vaccine responses in children with celiac disease (CD) (218–233) (Table 4). Most found that children with CD have

TABLE 2 Results with regard to sex from studies investigating intrinsic host factors that influence vaccine responses

Type of response	Vaccine and age group: measurement [reference(s)]			
	Higher vaccine responses in females	**Higher vaccine responses in males**	**No difference in vaccine responses between females and males**	**Inconsistent findings in vaccine responses between females and males**
Humoral responses	Dengue Adults: GMTs (95) Diphtheria Adults: SPRs (60), GMTs (146) HepA Children: GMTs (63, 142), SCRs (63), SPRs (142) Adults: GMTs (63, 65, 96–101, 142), SCRs (63, 101, 106), SPRs (65, 101, 103, 142) Adults with chronic liver disease: GMTs (102), SCRs (102) HIV-positive adults: SPRs (104) Elderly: GMTs (61), SPRs (61, 62) HepB Infants: GMTs (116) Children: GMTs (114, 115, 117) Adolescents: GMTs (105), SCRs (105) Adults: GMTs (69–71, 73, 76, 80, 100, 101, 107, 111), SCRs (70, 71, 76, 80, 101), SPRs (67–69, 72–75, 77, 78, 101, 107, 110, 111, 113) Adults on hemodialysis: SCRs (112) Diabetic adults: GMTs (108, 109), SPRs (108) Elderly: GMTs (61), SPRs (61) Hib Infants: GMTs (118) IPV Adults: SPRs (119) Measles Adolescents: GMTs (149) Mumps Children: GMTs (150) PCV13 Infants: GMTs (118) Rabies Children: SCRs (122) Adults: GMTs (120, 121) Rubella Children: SPRs (151) Adults: SPRs (151) Smallpox Adults: GMTs (123) Tetanus Adults: GMTs (60), SPRs (60), titers (147) TIV Adults: GMTs (90, 124, 126, 127, 129, 131, 133, 134), SPRs (90, 129, 133, 134) Elderly: GMTs (125, 130, 132), SCRs (130), SPRs (128)	Diphtheria Adolescents: titers (137) Adults: titers (135) Elderly: GMTs (138) MCV-A Adolescents: GMTs (139) Measles Infants: SCRs (154) PCV7 Elderly: GMTs (140) PPV23 Children: SCRs (122) Adult alcoholics: GMTs (142) Elderly: GMTs (83, 140, 141, 143, 144) Rubella Adolescents: GMTs (153) Tetanus Children: SPRs (89) Adults: GMTs (88), SPRs (89, 119) TIV Adults: GMTs (91)	Mumps Children: GMTs (155) Rabies Children: GMTs (148) Adults: GMTs (148) Rubella Children: GMTs (156)	YF Adults: GMTs (158, 159), SCRs (159), SPRs (157, 158)
Cellular responses	HSV Adults: CD4 T cell responses (145)	Rubella Adolescents: lymphoproliferative responses (153)		
Cytokine responses	Measles Children: IL-6 (152), IFN-γ (152), and TNF-α (152) production		Rubella Children: IL-10 (156) and IFN-γ (156) production	

TABLE 3 Results with regard to genetics from studies investigating intrinsic host factors that influence vaccine responses

Type of response	Vaccine (estimated degree of heritability in vaccine responses [%]) [reference(s)]	Variation in vaccine response and vaccine: MHC genes for which polymorphisms have been identified to be associated with variation in vaccine response [reference(s)]	Variation in vaccine response and vaccine: PRR genes for which polymorphisms have been identified to be associated with variation in vaccine response [reference(s)]	Variation in vaccine response and vaccine: proteins for which single-nucleotide polymorphisms in genes are associated with variations in vaccine responses [reference(s)]
Humoral responses	aP (53–65) (169) Diphtheria (49) (169) HepA (36) (170) HepB (61–91) (169–171) Hib (51) (172) Measles (90) (167, 168) Mumps (39) (168) OPV (60) (169) Rubella (46) (168) Tetanus (44) (169) Varicella (45) (173)	Higher antibody production HepB: HLA-DQB1*05 (178), HLA-DQB1*0602 (178), HLA-DQB1*0603 (178), HLA-DRB1*0102 (178), HLA-DRB1*0103 (178), HLA-DRB1*02 (176), HLA-DRB1*1301 (177, 178), HLA-DRB1*15 (178), HLA-DR7; DQ2, DR4; DQ3, DR15; DQ6, DR3; DQ2 (55) Rubella: HLA-A*02-C*03-B*15-AAAACGGGGC-DRB1*04-DQA1*03-DQB1*03-DPA1*01-DPB1*04 (190), A*02-C*03-B*15-DRB1*04-DQA1*03-DQB1*03-DPA1*01-DPB1*04 (190), HLA-DPB1, rs2064479 (188) TIV: HLA-DPB1*0401 (187), HLA-DQB1*0603 (186), HLA-DRB1*040 (187) Lower antibody production HepB: C4ADel (181), C4AQ0 (179–181), HLA-B8, SC01, DR3 (235), HLA-DPB*0201 (180), HLA-DRA, rs5000563 (182), HLA-DRB1*07(01) (174, 176, 177, 180, 181), HLA-DQA1*0201 (180), HLA-DQB1*0102 (178), HLA-DQB1*02(01) (174, 175, 179, 180), HLA-DQB1*0604 (178), HLA-DRB1*03 (177, 181), HLA-DRB1*1301 (181), HLA-DRB1*1302 (178), HLA-DR3 (extended B8, SC01) (183, 184), HLA-DR7 (extended B44, FC31) (184) Measles: HLA-DPA1*0201 (185), HLA-DRB1*03 (185) Mumps: HLA-DQB1*0303 (150), HLA-A*29-Cw*16-B*44 (569) Rubella: DRB1*13-DQA1*01-DQB1*06-DPA1*01-DPB1*04 (190), DRB1*15/16-DQB1*06-DPB1*03 (569), DRB1*04-DQB1*03-DPB1*03 (569) TIV: HLA-DRB1*07 (186)	Higher antibody production MCV-C: TRL3 (193) Lower antibody production Measles: TLR3 (192)	Variations in antibody production Diphtheria: IL-10 (196) HepB: FOXP1 (182), IL-4 (197), IL-4R (197), IL-10 promotor (198), IL-12B (196), TNF-α (196) TIV: IL-28B (199) Measles: CD46 (200, 201), CD209 (200), IL-2 (202), IL-6 (192), IL-7R (203), IL-10 (202, 203), IL-12RB (202–204), SLAM (201), TNF-α (192) MCV-C: CD44 (193) Mumps: IL-10RA, IL-12RB1 (150) PCV7/PPV23: IL-1β (196), IL-4 (205), IL-4R (196, 205), IL-10 (196), IL-12RB1 (196), IL-13 (196, 205) Rubella: CD209/DC-SIGN (206), IL-6 (206), leukocyte specific transcript 1 (190), lymphotoxin alpha (190, 207), MOG (206), PVR (206), PVRL2 (206), RARB (206), TNF-α (190) Smallpox: IL-18 (208) Tetanus: IL-4R (196)
Cellular responses		Higher lymphoproliferative responses Measles: HLA-A*26-Cw*12-B*28 (569), DRB1*03-DQB1*02-DPB1*04 (569), DRB1*04-DQB1*03-DPB1*03 (569) Mumps: HLA-B*1302 (150), HLA-B*3701 (150), HLA-B*3801 (150), HLA-DQA1*0101 (150), HLA-DQA1*0105 (150), HLA-DQB1*0201 (150), HLA-DRB1*0101 (150), HLA-DRB1*0701 (150), HLA-DRB1*1001 (150), HLA-A*26-Cw*12-B28 (569), DRB1*03-DQB1*02-DPB1*04 (569) Rubella: DRB1-DQA1-DQB1-DPA1-DPB1*13-*01-*06-*01-*03, DRB1-DQA1-DQB1-DPA1-DPB1*03-*05-*02-*01-*04 (191), DRB1*04-DQB1*03-DPB1*03 (569), DRB1*04-DQB1*03-DPB1*03 (569) Lower lymphoproliferative responses HepB: HLA-Bw54-DR4-DRw53-SQw4 (570, 571) Mumps: HLA-DQA1*0401 (150), HLA-DQA1*0501 (150), HLA-DRB1*0301 (150), HLA-DRB1*0801 (150), HLA-DRB1*1201 (150), HLA-DRB1*1302 (150)	Lower lymphoproliferative responses Measles: TLR3 (192)	Variations in lymphoproliferative responses Measles: IL-2 (202), IL-10 (202), IL-12RB (202) Mumps: IL-10RA, IL-12RB1 (150)

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TABLE 3 (Continued)

Type of response	Vaccine (estimated degree of heritability in vaccine responses [%]) [reference(s)]	Variation in vaccine response and vaccine: MHC genes for which polymorphisms have been identified to be associated with variation in vaccine response [reference(s)]	Variation in vaccine response and vaccine: PRR genes for which polymorphisms have been identified to be associated with variation in vaccine response [reference(s)]	Variation in vaccine response and vaccine: proteins for which single-nucleotide polymorphisms in genes are associated with variations in vaccine responses [reference(s)]
Cytokine responses	BCG (39–46) (169) Measles (90) (167) Pertussis (53–65) (169) Tetanus (64) (169)	Higher IFN-γ production Rubella: A*02-C*07-B*07 (191), A*03-C*04-B*35 (191), DRB1*03-DQA1*05-DQB1*02-DPA1*01-DPB1*03 (191) Higher IL-2 production Rubella: DRB1*04-DQA1*03- DQB1*03-DPA1*01-DPB1*02 (191), DRB1*04-DQA1*03-DQB1*03-DPA1*01-DPB1*04 (191) Higher IL-4 production Rubella: DRB1*15-DQA1*01-DQB1*06- DPA1*01-DPB1*02 (191), DRB1*07-DQA1*02-DQB1*02-DPA1*02-DPB1*11 (191) Higher IL-5 production Rubella: A*02-C*07-B*08 (191) Higher IL-6 production Rubella: A*24-C*07-B*07 (191) Higher IL-10 production Rubella: DRB1*03-DQA1*05-DQB1*02-DPA1*01-DPB1*02 (191) Higher IL-12p40 production Rubella: A*03-C*03-B*40 (191), A*03-C*07-B*07 (191), DRB1*07- DQA1*02-DQB1*03-DPA1*01-DPB1*04 (191) Higher TNF-α production Rubella: A*01-C*07-B*08-DRB1*03-DQA1*05-DQB1*02-DPA1*01-DPB1*04 (190), A*29-C*16-B*44 (191) Lower TNF-α production Rubella: DRB1*13-DQA1*01-DQB1*06-DPA1*01-DPB1*03 (191) Lower IL-2 production Rubella: DRB1*13-DQA1*01- DQB1*06-DPA1*01-DPB1*03 (191) Lower IL-5 production Rubella: DRB1*11-DQA1*05-DQB1*03-DPA1*01-DPB1*02 (191) Lower IL-6 production Rubella: DRB1*03-DQA1*05-DQB1*02- DPA1*01-DPB1*04 (191), AAACGGGGC-DRB1*01-DQA1*01-DQB1*05-DPA1*01-DPB1*04 (190) Lower IL-10 production Rubella: DRB1*03-DQA1*05-DQB1*02-DPA1*01-DPB1*04 (191) Lower IL-12p40 production Rubella: A*02-C*03-B*40 (191)	Higher granulocyte-macrophage colony-stimulating factor (GM-CSF) production Rubella: TLR3 (194) Higher IL-2 production BCG: TLR1, TLR6 (195) Higher IL-4 production Measles: TLR4 (192) Higher IFN-γ production BCG: TLR1, TLR6 (195) Measles: TLR5 (192), TLR6 (192) Rubella: RIG-I (194) Lower IL-10 production Rubella: RIG-I (194) Lower IFN-γ production Rubella: TLR3 (194) Lower TNF-α production Rubella: TLR3 (194) Variations in GM-CSF production Rubella: RIG-I (194), TLR3, TLR4 (194) Variations in IL-2 production Rubella: TLR3 (194), RIG-I (194) Variations in IL-2 production Rubella: RIG-I (194) Variations in TNF-α production Rubella: RIG-I (194)	Variations in GM-CSF production Rubella: CASP8 (194), RARB (194), TRIM5 (194), TRIM22 (194) Variations in IL-2 production Rubella: RARA (194), RARB (194), TRIM5 (194), TRIM22 (194) Variations in IL-4 production TIV: IL-28B (199) Variations in IL-6 production Measles: CD46 (200) Rubella: ADAR (210), PVR (210), TRIM22 (194) Variations in IL-10 production Measles: SLAM (200) Rubella: RARB (194), RXRA (194) Variations in IFN-α production Measles: CD46 (200, 201) Variations in IFN-γ production Rubella: ACO1 (211), butyrophilin (210), IL-10RB/IFNAR1 (210), PTPRD (211), RARB (194), RARG (194), TRIM22 (194) Measles: IL-2 (203), IL-7R (203), IL-10 (203), IL-12RB (204), SLAM (200), DC-SIGN promotor (209) Variations in TNF-α production Measles: CD46 (200) Rubella: TRIM5 (194), VDR (194)

