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Review

Negative immunomodulation by parasitic infections in the human response to vaccines

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Abstract

Parasitic infections are an important cause of global morbidity and mortality and are highly prevalent in "underdeveloped" countries. The presence of parasitic infections is associated with modulation of the immune system and changes in the response to bacterial and viral vaccines. The objective of this review was to compile, summarize and analyze information about immunomodulation by parasitic infections and its effects on the immune response to vaccines. We also identified the parasites most associated with immunomodulation of vaccine responses and those vaccines most affected. In addition, articles evaluating the effect of chemoprophylaxis for malaria on the immune response against vaccines were considered. The most affected vaccines are Bacillus Calmette-Guérin and bacterial polysaccharide vaccines. Malaria is the infection most associated with decreased response to vaccines; however, there are discordant results. Chemoprophylaxis for malaria did not change the immune response to vaccination. While parasitic infections can alter the immune response to vaccination, it is important to clarify the discrepancies and establish the mechanisms.

Key words: parasites; vaccines; immunomodulation; *Plasmodium*; helminths.

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Introduction

Infection and poverty are intrinsically linked problems that perpetually challenge human health. Malnutrition arises from poverty and is a major determinant of morbidity and mortality by infectious diseases. Malnutrition can determine the severity of infection, as well as the risk of death. A poor body condition weakens the immune system and increases the risk of infection, which leads to loss of appetite, and then, loss of nutrients that are used in the defense against infection. This leads to a vicious cycle with detrimental outcomes (malnutrition → immunosuppression → infection → increased malnutrition → increased immunosuppression → increased infection) [1,2].

Hunger and malnutrition, with few exceptions, result from "economic poverty" [3], which affects quality of life and lifestyle [3,4]. The populations with the highest poverty, and then, with the worst living conditions, are the most affected by parasitic infections. Tropical and subtropical zones of the world have, in addition to the greatest number of poor people, the optimal natural and social conditions for the maximum spread of parasitic infections. While populations living in temperate and frigid zones also live in poverty, the natural conditions are generally inadequate to support parasites development, and these infections are absent or very scarce. Human parasites have a global distribution, but undoubtedly they reach disproportionate levels in the tropics [5-7]

In tropical zones, patients are typically infected with multiple parasitic infections at once. It is already known that parasitic infections are associated with immune tolerance [8-10], and this tolerance allows the survival of the parasite in the host and minimizes the damage [11]. This means that infections by various parasites cause a nonspecific effect on the immune response. For that reason, the susceptibility to infections increases and acquired immunity is altered by limitation of the inflammatory response, which is essential to generate the immune response [12].