TABLE 4 Results with regard to comorbidities from studies investigating intrinsic host factors that influence vaccine responses

	Variation in vaccine response, vaccine, age group, measurement [reference(s)]			
Type of response	**Celiac disease**	**Diabetes mellitus**	**Chronic renal failure requiring hemodialysis**	**Chronic liver failure**
Humoral responses	Lower antibody production HepA Children: SPRs (225) HepB Infants: SPRs (221) Children: SPRs (219, 220, 222–226, 228, 231, 233) Adults: GMTs (227), SPRs (218, 227) No difference in antibody production HepA Children: GMTs (229), SPRs (229) HepB Children: GMTs (219, 232), SPRs (232) Adults: GMTs (232), SPRs (232) Hib Children: SPRs (219) Measles Children: GMTs (232), SPRs (232) Adults: GMTs (232), SPRs (232) Rubella Children: SPRs (219) Tetanus Children: SPRs (219) TIV Children: GMTs (230), SPRs (230)	Lower antibody production HepB Children: GMTs (232, 238), SPRs (232, 237–239) Adults: GMTs (232, 243–245), SPRs (242–245) Measles Children: SPRs (241) Monovalent influenza vaccine Adults: SCRs (90), SPRs (90) PPV23 Children: SPRs (240) Rubella Children: GMTs (241) No difference in antibody production Diphtheria Children: GMTs (240, 241) Hib Children: GMTs (240) HepB Children: GMTs (572), SPRs (232, 572) Adults: GMTs (572), SPRs (232, 572) Elderly: SPRs (248) Measles Children: GMTs (232, 241), SPRs (232) Adults: GMTs (232), SPRs (232) Rubella Children: SPRs (241) PCV7 Children: GMTs (240) Pertussis Children: SPRs (241) Tetanus Children: GMTs (240, 241)	Lower antibody production Diphtheria Adults: SPRs (250) HepB Adults: SPRs (252) IPV type 2 Children: GMTs (260) Tetanus Adults: GMTs (249), SPRs (249, 250) TIV Adults: GMTs (473), SPRs (473) No difference in antibody production IPV type 1 Children: GMTs (260), SPRs (260) IPV type 2 Children: SPRs (260) IPV type 3 Children: GMTs (260), SPRs (260) Faster weaning of antibodies Diphtheria Adults: (254) HepB Adults: (252, 255) Tetanus Adults: (251)	Higher antibody production Diphtheria Children: GMTs (260) IPV type 1 Children: GMTs (260) IPV type 3 Children: GMTs (260) Lower antibody production HepA Children: GMTs (265) Adults: GMTs (102, 261, 262), SPRs (263, 264) HepB Adults: GMTs, SPRs (242) Children: GMTs (265), SPRs (263, 265) No difference in antibody production Diphtheria Children: SPRs (260) HepA Children: SPRs (265) Adults: SPRs (102, 263) IPV type 1 Children: SPRs (260) IPV type 2 Children: GMTs (260), SPRs (260) IPV type 3 Children: SPRs (260) Tetanus Children: GMTs (260), SPRs (260)
Cytokine responses	Lower cytokine production Tetanus Children: IL-4 (219, 573)	No difference in cytokine responses TIV Children: IL-2 (247), granzyme B (247)		

lower antibody responses to HepB vaccination (218–228, 231–233), with more rapid waning of antibodies (227). A meta-analysis shows that, in retrospective studies, the SCR to HepB vaccination in children with CD is 54%, and that in prospective studies is 66% (compared to 95% in healthy individuals) (234). It has been postulated that the presence of HLA-DQ2 or -DQ8, which confers a genetic predisposition to CD, may be the driver of the lower responses to HepB vaccination in CD patients. However, the presence of HLA-DQ2 is associated with higher antibody responses to HepB vaccination

(55). Nevertheless, HLA-DR3, -DR4, and -DR7, which can also be found in patients with CD (229) and patients with diabetes mellitus (DM), are associated with lower responses to HepB vaccination (183, 184, 235). Children with CD and DM have lower SPRs after HepB vaccination than those of children that have DM only (228), suggesting that gluten might be a factor in decreasing HepB vaccine efficacy, and some studies suggest that the response rate to HepB vaccination correlates with gluten intake (220, 223). Children with CD who are on a strict gluten-free diet have no difference in SPRs to HepB vaccination compared to those of healthy children (222, 226). Apart from lower antibody responses to HepB vaccination, one study also showed that CD patients are less responsive to HepA vaccination (225). However, another study did not find a difference in antibody responses to HepA vaccination in CD patients compared to healthy controls (229). There is also no difference in antibody responses to tetanus (219), measles (236), rubella (219), Hib (219), and TIV (230) vaccination between children with CD and healthy children.

Children with DM have lower antibody responses to HepB (232, 237–239) vaccination, and possibly PPV23 (240), rubella (241), and measles (241) vaccination, but not to diphtheria (240, 241), Hib (240), PCV7 (240), pertussis (241), or tetanus (240, 241) vaccination. Adults with DM also have lower antibody responses to HepB (242–245) vaccination. Adding selenium to the HepB vaccine can increase antibody responses in patients with DM (246). It is unclear whether DM influences the antibody response to TIV vaccination. Some studies report lower responses after vaccination with a monovalent influenza vaccine in adults (90), while studies of elderly people with type II DM show no difference in antibody or cytokine responses to TIV vaccination (247, 248) (Table 4).

Adults with chronic renal failure who are on hemodialysis have lower antibody responses to diphtheria (249–251), HepB (252–255), and tetanus (249–251) vaccination, with faster waning of antibodies (252–255), especially when they suffer from additional diabetes mellitus (256–259). Children on hemodialysis have lower antibody responses to poliovirus type 2 (260). SPR after HepB vaccination is inversely associated with glomerular filtration rate (253). Factors responsible for lower vaccine responses in patients with chronic renal failure include malnutrition, uremia, and a generalized immunosuppressive state. Patients with chronic renal failure benefit from an increased vaccination dose (259).

Adults with chronic liver disease have lower GMTs after HepA vaccination (102, 261, 262) (with similar SPRs [102, 262] or lower SPRs [263, 264]) and lower GMTs and SPRs after HepB vaccination (242) than those of healthy adults. Children with chronic liver disease also have lower GMTs (265) and SPRs (263, 265) after HepB vaccination (265), with no difference in SCRs. However, in contrast, they have higher antibody responses to IPV and diphtheria (260) vaccination (Table 4).

Perinatal Host Factors

Gestational age. Preterm infants are at increased risk of infections, including vaccine-preventable infections. Differences in the immune system which render preterm infants less responsive to vaccination include diminished pathogen recognition by dendritic cells and macrophages and diminished T cell activity (especially Th1 activity) and diminished B cell interaction with T cells (266). Variations in vaccine responses between term and preterm infants depend on the specific vaccine. In comparison to those of term infants, preterm infants have significantly lower antibody levels after the first dose of DTP (267). Significantly lower GMTs also persist after primary immunization with three doses for diphtheria (268), HepB (268–270), Hib (269, 271–275), PCV7 (276, 277), poliovirus type 3 (269), and pertussis (267, 268, 278–280) vaccines. However, preterm infants reach sufficient SPRs for most vaccines (Table 5), with the notable exception of responses to HepB (269), Hib (269, 271–275), pertussis (279), and poliovirus type 3 (281) vaccines. In addition to having lower GMTs and SPRs, preterm infants can also have quicker waning of antibodies, as shown for antibodies produced in response to MCV-C (282) vaccination.

TABLE 5 Results with regard to infant factors from studies investigating perinatal factors that influence vaccine responses

	Timing of response, vaccine response, vaccine, age, measurement [reference(s)]		
Type of response	**Gestational age**	**Birth weight**	**Feeding**
Humoral responses	**After primary immunization with 3 doses (*2 doses)** Higher antibody production in preterm infants than in term infants PCV7 <37 weeks: GMTs (277) for serotypes 19F, 9V, and 4 Lower antibody production in preterm infants than in term infants Diphtheria 31–35 weeks: GMTs (268) <31 weeks: GMTs (268) HepB 24–36 weeks: GMTs (269), SPRs (269) <31 weeks: GMTs (268) <35 weeks: GMTs (270) Hib 24–36 weeks: GMTs (269, 271, 272), SPRs (269, 271, 272) <32 weeks: GMTs (271, 273), SPRs (271, 273) 23–32 weeks: GMTs (274),* SPRs (274)* <30 weeks: GMTs (275), SPRs (275) PCV7 <37 weeks: GMTs (276) IPV type 3 24–36 weeks: GMTs (269) <29 weeks: SPRs (281) Pertussis AGGs 2 and 3 <37 weeks: GMTs (278) aP 28–34 weeks: GMTs (267) FHA 25–35 weeks: GMTs (279), SPRs (279) PCT 31–35 weeks: GMTs (268) <31 weeks: GMTs (268) PT <32 weeks: GMTs (280) 25–35 weeks: GMTs (279), SPRs (279) <31 weeks: GMTs (268) No difference in antibody production between preterm and term infants Diphtheria 24–36 weeks: GMTs, SPRs (269) <32 weeks: GMTs (280) 28–34 weeks: SPRs (267) <37 weeks: GMTs, SPRs (278) 25–35 weeks: SPRs (268) Hib <29 weeks: GMTs (281), SPRs (281) MCV-C <32 weeks: GMTs (273), SPRs (273) 32–36 weeks: GMTs (282) OPV <36 weeks: SPRs (574) IPV type 1 24–36 weeks: GMTs, SPRs (269) <29 weeks: GMTs (281), SPRs (281) IPV type 2 24–36 weeks: GMTs, SPRs (269) <29 weeks: GMTs (281), SPRs (281) IPV type 3 24–36 weeks: SPRs (269) <29 weeks: GMTs (281) Pertussis AGGs 2 and 3 <37 weeks: SPRs (278) aP 28–34 weeks: SPRs (267) FHA 24–36 weeks: GMTs, SPRs (269) <32 weeks: GMTs (280) <37 weeks: GMTs, SPRs (278) PCT 25–35 weeks: SPRs (268)	**After primary immunization with 3 doses** Lower antibody production in VLBW infants than in LBW infants Pertussis (PT): GMTs (285), SPRs (285) Hib: SPRs (285) IPV type 3: GMTs (285) Lower antibody production in LBW infants than in infants with a normal birth weight HepB: SPRs (286) Hib: SPRs (272) No difference in antibody production between VLBW and LBW infants Diphtheria: GMTs (285), SPRs (285) HepB: GMTs (285), SPRs (285) IPV type 1: GMTs (285), SPRs (285) IPV type 2: GMTs (285), SPRs (285) IPV type 3: SPRs (285) Pertussis FHA: GMTs (285), SPRs (285) PRN: GMTs (285), SPRs (285) PT: GMTs (285), SPRs (285) Tetanus: GMTs (285), SPRs (285) No difference in antibody production between VLBW and LBW/normal-birth-weight infants Pertussis FHA: GMTs (279) PT: GMTs (279) No difference in antibody production between LBW and normal-birth-weight infants PCV7: GMTs (277), SPRs (277) Measles: SCRs (287) **After a booster at 18–24 months** Lower antibody production in VLBW infants than in LBW infants Diphtheria: GMTs (285) HepB: GMTs (285), SPRs (285) No difference in antibody production between VLBW and LBW infants Diphtheria: SPRs (285) IPV type 1: GMTs (285), SPRs (285) IPV type 2: GMTs (285), SPRs (285) IPV type 3: SPRs (285) Pertussis FHA: GMTs (285), SPRs (285) PRN: GMTs (285), SPRs (285) PT: GMTs (285), SPRs (285) Tetanus: GMTs (285), SPRs (285)	Higher antibody production in breastfed than in formula-fed infants Diphtheria: IgA % standard plasma in saliva (292), IgG % standard plasma in serum (292) Hib: IgA median antibody titer in serum (291), IgM median antibody titer in serum (291), IgG median antibody titer in serum (291), IgG GMTs in serum (290) OPV: IgA % standard plasma in saliva (292), IgG % standard plasma in serum (289, 292), IgM % standard plasma in stool (292) Tetanus: IgA % standard plasma in saliva (292), IgM % standard plasma in stool (292) Lower responses in breastfed infants than in formula-fed infants OPV: SCRs (295)

(Continued on next page)

TABLE 5 (Continued)

Type of response	Timing of response, vaccine response, vaccine, age, measurement [reference(s)]		
	Gestational age	Birth weight	Feeding
	PRN 24–36 weeks: GMTs, SPRs (269) <32 weeks: GMTs (280) PT 24–36 weeks: GMTs (269), SPRs (269) <37 weeks: GMTs, SPRs (278) Tetanus 24–36 weeks: GMTs (269), SPRs (269) <29 weeks: GMTs (281), SPRs (281) <32 weeks: GMTs (280) 28–34 weeks: SPRs (267) <37 weeks: GMTs, SPRs (278)		

Preterm infants have lower vaccine responses not only after primary immunization but also after booster doses. At 2 to 3 years of age, they have lower antibody responses to HepB (270, 283), Hib (283), and poliovirus type 3 (283) vaccination, and at the age of 5 years, they have lower responses to HepB (283) and pertussis (284) vaccination, as well as reduced lymphoproliferation and cytokine responses in the latter case.

Birth weight. One month after the third dose of DTaP-Hib-IPV-HepB vaccination given at 2, 4, and 6 months, very-low-birth-weight (VLBW; less than 1.5 kg) infants have significantly lower GMTs to aP and poliovirus type 3 and lower SPRs to Hib than infants with a low birth weight (LBW; 1.5 to 2 kg), while both groups have similar GMTs and SPRs after diphtheria, tetanus, and HepB (285) vaccination. However, 1 month after a booster dose given at the age of 18 to 24 months, the SPR to HepB in VLBW infants is lower than that in LBW infants, and there is a trend toward lower GMTs for all other vaccine components (285) (Table 5). Similarly, 1 month after completing a 3-dose HepB schedule given at 0, 1, and 6 months, LBW infants have lower GMTs to HepB vaccine than infants with a normal birth weight (286). A decreasing birth weight is associated with a progressive reduction in antibody responses to Hib (272) vaccination. However, there is no difference in GMTs after a 3-dose schedule of PCV7 vaccine between LBW infants and infants with a normal weight (277) and no correlation between birth weight and SCRs after measles vaccination (287).

In one study, the antibody response to *Salmonella enterica* serovar Typhi vaccination (but not rabies vaccination) in adults was reported to be related to birth weight (288).

Breastfeeding. After routine vaccination, compared to formula-fed infants, breastfed infants have higher serum IgG levels after diphtheria (289), Hib (290, 291), and OPV (289, 292) vaccination, higher salivary IgA levels after tetanus, diphtheria, and OPV vaccination (289), and higher stool IgM levels after tetanus and OPV vaccination (289) (Table 5).

While one meta-analysis summarizing studies on the effect of breastfeeding on the antibody response to oral rotavirus vaccine (ORV) reports reduced SCRs in breastfed infants in all included studies (293), another meta-analysis reports decreased responses in only 3 of 16 studies (294). However, in all the included studies, only one dose of ORV was given, and infants with mixed feeding were sometimes classified as breastfed and sometimes as nonbreastfed. More recent studies show that higher levels of rotavirus-specific IgA in breast milk lead to lower SCRs in infants after ORV (a 2-fold increase is associated with a 22% decrease in SCR) (295). IgA levels in breast milk depend on geographic location: Indian women have higher levels than those in Korean and Vietnamese women and American women (296). Additionally, the neutralizing activity of IgA in breast milk from Indian women is higher than that in breast milk from American women (296). Three studies investigating withholding breastfeeding for an hour before and after ORV showed no effect on rotavirus-specific IgA SCRs in infants (297–299).

Maternal antibodies. Preexisting maternal antibodies inhibit infant antibody responses to vaccination (14) (Table 6). After primary immunization, a 2-fold higher

TABLE 6 Results with regard to maternal factors from studies investigating perinatal factors that influence vaccine responses

Type of response	Vaccine response and vaccine: measurement [reference(s)]			
	Maternal antibodies associated with lower infant responses to vaccination	Maternal high body mass index	Maternal malnutrition	Antenatal steroids
Humoral responses	Lower antibody production HepA: GMTs (305, 306) Diphtheria: GMTs (14) Measles: SCRs (49) OPV: titers (575) ORV: SCRs (295, 296, 307–310) Pertussis PRN: GMTs (14) IPV: GMTs (14) Tetanus: GMTs (14)		Lower antibody production OPV: SPRs (326) ORV: SPRs (326)	Lower antibody production Tetanus: GMTs (280)
Cytokine responses		Lower cytokine production BCG: IL-2 (325)		

maternal antibody level results in approximately one-fourth lower postvaccination GMTs in infants (28% to IPV, 24% to diphtheria, 22% to pertactin, and 13% to tetanus). Maternal antibodies also influence infant vaccine responses after booster doses in the second year of life (14).

A meta-analysis summarizing 16 studies investigating the influence of maternal antibodies on responses to measles vaccination shows that the presence of maternal antibodies decreases SCRs, on average, by 33.2% (49). However, maternal antibodies to measles virus in infants decrease quickly, and by the age of 5 months, only 12% of infants have protective levels. Maternal age is the only factor associated with maternal measles antibody levels (300, 301), while maternal weight has no influence (300). Measles-vaccinated women have significantly lower GMTs than those of women with naturally acquired immunity (301, 302).

Maternal antibodies against HepA in infants remain high during the first 6 months but then drop quickly, with only approximately 37% of infants having protective titers by the age of 12 months (303, 304). When the HepA vaccine is given to infants within the first 6 months of life, GMTs in those without maternal antibodies are significantly higher at the age of 12 to 15 months than those in infants with maternal antibodies. However, there is no difference in SPRs (305, 306). For ORV, transplacental transfer of maternal antibodies (307–309) and transfer of antibodies through breast milk (295, 296, 310) lead to decreased infant vaccine responses, in a dose-dependent matter.

The amount of maternal antibodies transferred to infants depends on several factors, including maternal antibody levels, IgG subclass, gestational age, and placental characteristics (311). The transfer of maternal antibodies can be optimized by maternal vaccination during pregnancy. This strategy is currently recommended for vaccination against tetanus, pertussis, and influenza. However, appropriate timing of vaccination during pregnancy is important. For example, Tdap given during the second trimester of pregnancy leads to significantly higher neonatal antibodies than those obtained when it is given during the third trimester (312).

Maternal infections during pregnancy. Most studies do not find an association between maternal infection with filariae, hookworm, malaria parasites, *Mansonella perstans*, or *Schistosoma mansoni* during pregnancy and infant antibody responses to diphtheria (313, 314), HepB (313–315), Hib (314), pertussis (314), and tetanus (313, 316) vaccination. However, one study shows that maternal infection with malaria parasites, filariae, or hookworm is independently associated with lower infant antibody responses to Hib vaccination (313), while another study shows that maternal infection with *S. mansoni* is associated with lower infant antibody responses to HepB vaccination (317). Maternal malaria during pregnancy is associated with lower infant SPRs after measles vaccination (318). The presence of multiple maternal infections is associated with lower

infant antibody responses to Hib, diphtheria, and tetanus (313) vaccination. In contrast, maternal infection with *Strongyloides* during pregnancy is associated with higher antibody responses to Hib, HepB, and pertussis toxin (PT) (314) vaccination.

Maternal infection with *M. perstans* during pregnancy is associated with higher infant IL-10 responses after BCG and tetanus vaccination, but there are no differences in gamma interferon (IFN-γ), IL-5, and IL-13 (319) production. Maternal infection with filariae (320), *Trypanosoma cruzi* (321), or *S. mansoni* (320) during pregnancy is associated with lower IFN-γ production in children after BCG vaccination, while other helminth infections show no effect on infant responses to BCG vaccination (319, 322, 323). Empiric treatment of mothers with albendazole or praziquantel during pregnancy does not influence infant vaccine responses to BCG (324), diphtheria (314), HepB (314), Hib (314), measles (324), pertussis (314), or tetanus (324) vaccination (Table 7).

Other maternal factors. In infants, cytokine responses to BCG vaccination correlate inversely with maternal body mass index (BMI) (325). On the other hand, maternal malnutrition is associated with lower infant antibody responses to OPV and ORV vaccination, while it does not influence responses to parenteral vaccines (326).

It has been suggested that low maternal education status is associated with higher infant GMTs to tetanus vaccination (327) and lower infant IFN-γ and IL-5 production after tetanus vaccination (319), while a lower maternal socioeconomic status is associated with lower infant IL-10 production after tetanus vaccination (319) (Table 8). However, this might be confounded by other factors, such as malnourishment and nonadherence to vaccination schedules.

Maternal tetanus immunization during pregnancy is associated with higher infant antibody responses to tetanus vaccination, while the presence of a maternal BCG scar is associated with lower infant IL-5 (319), IL-10 (323), and IL-13 (319) responses after BCG vaccination (319).