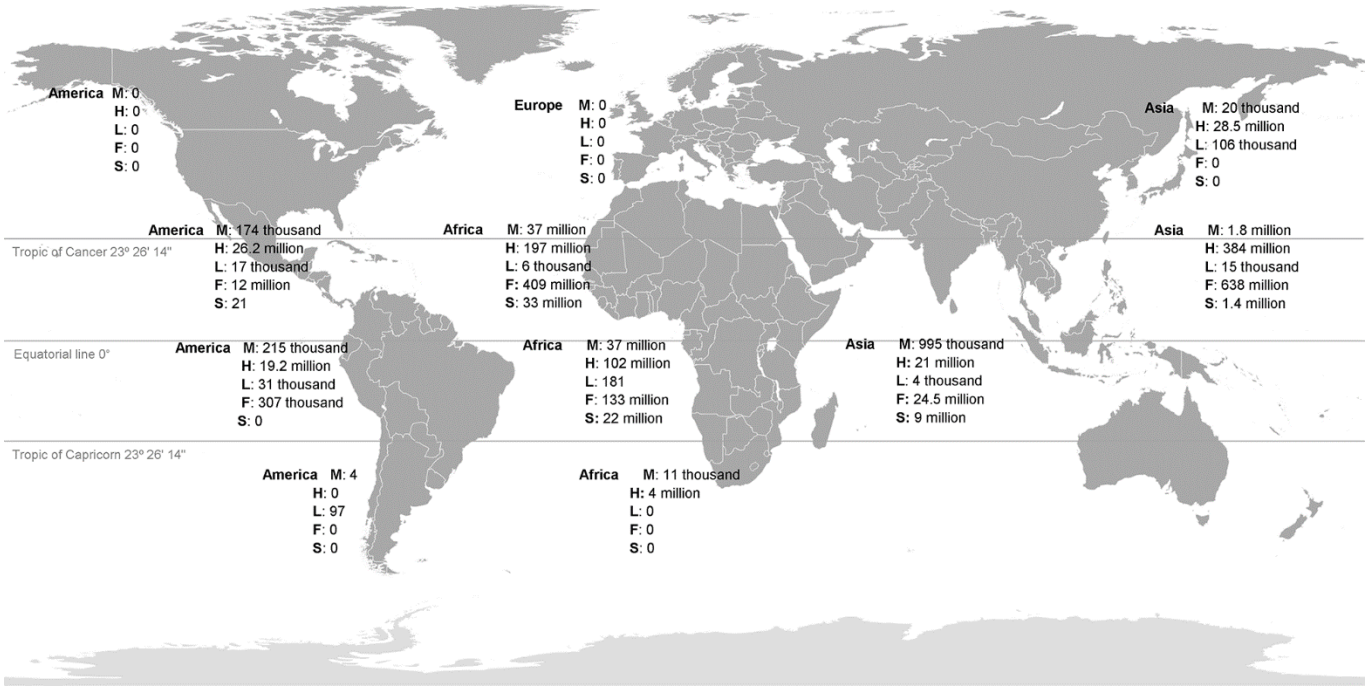
The life cycle of several parasites involves an insect that operates as a vector or an animal as a reservoir (malaria, leishmaniosis, Chagas disease, trypanosomosis, filarioidosis, onchocercidosis, *etc*.). Vector-borne diseases account for more than 17% of all infectious diseases and cause more than 1 million of deaths every year [13]. This situation implies that natural and social conditions contribute to the reproduction and transmission of parasites and their

vectors. Among the most prevalent parasitic diseases in the world are geohelminthosis, malaria, schistosomosis, onchocercidosis, filarioidosis and leishmaniosis. Figure 1 shows the wide territory covered by parasitic infections, and their importance in public health. It is crucial to note that in tropical areas, there is abundant diversity of parasites and the greatest risk to acquire these infections.

The parasitic infections mentioned above (except leishmaniosis) can cause chronic and asymptomatic infections and constantly stimulate the immune system, which leads to a greater modulation of the immune system, i.e. high regulation or control of the immune response [14]. In addition, multiple co-infections can occur in different endemic areas and complicate the scenario. For geohelminthosis, filarioidosis and trematodiosis, a high regulation of the immune response has been described [15-17]. This regulation is associated with tolerance to the parasitic infections, which leads to: a) limitation of the acute immune response against other pathogens; b) reduction of the antigen-specific response; and c) deficiency in the acquired immune response [15-17]. Malaria usually is an acute disease, but can also be a chronic asymptomatic infection, which is mostly associated with increased regulation of the immune response [18,19].

Helminthosis (the most widely distributed parasite) is caused by extracellular parasites, and therefore is associated with a Th2 immune response. The chronicity of infection results in the constant stimulation of the immune system [20]. The Th2 response is characterized by the increase of regulatory-associated cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β). These cytokines condition the differentiation of immune cells with regulatory profiles that promote tolerance in the infected subject [21]. The immune cells differentiated by these cytokines are the regulatory T cells (Treg) and the macrophages with alternative activation (M2). These cells induce amplification of the production of regulatory cytokines (IL-10 and TGF-β) and, therefore, more differentiation of these cell types [22]. Several studies have associated parasitic infections with increased IL-10 and regulatory cells [23-25]. This modulation limits the proliferation of immune effector cells such as $CD4^+$ T, $CD8^+$ T, and natural killer cells (NK), which are important in vaccination and defense against other pathogens. The limitation of the effector T cells prevents the amplification of the immune response necessary to develop adequate immune memory [26].

Figure 1. Global epidemiology of parasitic infections according to latitude.