Infants who are exposed to HIV during pregnancy but remain uninfected have lower IFN-γ, IL-5, and IL-13 responses after tetanus and BCG vaccination (319). Antenatal, but not postnatal, steroids decrease infant antibody production in response to tetanus vaccination (280) (Table 6).

Extrinsic Factors

Infections. Most studies show no difference in antibody responses to MMR vaccination between children with diarrhea (287, 328), fever (287, 328), or afebrile upper respiratory tract infections (URTI) (329–332) and healthy children. However, studies have reported lower SCRs after measles (330) and varicella (331) vaccination for children with URTI (without differences in GMTs), lower GMTs after Hib vaccination in children with fever (333), and lower GMTs and SCRs for children with diarrhea after OPV vaccination (334, 335). Concurrent infection with nonpoliovirus enteroviruses at the time of vaccination with OPV reduces SCRs against poliovirus type 1 but not type 2 or 3 (334) (Table 9).

Children who are infected with Epstein-Barr virus (EBV) have reduced antibody responses to meningococcal polysaccharide (MPV) and measles vaccination. However, infants who are infected with both EBV and cytomegalovirus (CMV) have responses similar to those of uninfected infants, suggesting that the effects of EBV infection might be countered by CMV infection (336). Children who are infected with CMV also have higher GMTs after vaccination with measles vaccine (337), while results from studies investigating vaccine responses in CMV-seropositive adults are conflicting. Studies report higher antibody responses to TIV vaccination in young adults (GMTs) (338) and elderly people (SCRs) (248) who are seropositive for CMV than in seronegative individuals, while other studies show reduced antibody responses (SCRs) (339, 340), lower B and T cell activation (341), and switched memory B cells (339) in response to TIV vaccination in CMV-seropositive individuals (Table 9).

Adults who are infected with HIV have lower SPRs after vaccination with HepA vaccine. A lower viral load and higher CD4 cell count are predictors of a higher response to vaccination (104). Pregnant women who are infected with HIV have lower cytokine

TABLE 7 Results with regard to maternal infections from studies investigating perinatal factors that influence vaccine responses

Type of response	Vaccine response and vaccine: measurement [reference(s)]							
	Filariasis	**Helminths**	**Hookworm**	**Malaria**	***Mansonella perstans***	**Schistosomiasis**	**Strongyloidiasis**	***Trypanosoma cruzi***
Humoral responses	Lower antibody production Hib: GMTs (313) No difference in antibody production Diphtheria: GMTs (313) HepB: GMTs (313) Tetanus: GMTs (313)		Lower antibody production Hib: GMTs (313) No difference in antibody production aP: GMTs (314) Diphtheria: GMTs (313, 314) HepB: GMTs (313, 314) Hib: GMTs (314) Tetanus: GMTs (313)	Lower antibody production Hib: GMTs (313) Measles: SPRs (318) No difference in antibody production Diphtheria: GMTs (313) HepB: GMTs (313) Tetanus: GMTs (313, 316)	No difference in antibody production aP: GMTs (314) Diphtheria: GMTs (314) HepB: GMTs (314) Hib: GMTs (314)	Lower antibody production HepB: GMTs (317) No difference in antibody production aP: GMTs (314) Diphtheria: GMTs (313, 314) HepB: GMTs (313–315) Hib: GMTs (314) Tetanus: GMTs (313)	Higher antibody production Hib: GMTs (314) HepB: GMTs (314) PT: GMTs (314)	
Cytokine responses	Lower cytokine production BCG: IFN-γ (320)	No difference in cytokine production BCG (319, 322, 323)			Higher cytokine production BCG: IL-10 (319) Tetanus: IL-10 (319) Lower cytokine production BCG: IL-5 (323)	Lower cytokine production BCG: IFN-γ (320)		Lower cytokine production BCG: IFN-γ (321)

TABLE 8 Results with regard to other maternal factors from studies investigating perinatal factors that influence vaccine responses

Type of response	Vaccine response and vaccine: measurement [reference(s)]			
	Low maternal education status	Low maternal socioeconomic status	Maternal treatment with albendazole or praziquantel during pregnancy	Maternal vaccination
Humoral responses	Higher antibody production Tetanus: GMTs (327)		No difference in antibody production aP: GMTs (314) Diphtheria: GMTs (314) HepB: GMTs (314) Hib: GMTs (314)	Maternal tetanus vaccination during pregnancy Higher antibody production (GMTs) to tetanus in infants (319)
Cytokine responses	Lower cytokine production Tetanus: IFN-γ (319), IL-5 (319)	Lower cytokine production Tetanus: IFN-γ (319)		Presence of maternal BCG scar associated with lower production in infants IL-5 (319) IL-10 (323) IL-13 (319)

responses to BCG (319, 323) and tetanus (319) vaccination. Infants who are infected with HIV have lower cytokine responses after vaccination with BCG (319, 323), measles (337), and tetanus (319) vaccines and lower antibody responses after vaccination with measles vaccine (318). Children who are infected with HIV have quicker waning of antibodies after vaccination with HepA vaccine (342).

Individuals who are chronically infected with either hepatitis B or hepatitis C virus have lower antibody responses to HepA vaccination (102, 263, 343, 344).

Parasites. Infants who are symptomatically infected with malaria parasites have lower antibody responses to Hib (333), measles (318), MCV-C (345), *Salmonella* Typhi (intradermal), and tetanus (345–347) vaccination and lower cytokine responses (IFN-γ, IL-5, and IL-13) after vaccination with tetanus (319) and BCG (319, 323) vaccines (Table 10). Children with asymptomatic malaria have lower GMTs after MCV-C (94, 348) and aP (349) vaccination but no difference in antibody responses to tetanus vaccination (350, 351). Malaria prophylaxis given to children prior to vaccination has no influence on GMTs or SCRs after diphtheria (352–355), IPV (355), measles (352, 353, 356), OCV (357), OPV (353), pertussis (352), *Salmonella* Typhi (353, 357), or tetanus (352–355, 358, 359) vaccination. Malaria prophylaxis also has no influence on the size of the tuberculin skin reaction after BCG vaccination (353). However, GMTs after vaccination with MCV-A and MCV-C are (transiently) higher in children who are on malaria prophylaxis (348, 353).

Individuals who are infected with *Onchocerca volvulus* produce fewer antibodies and have less proliferation of mononuclear cells and lower IFN-γ production (360) after tetanus vaccination, and individuals who are infected with *S. mansoni* produce less IFN-γ (361) after tetanus vaccination. In children and adults with *Ascaris lumbricoides* infection, antibody and cytokine responses (IFN-γ and IL-2) to OCV are diminished but can be partially restored by albendazole treatment prior to vaccination (362, 363). Childhood helminth infections are not associated with cytokine responses after BCG vaccination. Empiric quarterly albendazole treatment during the first 5 years of age leads to less IFN-γ and IL-13 production after vaccination with BCG (323). In contrast, albendazole treatment in individuals with proven helminth infection leads to more T cell proliferation (364) and IFN-γ (364, 365) and IL-12 (365) production after BCG vaccination but to less transforming growth factor beta (TGF-β) and concanavalin A production (365) (Table 11). Infants who are congenitally infected with *Trypanosoma cruzi* have stronger *in vitro* IFN-γ responses after vaccination with diphtheria, HepB, and tetanus vaccines (321) (Table 10).

Antibiotics, probiotics, and prebiotics. There are no studies of humans that have investigated the effects of antibiotics on vaccine responses. However, a study in mice showed that administration of clarithromycin or doxycycline leads to lower antibody responses after vaccination with a HepB, tetanus, or PPV23 vaccine, while administra-

TABLE 9 Results with regard to symptoms or infections from studies investigating extrinsic factors that influence vaccine responses

Type of response	Vaccine response, vaccine, age group, measurement [reference(s)]						
	Diarrhea	**Fever**	**URTI**	**CMV infection**	**EBV infection**	**Hepatitis B virus infection**	**Hepatitis C virus infection**
Humoral responses	Lower antibody production OPV Infants: GMTs (335) Children: SCRs (334) No difference in antibody production Measles Infants: SCRs (287) Children: GMTs (328), SCRs (328)	Lower antibody production Hib Children: GMTs (333) No difference in antibody production Measles Infants: SCRs (287)	Lower antibody production Measles Infants: SCRs (330) Varicella Children: SPRs (331) No difference in antibody production Measles Infants: SCRs (287) Children: GMTs (329, 331), SCRs (329, 331, 332) Mumps Children: GMTs (329, 331), SCRs (329, 331) Rubella Children: GMTs (329, 331), SCRs (329, 331, 332) Varicella Children: GMTs (331)	Higher antibody production Influenza Adolescents: GMTs (338) Elderly: SCRs (248) Lower antibody production Measles Infants: GMTs (337) Influenza Adults: SCRs (339, 340)	Lower antibody production Measles Infants: median IgM and IgG levels (336) MPV Infants: median IgM and IgG levels (336)	Lower antibody production HepA Adults: SPRs (263) HepB Adults: SPRs (263)	Lower antibody production HepA Adults: GMTs (343), SPRs (102, 263, 343) HIV-coinfected adults: SPRs (344) HepB Adults: SPRs (263)
Cellular responses				Lower cellular responses TIV Adults: switched memory B cells (339) Adults: B and T cell activation (341)			

TABLE 10 Results with regard to parasitic infections from studies investigating extrinsic factors that influence vaccine responses

	Vaccine response, vaccine, age group, measurement [reference(s)]					
Type of response	**HIV infection**	***Ascaris lumbricoides***	**Malaria**	***Onchocerca volvulus***	***Schistosoma mansoni***	***Trypanosoma cruzi***
Humoral responses	Lower antibody production HepA Adults: SPRs (104) Measles Infants: SPRs (318)	Lower antibody production OCV Children: GMTs (363), SCRs (363)	Lower antibody production Hib Children: GMTs (333) MCV-C Children: GMTs (94, 345, 348) Measles Infants: SPRs (318) PT Infants: GMTs (349) *Salmonella* Typhi Children: GMTs (345, 346) Tetanus Children: GMTs (346, 347) No difference in antibody production Tetanus Children: GMTs (351)	Lower antibody production Tetanus Adults: GMTs (360)		
Cellular responses				Lower cellular responses Tetanus Adults: proliferation of mononuclear cells (360)		
Cytokine responses	Lower cytokine production BCG Infants: IFN-γ (319, 323), IL-5 (319, 323), IL-10 (319), IL-13 (319, 323) Women: IFN-γ (319, 323), IL-5 (319), IL-13 (319, 323) Measles Infants: IFN-γ (337) Tetanus Infants: IFN-γ (319), IL-5 (319), IL-13 (320) Women: IFN-γ (319), IL-5 (319), IL-13 (319)	Lower cytokine production OCV Adults: IFN-γ (362), IL-2 production (362)	Lower cytokine production BCG Women: IFN-γ (319, 323), IL-5 (319), IL-13 (319) Tetanus Women: IFN-γ (319), IL-5 (319), IL-13 (319)	Lower cytokine production Tetanus Adults: IFN-γ (360)	Lower cytokine production Tetanus Adults: IFN-γ (361)	Higher cytokine production Diphtheria Women: IFN-γ (321) HepB Women: IFN-γ (321) Tetanus Women: IFN-γ (321)

TABLE 11 Results with regard to antiparasitic treatment from studies investigating extrinsic factors that influence vaccine responses

	Vaccine response, vaccine, age group, measurement [reference(s)]				
Type of response	**Responses after treatment with albendazole**	**Responses on prophylaxis with amodiaquine**	**Responses on prophylaxis with atovaquone-proguanil**	**Responses on prophylaxis with chloroquine**	**Responses on prophylaxis with sulfadoxine-pyrimethamine**
Humoral responses	Higher antibody production OCV, *A. lumbricoides* Children: GMTs (363)	No difference in antibody production Diphtheria Infants: median titers (355) Children: GMTs (352), SCRs (352) IPV Infants: median titers (355) Measles Children: GMTs (352), SCRs (352), SPRs (356) Pertussis Children: GMTs (352), SCRs (352) Tetanus Infants: median titers (355) Children: GMTs (352), SCRs (352), titers (358, 359)	No difference in antibody production OCV Children: GMTs (357) *Salmonella* Typhi Children: GMTs (357)	Higher antibody production MCV-A Children: GMTs (348, 353) MCV-C Children: GMTs (348, 353) No difference in antibody production Diphtheria Children: GMTs (353) Measles Children: GMTs (353) OPV Children: GMTs (353) *Salmonella* Typhi Children: GMTs (353) Tetanus Children: GMTs (352, 353), SCRs (352)	No difference in antibody production Diphtheria Infants: SCRs (354) Measles Infants: SCRs (354) Tetanus Infants: SCRs (354)
Cellular responses	Higher cellular response BCG, any helminth Adults: T cell proliferation (364)			No difference in cellular response BCG Children: tuberculin skin test (353)	
Cytokine responses	Higher cytokine production BCG, any helminth Adults: IFN-γ (364, 365), IL-2 (365), IL-12 (365) OCV, *A. lumbricoides* Adults: IL-2 (362) Lower cytokine production BCG, any helminth Adults: concanavalin A (365), TGF-β (365) BCG, empiric treatment Female adults: IFN-γ (323), IL-13 (323)				

TABLE 12 Results with regard to microbiota from studies investigating extrinsic factors that influence vaccine responses

Type of response	Bacterium/bacterial group, age group, affected vaccine response (reference)		
	Higher relative abundance in intestinal microbiota associated with higher vaccine responses	**Higher relative abundance in intestinal microbiota associated with lower vaccine responses**	**Higher relative abundance in nasopharyngeal microbiota associated with higher vaccine responses**
Humoral responses	Phylum *Actinobacteria* Infants: OPV (385), HepB (385) Phylum *Firmicutes* Infants: ORV (386)	Phylum *Proteobacteria* Infants: OPV (385) Phylum *Bacteroidetes* Infants: ORV (386)	*Bacteroides ovatus* Adults: LAIV (390) *Lactobacillus helveticus* Adults: LAIV (390) *Prevotella melaninogenica* Adults: LAIV (390) *Streptococcus infantis* Adults: LAIV (390) *Veillonella dispar* Adults: LAIV (390)
Cellular responses	Phylum *Actinobacteria* Infants: BCG (385), OPV (385), tetanus (385) Phylum *Firmicutes* Adults: *Salmonella* Typhi (387)	Phylum *Proteobacteria* Infants: BCG (385), HepB (385), OPV (385), tetanus (385)	

tion of ampicillin leads to higher antibody responses after vaccination with a live attenuated *Salmonella* Typhi vaccine (366). A study in calves showed that concurrent administration of oxytetracycline leads to lower antibody responses to subcutaneous vaccination with *Brucella abortus* vaccine (367).

The effects of probiotics on vaccine responses are detailed in a recent systematic review (368). A beneficial effect of probiotics has been reported for responses to diphtheria (369), HepA (370), Hib (371), IPV (372), OCV (373), ORV (374), OPV (375), and TIV (376–380) vaccination. However, the choice of probiotic strains and dose as well as the duration and timing of administration varied largely between studies.

Studies investigating the effects of nutritional supplements containing a mix of probiotics (*Lactobacillus paracasei* [381] or *Bifidobacterium longum* bv. *infantis* [341, 382]) and prebiotics (fructo-oligosaccharides [381] or gluco-oligosaccharide [341, 382]) show no effect of the supplements on antibody responses to TIV (381–383) or PPV23 (381, 383) vaccination or on B or T cell responses (341) to TIV vaccination.

Microbiota. There is an association between the intestinal microbiota and vaccine responses (384). In infants, a higher relative abundance of actinobacteria (especially the species *B. longum*) has been associated with either higher antibody or cellular vaccine responses to BCG (385), HepB (385), IPV (372), OPV (385), and tetanus (385) vaccination. In contrast, a higher relative abundance of proteobacteria (especially *Pseudomonadales*) has been associated with lower responses to these vaccines (385). Additionally, a higher relative abundance of *Firmicutes* bacteria (families *Lachnospiraceae* and *Ruminococcaceae*) has been associated with higher humoral responses to ORV (386) in infants and cellular responses to *Salmonella* Typhi (387) in adults. Additionally, in infants, one study found a higher relative abundance of *Bacteroidetes* organisms to be associated with lower humoral responses to ORV (386), while another study did not find any association between the composition of the intestinal microbiota and responses to ORV (388) (Table 12). Children with small bowel bacterial overgrowth have reduced antibody responses to OCV (389).

The one study which investigated the influence of the respiratory microbiota on vaccine responses shows a positive association between the presence of *Bacteroides ovatus*, *Lactobacillus helveticus*, *Prevotella melaninogenica*, *Streptococcus infantis*, and *Veillonella dispar* in the nasopharynx and influenza virus-specific H1 IgA levels in nasal washings after vaccination with live attenuated influenza virus (LAIV) (390).

Preexisting immunity. Individuals with higher prevaccination tetanus antibody titers have higher SPRs after booster vaccination (60), while the antibody response to diphtheria is not affected by prevaccination titers (391). Similarly, the antibody response to TIV is positively associated with prevaccination titers (93). Elderly people who have low antibody titers against influenza virus before vaccination might not seroconvert after one dose of TIV (392). Further, priming with an antigen different from that included in the TIV vaccine leads to lower SCRs and GMTs (393, 394) than those obtained after priming with similar antigens. Further evidence that preexisting immunity influences vaccine responses comes from studies showing that individuals who have antibodies against flaviviruses have higher antibody responses to dengue fever vaccination (95). Previous exposure to Hib-like environmental bacteria increases antibody responses to Hib vaccination (327). In contrast, there is evidence that lower cytokine production after BCG vaccination can be explained partly by previous exposure to other mycobacteria (395–397). However, this is not the case in all studies (398). The evidence for antibody responses to HepB vaccination is also conflicting, with one study showing higher antibody responses in those who are anti-HBc positive (242) and another showing lower responses (72). For OCV, SCRs have been observed to be lower for individuals with preexisting immunity (399).

Behavioral Factors

Smoking. Smoking leads to lower antibody responses to HepB vaccination in some (66, 68, 69, 74, 75, 78, 80, 400) but not all studies (81, 100, 401, 402) and to increased antibody responses to YF vaccination (157). Smoking has no influence on GMTs after human papillomavirus (HPV) vaccination, but it increases the risk of having low-avidity antibodies after vaccination (403). Smokers have higher SCRs after vaccination with LAIV, but waning of antibodies is quicker in smokers than in nonsmokers after vaccination with LAIV and TIV (404) (Table 13).

Alcohol consumption. Alcohol intake has been found not to influence antibody responses to HepA (405) or HepB (68, 69, 81, 402, 406) vaccination but might influence responses to pneumococcus vaccination (142). After vaccination with PPV23, alcoholics have lower SCRs to serotypes 3, 4, 7F, 8, and 19F (however, this is significant only for serotypes 3 and 19F) (142) (Table 13).

Exercise. A small study showed that antibody responses to tetanus vaccination were higher in runners vaccinated after they completed a marathon than in a nonrunner control group (407). However, a larger study found no differences in antibody responses to diphtheria, tetanus, and PPV23 vaccines given to triathletes after they completed a race compared to the responses in triathletes vaccinated when they had not been exercising or in vaccinated sedentary controls (408). A further study reports higher GMTs to TIV (only to A/Panama [H3N2]) in females who used an ergometer in the 45 min before vaccination (409), and one study showed that active participants over the age of 62 years (defined as more than 20 min of vigorous exercise three or more times per week) had higher antibody responses to TIV than those of sedentary participants (410), while other studies with interventions to increase physical activity in adults do not show an association between increasing exercise and antibody responses to TIV (411) or PPV23 (412) vaccination (Table 13).

One study showed that eccentric exercise of the arm before administration of TIV leads to increased interferon gamma production (with the increase in cytokine production correlating with the increase in arm circumference) in males and antibody production in females (124). The increase in antibody response to TIV vaccination through exercise varies among different vaccine strains, with low-immunogenicity strains being particularly responsive to augmentation through exercise (127). However, a follow-up study could not confirm an association between eccentric exercise of the arm and the humoral or cellular vaccine response to TIV (413) (Table 13).

Acute psychological stress. In elderly people, positive mood on the day of vaccination is associated with higher antibody responses to TIV (414). In contrast, mental stress before vaccination leads to higher GMTs after TIV vaccination in females (only to

TABLE 13 Results from studies investigating behavioral factors that influence vaccine responses

	Vaccine response, vaccine, age group, task or characteristic, measurement [reference(s)]					
Type of response	**Smoking**	**Alcohol consumption**	**Exercise**	**Acute psychological stress**	**Chronic psychological stress**	**Sleep deprivation**
Humoral responses	Higher antibody production LAIV Adults: SPRs (404) YF Adults: SPRs (157) Lower antibody production HepB Adults: GMTs (66, 68, 69, 74, 75, 78, 80, 400), SCRs (66, 68, 69, 74, 75, 78, 80, 400), SPRs (66, 68, 69, 74, 75, 78) Quicker weaning of antibodies LAIV Adults: SPRs (404) TIV Adults: SPRs (404) Lower avidity of antibodies HPV Female adults (403) No difference in antibody production HepA Adults: SPRs (405) HepB Adolescents: SPRs (401) Adults: GMTs (81, 100) Pregnant women: SCRs (402) HPV Female adults: GMTs (403)	Lower antibody production PPV23 Adults: GMTs (142), SPRs (142) No difference in antibody production HepA Adults: SPRs (405) HepB Adults: GMTs (69, 81, 406), SCRs (406), SPRs (68, 69, 406) Pregnant women: SCRs (402)	Higher antibody production Tetanus Male adults, run: % standard plasma (407) TIV Female adults, eccentric arm exercise: GMTs (124) Female adults, ergometer: GMTs (409) Elderly, vigorous exercise: GMTs (410) No difference in antibody production Diphtheria Adult males, triathlon: GMTs (408) Tetanus Adult males, triathlon: GMTs (408) TIV Adult males, eccentric arm exercise: GMTs (413) Adults, increased exercise: GMTs (411) PPV23 Adult males, triathlon: GMTs (408), increased exercise (412)	Higher antibody production MCV-A Male adults, mental task: GMTs (139) TIV Female adults, mental task: GMTs (409) Elderly, good mood on day of vaccination: GMTs (414)	Higher antibody production HepB Adolescents, chronic stress: GMTs (435) Lower antibody production HepB Adolescents, stressful life events: SCRs (431) Adolescents, chronic stress: GMTs (432, 433), SPRs (430) MCV-C Adolescents, perceived stress: GMTs (434) MPV-C Adolescents, stressful life events: GMTs (423) PPV23 Children, kindergarten entry (441): GMTs Elderly, chronic stress: GMTs (420) Rubella Adults, low self-esteem: GMTs (438) TIV Adolescents, stressful life events: GMTs (423) Adolescents, loneliness: GMTs (424) Adults, perceived stress: GMTs (411, 421, 422) Elderly, chronic stress: GMTs (419), SCRs (416–418) Elderly, perceived stress: GMTs (410) No difference in antibody production HepB Adolescents, chronic stress: GMTs (437), SPRs (437), titers (436, 437) TIV Adults, chronic stress: GMTs (425, 426) MPV-A Adolescents, stressful life events: GMTs (423)	Lower antibody production HepA Adults, night after vaccination: GMTs (443) Adult males, night after vaccination: GMTs HepB Adults, 7 nights around vaccination: GMTs (442), SPRs (442) TIV Adult males: GMTs 7 nights after vaccination (445) No difference in antibody production TIV Elderly: GMTs (414) Adults with obstructive sleep apnea: GMTs (446), SCRs (446)

(Continued on next page)

TABLE 13 (Continued)

	Vaccine response, vaccine, age group, task or characteristic, measurement [reference(s)]					
Type of response	**Smoking**	**Alcohol consumption**	**Exercise**	**Acute psychological stress**	**Chronic psychological stress**	**Sleep deprivation**
Cellular responses					Lower cellular responses HepB Adolescents, stressful life events: blastogenic response (431) TIV Adults, chronic stress: specific CD8 T cells (425)	Lower cellular responses HepA Specific Th cells (444)
Cytokine responses			Higher cytokine production TIV Males, eccentric arm exercise: IFN-γ (124) No difference in cytokine production TIV Adult males, eccentric arm exercise: IFN-γ (413)		Higher cytokine production TIV Elderly, chronic stress: IL-6 production (419) Lower cytokine production TIV Elderly, chronic stress: IL-1β (416, 417) Elderly, chronic stress: IL-2 (416, 417) Elderly, perceived stress: IL-2 (410) No difference in cytokine production TIV Adults, chronic stress: IFN-γ (426) Adults, chronic stress: IL-4 (426) Elderly, chronic stress: IL-6 (416)	

A/Panama [H3N2]) (409) and to higher GMTs to MCV-A in males (139). Individuals who have greater blood pressure reactions (with evidence of delayed diastolic blood pressure recovery) toward the end of a mental arithmetic stress task that causes aversive stimuli have higher SCRs after vaccination with MPV-A (415) and TIV (to A/Panama [H3N2] and B/Shandong) (Table 13).

Chronic psychological stress. Many studies report (mostly negative) associations between chronic psychological stress and vaccine responses. For example, elderly people who suffer from stress by being caregivers of relatives with dementia have lower antibody responses (416–419), less IL-1β and IL-2 production (410, 416, 417), and more IL-6 production (419) after vaccination with TIV, as well as lower antibody responses after vaccination with PPV23 (420). In contrast, greater optimism in elderly people is associated with higher antibody responses (411) and more IL-10 production (410) after vaccination with TIV. Adults with high perceived stress, stressful life events, or loneliness also have lower antibody (410, 421–424) and cellular (425) responses after vaccination with TIV. This is not the case for adults who care for patients with multiple sclerosis (426). Responses to influenza A/H1N1 and B viruses appear to be more sensitive to the influence of psychological stress than those to A/H3N2 viruses (427). Having better social support or being married is associated with higher antibody responses to HepB (417) and TIV (423, 428) vaccination, while bereavement is associated with lower antibody responses to TIV (428) (however, one study reports lower antibody responses to TIV vaccination in patients with better social support [429]). Mindfulness-based stress reduction exercises do not influence antibody responses to TIV vaccination (411).

Young adults with stressful life events, chronic stress, and a low level of psychological well-being can have lower antibody responses to HepB (430–433) and MCV-C (434) vaccination. However, in contrast, one study shows higher antibody responses to HepB vaccination in young adults with chronic stress (435), and some studies do not find any associations between psychological stress and antibody responses to HepB vaccination (436, 437). Antibody responses might also be influenced by coping mechanisms. For example, individuals who accept the reality of stressful situations have higher antibody responses to HepB vaccination, while individuals who cope by substance use (430) or have high trait negative affect (436) have lower responses. High internalizing behavior, neuroticism, and low self-esteem are associated with lower antibody responses to rubella vaccination (438), while children with internalizing mood symptoms (depressive or anxious symptoms) have higher antibody responses to MCV-4 (439). One study found no association between coping mechanisms and antibody responses to HepB vaccination (432).

Observed negative/conflict behaviors in an interaction task between parents and children predicts lower antibody responses to serotype C after MCV-4 vaccination in children (440). Children who have higher salivary cortisol levels after starting kindergarten have lower antibody responses to PPV23 (441) (Table 13).

Sleep. Short sleep duration, but not subjective sleep quality, in the week around vaccination is associated with lower antibody responses to HepB vaccination (442). Deliberate sleep deprivation during the night after HepA vaccination is associated with lower antibody levels (443, 444) and specific Th cell responses (444), while high sleep slow-wave activity is associated with higher antibody responses (444). Deliberate sleep deprivation 1 week after vaccination with TIV is also associated with lower antibody responses (445), while no association is found between sleep duration (414) or obstructive sleep apnea (446) and antibody responses to TIV vaccination (Table 13).

Nutritional Factors

Body mass index. Many studies in adults show that an increase in body mass index (BMI) is inversely correlated with antibody responses to HepA (61, 447) and HepB (61, 66, 68, 77, 78, 80, 100, 259, 401, 402, 448–454) vaccination. After vaccination with TIV, an increase in BMI is initially correlated with higher antibody responses. However, 12 months after vaccination, a higher BMI is associated with a greater decline in

antibodies, and obese individuals also have fewer specific CD8 T cells and less IFN-γ production (449) (Table 14).

Nutritional status. Many vaccine responses are not influenced by malnourishment. However, malnourished children are reported to have lower antibody responses to HepB (455), MPVS (456), measles (318, 457–459), OPV (335), pertussis (460), *Salmonella* Typhi (461), and tetanus (462) vaccination. Additionally, malnourished children have smaller tuberculin skin reactions after BCG vaccination (463–465) (Table 14).

Micronutrients (vitamins A, D, and E and zinc). Vitamin D plays an important role in innate, humoral, and cellular immune responses (466). However, its role in influencing vaccine responses is not clear (466). Most studies reporting on the effects of vitamin D on vaccine responses have investigated responses to TIV. The results of these studies are conflicting (Table 14). In adults, there is no association between vitamin D levels or administration of vitamin D and antibody responses to TIV (467–469). In children, some studies find no association between vitamin D levels or administration of vitamin D and antibody responses to TIV (470, 471), while others show a trend toward decreased SPRs against TIV in children with vitamin D deficiency (472). In contrast, after vaccination with LAIV, higher antibody responses against two influenza B virus strains were observed in children with low vitamin D levels, while there was no association between vitamin D levels and GMTs against the A strain of the LAIV vaccine (471). In adult dialysis patients, parenteral calcitriol treatment leads to higher antibody responses to TIV (473). Additionally, there is also a clear association between vitamin D deficiency in hemodialysis patients and diminished antibody responses to HepB vaccine (474). In children with idiopathic nephrotic syndrome, there is no correlation between vitamin D levels and antibody responses to PPV23 (475). In asplenic patients vaccinated against Hib, MCV-C, and PCV7, there is no correlation between vitamin D levels and vaccine antibody levels (476). Adults receiving vitamin D supplementation before a booster dose of tetanus have higher antibody levels against tetanus (477). Infants receiving supplementation with vitamins A and D have stronger tuberculin skin reactions (478) and lower IFN-γ responses after BCG vaccination.

Studies investigating coadministration of vitamin A and measles vaccine also report conflicting results. Vitamin A given simultaneously with a measles vaccine at 6 months of age leads to lower SCRs (154), but only in infants with maternal antibodies. Vitamin A given simultaneously with measles vaccination at 9 months of age does not lead to a difference in GMTs and SCRs at the age of 12 months (479) but does lead to higher GMTs at the ages of 18 months (35) and 6 to 8 years (480), especially in boys. Vitamin A given simultaneously with measles vaccination at 9 months of age to malnourished infants leads to significantly higher GMTs (479). In children with and without vitamin A deficiency, there is no difference in antibody responses to diphtheria and tetanus vaccination (481). In elderly people who are not vitamin deficient, there is no association between levels of vitamin A, vitamin E, or zinc and antibody responses to TIV (482). Polymorphisms of vitamin A and D receptor are associated with lower antibody responses to HepB vaccination (483) and with variations in cytokine responses after rubella and measles vaccination (194, 484).

Enteropathy. Enteropathy is defined as intestinal inflammation not necessarily associated with diarrhea. It occurs more frequently in individuals exposed to poor sanitary conditions. It is often proposed that enteropathy is one of the mechanisms behind the lower effectiveness of oral vaccines in developing countries. However, only one study has investigated the effect of enteropathy on vaccine responses. That study found that infants with enteropathy have lower SPRs against OPV and ORV but not against parenteral vaccines (326).

Environmental Factors

Rural versus urban environment. Children living in rural areas have higher antibody responses to tetanus (351) and an experimental malaria vaccine (485, 486). They have a Th1-skewed response (IL-5 production) to tetanus and TIV vaccination, while children living in semiurban areas have a Th2-skewed response (IFN-γ production) (351, 487).

TABLE 14 Results from studies investigating nutritional factors that influence vaccine responses

	Vaccine response, vaccine, age group, measurement [reference(s)]			
Type of response	**Higher body mass index**	**Malnourishment**	**Low vitamin D levels**	**Enteropathy**
Humoral responses	Higher antibody production TIV Adults: GMTs (449) HepB Adults: GMTs (101) Lower antibody production HepA Adults: GMTs (447), SCRs (447) Elderly: GMTs (61), SPRs (61) HepB Children: GMTs (448) Adolescents: SPRs (401), titers (453) Adults: GMTs (77, 100, 449), SCRs (80, 450), SPRs (66, 68, 77, 78, 450, 454) Women: SPRs (451) Elderly: GMTs (61), SPRs (61) Pregnant women: SCRs (402) Dialysis patients: SPRs (259) TIV Adults: GMTs (449) No difference in antibody production HepA (61, 447) Adults: SPRs (405)	Lower antibody production HepB Children: GMTs (455), SPRs (455) MPVs A and C Children: GMTs (456) Measles Children: GMTs (457, 458), SCRs (458, 459), SPRs (318) OPV Infants: GMTs (335) Pertussis (PT) Infants: GMTs (460) *Salmonella* Typhi Children: GMTs (461), SPRs (461) Tetanus Children: GMTs (462) No difference in antibody production Diphtheria Infants: GMTs (335) Children: GMTs (462, 576), SPRs (576) HepB Infants: GMTs (162) Children: GMTs (577), SPRs (577) Hib Infants: GMTs (162) Measles Infants: GMTs (335) Children: GMTs (576, 578), SCRs (287, 578–580), SPRs (576) MCV-C Children: GMTs (94) MPVs A and C Children: GMTs (576), SPRs (576) OPV Children: GMTs (576), SPRs (576) PPV23 Children: SPRs (122) Rabies Children: SPRs (122) *Salmonella* Typhi Children: GMTs (576), SPRs (576) Smallpox Children: GMTs (578), SCRs (578) Tetanus Infants: GMTs (335) Children: GMTs (457, 462, 576, 581), SPRs (576), titers (359)	Higher antibody production LAIV B strain Children: GMTs (471) Lower antibody responses TIV Children: SPRs (472) No difference in antibody production HepB Adults with chronic kidney disease: GMTs (474), SPRs (474) Hib Asplenic adults: GMTs (476) LAIV A strain Children: GMTs (471) MCV-C Asplenic adults: GMTs (476) PCV7 Asplenic adults: GMTs (476) PPV23 Children with nephrotic syndrome: GMTs (475) TIV Children: GMTs (470, 471), SCRs (470), SPRs (470) Adults: SCRs (467), SPRs (467) HIV-infected adults: SCRs (469), SPRs (469)	Lower antibody production OPV Infants: SPRs (326) ORV Infants: SPRs (326) No difference in antibody production Diphtheria Infants: SPRs (326) Hib Infants: SPRs (326) Measles Infants: SPRs (326) Tetanus Infants: SPRs (326)
Cellular responses	Lower cellular responses TIV Adults: specific CD8 T cells (449)	Lower cellular response BCG Children: size of tuberculin skin reaction (463–465) No difference in cellular responses Tetanus Children: lymphoproliferation (582)		
Cytokine responses	Lower cytokine production TIV Adults: IFN-γ (449)			

In contrast, humoral and cellular responses to TIV are lower in children living in rural areas than in those living in semiurban areas (487). Similarly, antibody responses to HepB vaccination (161, 486, 488) and cytokine responses after vaccination with BCG (323) are lower in children and adults living in rural areas.

Geographic location. Children living in developing countries have higher antibody responses to Hib (489), diphtheria (489), PCV7 (490), and pertussis (489) vaccination but lower antibody responses to measles (491–493), OCV (494), OPV (495, 496), and *Salmonella* Typhi (497) vaccination. Adults in developing countries have lower antibody responses to HepB vaccination (498). Children living in developed countries have a Th2-skewed response to BCG vaccination, with more IFN-γ production (396, 398, 499, 500), while children in developing countries have a Th1-skewed response (499).

Season. There is an association between month of administration and antibody responses to pertussis (460), PPV23 (146), rabies (146), and *Salmonella* Typhi (146) vaccination but no association between month of vaccine administration and antibody responses to diphtheria (146), HepB (146), and tetanus (146) vaccination (Table 15). African infants born in the wet season have stronger CD154 vaccine responses to BCG than those of infants born in the dry season (325). In adolescents, antibody responses (GMTs) to HepB vaccination are lower in individuals who receive their first and second doses in summer than in those who receive them in winter. However, after the third dose, no statistically significant difference in GMTs is found. It has been suggested that these variations in vaccine responses may be explained through differences in exposure to UV irradiation (501). Nevertheless, exposing healthy volunteers to UVB on five consecutive days before HepB vaccination does not lead to a difference in GMTs or cellular vaccine responses (in a lymphocyte stimulation test) between UVB- and non-UVB-exposed individuals (502).

Family size. A larger number of people living in the household is associated with superior antibody responses to Hib vaccine (327).

Toxins. One study compared vaccine responses in lead-exposed children with metabolic impairment to those in healthy children and did not find a difference in antibody responses to tetanus (503). Another study showed that early-life arsenic exposure leads to decreased antibody levels to mumps virus after vaccination with MMR (504). It has also been suggested that pre- and postnatal (breast milk) exposure to polychlorinated biphenyls and dioxins leads to lower antibody responses to measles and mumps viruses (505).

Vaccine Factors

Vaccine type, product, and strain. Immune responses vary widely with different vaccine types and products. For example, live vaccines usually induce high vaccine responses leading to life-long protection, often after just one dose, while inactivated, subunit, or toxoid vaccines usually require several doses, including booster doses, to achieve similar protection. Responses to different subunit vaccines also vary. Polysaccharide vaccines induce a T cell-independent vaccine response which does not induce immune memory and is therefore short-lived. Such vaccines are not protective in children under 2 years of age and do not decrease nasopharyngeal carriage. In contrast, polysaccharide-protein-conjugated vaccines have superior immunogenicity, protect infants under 2 years of age, and reduce nasopharyngeal carriage. The responses to similar vaccines against the same disease can also vary according to specific product or strain. This has been shown, for example, for BCG (323, 506, 507), HepB (107, 508), TIV (86), PCV7 (490), rabies (509), and measles (49) vaccines. However, detailed discussion of this topic is beyond the scope of this review.

Adjuvants. Adjuvants are added to vaccines to elicit stronger immune responses. There is great variation in the magnitude and quality of vaccine responses depending on which adjuvants are added to a vaccine (510). For example, the new adjuvant MF59 increases antibody affinity and cross-protection against TIV (511, 512), and compared to those obtained with the standard HepB vaccine, a vaccine containing the new adjuvant AS04 induces higher SPRs and GMTs (513).

TABLE 15 Results from studies investigating environmental factors that influence vaccine responses

	Vaccine response, vaccine, age group, measurement [reference(s)]						
Type of response	**Living in rural areas**	**Living in developing countries**	**Season**	**Larger family size**	**Arsenic exposure**	**Lead exposure**	**Polychlorinated biphenyls and dioxins exposure**
Humoral responses	Higher antibody production Tetanus Children: GMTs (351) Malaria (PfAMA1, PfRh5) Children: GMTs (485) Lower antibody production HepB Adolescents: SPRs (161) Children: SPRs (486, 488) TIV Children: GMTs (487)	Higher antibody production Hib Infants: GMTs (489), SPRs (489) Diphtheria Infants: GMTs (489) PCV7 Children: GMTs (490) Pertussis (FHA) Infants: GMTs (489) Pertussis (PT) Infants: GMTs (489) Tetanus Infants: GMTs (489) Lower antibody production HepB Adults: SPRs (498) Measles Children: GMTs (491–493), SCRs (491–493) OCV Children: GMTs (494) OPV Children: SCRs (495, 496) *Salmonella* Typhi: SCRs (497), SPRs (497) No difference in antibody production Diphtheria Infants: SPRs (489) Pertussis (FHA) Infants: SPRs (489) Pertussis (PT) Infants: SPRs (489) Tetanus Infants: SPRs (489)	Association between month of administration and antibody production Pertussis (PT) Infants: GMTs (460) PPV23 Children: GMTs (146) Rabies Children: GMTs (146) Adults: GMTs (146) *Salmonella* Typhi Adults: GMTs (146) No association between month of administration and antibody production Diphtheria Infants: GMTs (146) HepB Infants: GMTs (146) Tetanus Infants: GMTs (146)	Higher antibody production Hib Infants: GMTs (327)	Lower antibody levels Mumps Infants: GMTs (504)	No difference in antibody production Tetanus Children: titers (503)	Lower antibody levels Measles Children: GMTs (505) Mumps Children: GMTs (505)
Cellular responses	Differences in cellular responses Tetanus Skewed towards Th1 (351) TIV Skewed towards Th1 (487)	Lower cellular response BCG Smaller tuberculin skin reaction (396), skewed towards Th1 (499)	Higher cellular response BCG CD154 (325)				
Cytokine responses	Higher cytokine production Tetanus IL-5 (351) TIV IL-5 (487) Lower cytokine production Tetanus IFN-γ (351) TIV IFN-γ (487)	Lower cytokine production BCG IFN-γ (396, 398, 500)					

Vaccine dose. A study investigating IPV showed that there is a linear relationship between the dose of administered antigen and antibody responses (514). With ORV, the inhibitory effect of transplacental or breast milk-transferred maternal antibodies can be overcome by increasing the vaccine dose (309).

In adolescents receiving HepB vaccination, 10 μg instead of the more commonly used 20-μg dose is sufficient to induce seroprotection (454). However, it leads to lower GMTs (71, 515) and SCRs (71). In patients with end-stage kidney disease, 80 μg of HepB vaccine increases the likelihood of persistent protective antibodies (259).

For the Hib vaccine, it has been shown that even one-eighth the usually given dose leads to adequate antibody titers associated with long-term immunity (516).

For TIV, it has been shown for elderly people that higher doses of antigens are associated with higher antibody responses (130, 517), while in previously immunized participants of 18 to 49 years of age, half the usual vaccine dose leads to comparable SCRs and GMTs, especially in females (126).

Administration Factors

Vaccination schedule. A further factor influencing vaccine responses is the spacing of vaccine doses. Schedules that have longer intervals between vaccine doses usually lead to higher immune responses. For example, antibody responses to aP are significantly higher after a 2-month to 4- to 6-month schedule than after an accelerated 2-month to 3- to 4-month schedule (349). Similarly, antibody responses to DTP vaccination are higher after a 3-month to 5- to 9-month schedule than after an accelerated 2-month to 3- to 4-month schedule (518). For HepB vaccination, increased time between the first and second doses or the second and third doses also correlates with increasing GMTs and SPRs (117, 401). However, one study showed lower GMTs after HepB vaccination on a 0-month to 12- to 24-month schedule than after a 0-month to 1- to 6-month schedule (448), and similarly, another study also showed that individuals who have an interval of more than 1 month between the first and second doses have lower SPRs (79).

In contrast, GMTs after HepA vaccination are higher after a 0-month to 1- to 12-month schedule than after a 0-month to 6- to 12-month schedule (99) or a 0-month to 1- to 2-month schedule (64).

In infants receiving two doses of measles, mumps, rubella, and varicella virus vaccination (MMRV), GMTs are higher to all components of the vaccine when the doses are given 12 months apart instead of 4 weeks apart (519). When influenza vaccination is given to children below the age of 24 months, there is no difference in antibody responses if one priming dose is given in spring followed by the second dose in fall or if both doses are given in fall (520).

Vaccination site. In adults, HepB vaccination given in the buttock area leads to lower responses than those obtained when it is given in the upper arm (521–524). However, this is not the case for infants (525). In children receiving Hib vaccination, there is also no difference in GMTs between children who receive the vaccination in the vastus lateralis and those who receive it in the deltoid muscle (526). Similarly, there is no difference in GMTs after HepB vaccination in infants who receive the vaccine in the anterolateral thigh compared to those who receive it in the ventrogluteal region (8).

Vaccination route. Intramuscular administration of TIV leads to higher antibody responses than those obtained by subcutaneous administration (125). However, there is no difference in antibody responses to diphtheria (137), PPV23 (143), or tetanus (137) vaccination after intramuscular or subcutaneous administration. For HepB and rabies vaccines, a lower dose given intradermally induces an antibody response similar to that induced by a larger intramuscular dose (148, 527–529). Intramuscular vaccination relies on a T cell-mediated response, while intradermal vaccination activates a dendritic cell-mediated response, which requires lower antigen doses (530). Individuals who do not respond to intramuscular HepB vaccination might respond to intradermal administration (531, 532). While 5 μg given intradermally leads to higher SCRs than those obtained with 40 μg given intramuscularly (533), 2 μg given intradermally leads to

lower SPRs (74) and GMTs (75) than those obtained with 20 μg given intramuscularly (75). There is no difference in time required to seroconvert or time to peak antibody titer (75).

Needle size. The size of the needle used to administer vaccines has not been found to influence vaccine responses (534, 535).

Time of day. Studies investigating diurnal variations in antibody responses to TIV in adults show conflicting results. One study showed that individuals receiving the vaccine in the morning have significantly higher antibody responses to the H1N1 A strain and a trend toward higher responses to the B strain, while the time of vaccine administration has no influence on responses to the H3N2 A strain (536). A second study indicated that diurnal variations in antibody responses after TIV are strain specific (537). Additionally, a third study showed higher GMTs to TIV after morning (compared to afternoon) vaccination, but only in men (538). The same has been shown for GMTs after HepA vaccination, but again only in men (538).

Coadministered vaccines. A vast number of studies have investigated the influence of concurrent administration of live vaccines on vaccine responses. Two meta-analyses summarized RCTs comparing vaccine responses in infants receiving either one dose of MMRV or MMR and V as separate vaccines (539, 540). The first meta-analysis, which included 10 RCTs, did not find any difference in GMTs to any of the vaccine components (540). However, the second meta-analysis, which included 24 RCTs, showed that after a single vaccination in children of 9 to 24 months of age, GMTs against mumps and varicella viruses are comparable between infants receiving MMRV and those receiving MMR and V (MMR+V) or MMR. In contrast, individuals receiving MMRV achieve significantly higher GMTs to measles virus than those in individuals receiving MMR+V or MMR. GMTs to rubella virus are reduced in those receiving MMRV compared to those in individuals receiving MMR+V or MMR (539). MMRV also leads to lower SCRs than those with MMR+V or MMR, but this is likely confounded by lower virus antigen doses in early vaccines (539). In investigations of immune responses after two vaccine doses, similar GMTs to most vaccine viruses are observed (541–545). However, there is a tendency toward higher varicella (541, 542, 544, 545) and mumps (541, 543–545) GMTs and lower measles (542–544) and rubella (541, 544, 545) GMTs in groups receiving MMRV as a second dose than in those receiving MMR+V. Concurrent administration of LAIV with MMR+V does not influence GMTs or SPRs against any of the vaccine components (546). YF vaccine given simultaneously with the MMR vaccine leads to lower SCRs than those obtained when the vaccines are given 1 month apart (61% versus 71% for mumps, 90% versus 97% for rubella, and 70% versus 87% for YF), while SCRs for measles are not influenced by simultaneous vaccination (547). One study suggests that a live attenuated Japanese encephalitis (JE) vaccine given 30 days before a YF vaccine might interfere with SCRs to YF vaccination (548). However, a subsequent study did not find a difference in SCRs to YF vaccine whether JE was given 30 days before, simultaneously with, or after the vaccine. For JE, even though there were also no significant differences in SCRs between individuals given the two vaccinations at the same time and those receiving them 30 days apart, GMTs were significantly higher in participants who receive JE 30 days before YF rather than the other way around or at the same time (549).

Studies show that simultaneous administration of nonlive vaccines with MMR or V vaccine does not influence the response to any of the vaccine components. This includes 7-valent conjugated pneumococcal (Pn) (550–552), 10-valent Pn-Hib (553), meningococcal C (MenC) (554), DTaP-HBV-IPV-Hib (555), and HepA (551, 552) vaccines.

An additional dose of acellular pertussis (aP) vaccine at birth might lead to subsequently lower HepB (52, 53), Hib (52, 53), and diphtheria (556) GMTs.

Studies investigating the influence of coadministering BCG vaccine show that it leads to significantly higher levels of antibodies against HepB, OPV, PCV7, and TIV but not against DTaP-Hib or *Salmonella* Typhi (557).

There are several studies which show that concomitant administration of OPV reduces vaccine responses to ORV (558, 559). Infants who receive the two vaccines

concomitantly are less likely to seroconvert than those who receive both vaccines in a staggered manner (558). The interference is greater after the first dose of OPV, presumably because the first dose is associated with the greatest intestinal replication of vaccine poliovirus strains (559). However, when the vaccines are given concomitantly after the age of 3 months, neither OPV nor ORV influences vaccine responses (560).

There is less interference reported with coadministration of nonlive vaccines. Coadministration of PCV7 vaccine with either acellular pertussis or whole-cell pertussis vaccine has no effect on the immunogenicity of the PCV7 vaccine, expect for that against serotype 14, for which the specific antibody response is lower when the vaccine is given with the acellular pertussis vaccine (490). One RCT showed that when DPT-IPV and Hib are given together as a single dose, the antibody response to tetanus is significantly lower than that obtained when DPT-IPV is given at an injection site different from that used for Hib or given 6 months apart (561). A Cochrane review summarizing studies that compared the immunogenicities of the combined DTP-HBV-Hib vaccine and the DTP-HBV and Hib vaccines given at separate sites did not find conclusive results, as only one study reported significantly lower immunological responses to Hib and tetanus when the vaccine components were given in a combined vaccine (562).

Coadministered drugs. Several studies have investigated the effect of concurrent administration of paracetamol around the time of vaccination. A review summarizing 13 RCTs which investigated the influence of prophylactic antipyretic administration after vaccination shows that infants receiving paracetamol after each of 3 doses of routine vaccination have lower GMTs to all Pn serotypes, Hib, diphtheria, tetanus, and pertactin but not to pertussis toxin, filamentous hemagglutinin (FHA), HepB, or IPV. After a booster dose, lower GMTs persisted in the prophylactic paracetamol group for all Pn serotypes, diphtheria, and tetanus (563). The one study that investigated the effect of ibuprofen administration around the time of vaccination shows that GMTs to FHA and tetanus are diminished after primary administration but not after a booster dose, while responses to conjugated Pn vaccine are not affected (564). Further, a recent large study in elderly individuals showed that the intake of statins diminishes GMTs to TIV (565). Similarly, preterm infants who receive dexamethasone for chronic lung disease have significantly lower GMTs against Hib after basic immunization with 3 doses (566).

CONCLUDING REMARKS

This review summarizes many important (and often unrecognized or underappreciated) factors that might affect how individuals respond to vaccines (Fig. 1). There is solid evidence that intrinsic factors, such as genetics, sex, age at time of vaccination, and comorbidities, as well as vaccine-related factors, such as choice of vaccine products, adjuvants, and vaccination schedule, strongly influence vaccine responses. Good evidence also exists for the interaction between maternal antibodies and vaccine responses in infants. In contrast, the available data on the influence of other perinatal factors, such as birth weight or feeding method, or on the influence of infections, antibiotics, the microbiota, and nutrition are less robust. For smoking, alcohol consumption, psychological stress, and exercise, the data from different studies are inconsistent. Many studies report differences in vaccine responses depending on geographic region. However, many other factors, such as preexisting immunity, nutritional status, and other behavioral factors, as well as genetics and the microbiota, might confound this observation. The potential for confounding also exists for many of the other factors discussed in this review, as the response to vaccination is complex, likely involving the interplay of multiple different factors. It is therefore important not to overinterpret findings from single studies.

There are many different methods for quantifying vaccine responses (Fig. 2). However, most studies investigating vaccine responses quantify antibodies. The antibody concentration defined as a protective correlate varies depending on whether it relates to protection against colonization, mucosal disease, or invasive disease. However,

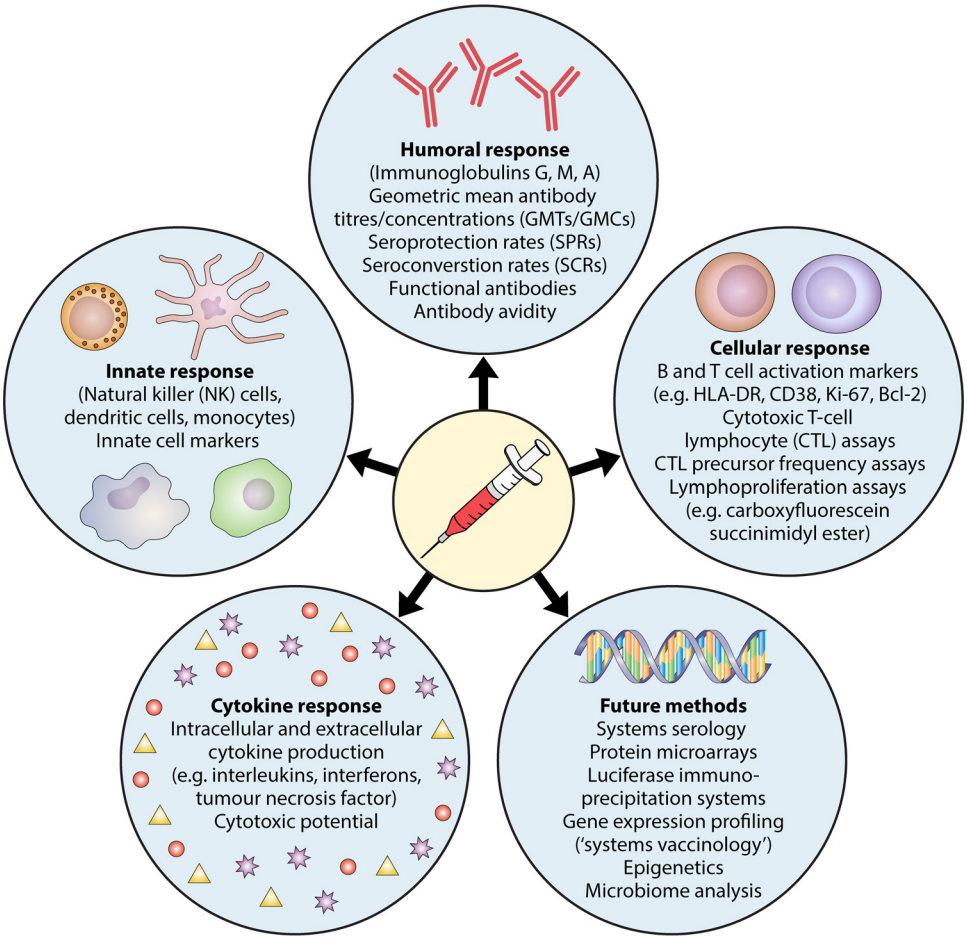

FIG 2 Methods for quantifying vaccine responses.

vaccine responses are far more complex than just measurable antibody concentrations. Other parts of the immune system, such as innate, cellular, and cytokine responses, also play a crucial role in vaccine efficacy. The complex interplay between these different components of the immune system in vaccine responses is not fully understood, and surrogate markers of vaccine-induced protection are imperfect. As most vaccines induce very high antibody responses, small differences in antibody concentrations between groups of individuals may not be clinically significant in terms of protective efficacy, may be relevant only in individuals with poor responses, or may impact only the duration of protection. Moreover, the quality of antibody response is an important consideration, as only a subset of total detectable antibody can neutralize pathogens. SPRs or GMCs do not take this into account and are therefore imperfect correlates of protection. Further, the level of antibody response *in vitro* does not necessarily correlate with health outcomes. For example, seroconversion does not mean full protection against a disease, and nonseroconversion is not necessarily associated with susceptibility (567). Moreover, antibody levels wane with time, but seronegative individuals can still be protected through other immune mechanisms, as shown, for example, after HepB vaccination (568).

This review provides an overview of the current evidence for factors that might influence vaccine responses and identifies factors that require further investigation. Important topics for future studies include the influences of the microbiota (intestinal and respiratory), concurrent infections, and antibiotics on vaccine responses. Further important lines of investigation include the association between preexisting immunity and vaccine responses, as well as the influence of behavioral factors. Understanding

these interactions in more depth will open new avenues for improving vaccine immunogenicity and effectiveness as well as designing vaccine schedules that optimize the benefits of vaccination.

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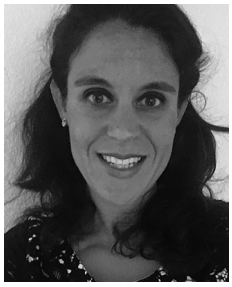

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