Malaria (**M**): number of cases reported in 2014 [71]; Geohelminthosis **(H)**: number of children requiring preventive therapy (TP) in 2014 [72]; Leishmaniosis (**L**): number of cases of cutaneous and visceral Leishmaniosis reported in 2013 [73]; Filarioidosis (**F**): number of people requiring preventive therapy (TP) in 2014 [74]; Schistosomosis (S): Number of people treated for this disease in 2014 [75]; Image taken and modified from: https://commons.wikimedia.org/w/index.php?curid=3231806. By Frank Bennett.

Table 1. Effect of parasitic infections on the immune response to vaccines.

Parasitic infection	Reference	Population age range	Exposition factor	Average (CI)		p	Authors' conclusion
Tetanus toxoid							
Filarioidosis	Cooper *et al.*, 1999 [33] Ecuador	Subjects (5-70 years old)	Infection by *Onchocerca volvulus*	Study groups	Antibody levels UI/mL	NS	Infection by *O. volvulus* does not affect the generation of tetanus protection.
				Infected (n = 193)	1.32 (1.15-1.74)		
				Uninfected (n = 85)	1.41 (0.84-1.44)		
	Prost *et al.*, 1983 [38] Burkina Faso	Subjects (9-34 years old)	Infection by *O. volvulus*	Study groups	Antibody levels UI/mL	**0.001**	Infection by *O. volvulus* decreases humoral immunity.
				Infected (n = 28)	0.07 (0.056-0.084)		
				Uninfected (n = 27)	2.41 (1.93-2.90)		
	Nookala *et al*., 2004 [39] India	Subjects, adults (20-66 years old)	Infection by *Wuchereria bancrofti*	Study groups	Antibody levels UI/mL	**0.0002**	Infection by *W. bancrofti* altered the immune response against tetanus toxoid.
				Infected (n = 40)	149 (73.5-583)		
				Uninfected (N = 10)	910.2 (416.5-1989)		
	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *Brugia malayi or W. bancrofti*	Sensitized (n = 167)	NI	NS	The levels of IgG against tetanus toxoid were not affected in children sensitized by filariasis.
				Unexposed (n = 110)			
Malaria	Greenwood *et al*., [35] 1972 Nigeria	Children (6 months-6 years old)	Acute malaria by *Plasmodium falciparum*	Infected (n = 51)	NI	**< 0,02**	In children with acute *P. falciparum* malaria, a form of immunosuppression was demonstrated.
				Uninfected (N = 34)			
	Corrigall *et al*., 1988 [49] Papua New Guinea	Children (8-11 years old)	Asymptomatic malaria by *P. falciparum, P. vivax* and *P. malariae*	Infected (n = 51)	NI	> 0,1	Malaria did not affect the immune response against tetanus toxoid
				Uninfected (N = 34)			
	Cumberland *et al*., 2007 [36] Kenya	Pregnant women (> 14 years old)	Placental malaria by *P. falciparum*	Study groups	Antibody levels UI/mL	NI	IgG levels are significantly low in women with active-chronic or past placental malaria
				Infected (n = 312)	2.39 (1.46-4.12)		
				Uninfected (n = 291)	3.64 (3.13-4.23)		
	van Riet *et al*., 2007 [50] Gabon	Children (7-12 years old)	Acute malaria by *P. falciparum*	Infected (n = 11)	NI	NI	Acute *P. falciparum* infection did not affect the response against the boosts of the tetanus toxoid vaccine.
				Uninfected (n = 42)			
	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *P. falciparum*	Sensitized (n = 188)	NI	NS	The levels of IgG against tetanus toxoid vaccine were not affected in children sensitized by *P. falciparum.*
				Unexposed (n = 179)			
Schistosomosis	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *Schistosoma haematobium*	Sensitized (n = 238)	NI	NS	The levels of IgG against tetanus toxoid vaccine were not affected in children sensitized by *S. haematobium.*
				Unexposed (n = 90)			

Table 1 (continued). Effect of parasitic infections on the immune response to vaccines.

Diphtheria toxoid							
Parasitic infection	**Reference**	**Population age range**	**Exposition factor**	**Average (CI)**		**p**	**Author's conclusion**
Filarioidosis	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *B. malayi* or *W. bancrofti*	Study groups	Antibody levels	NS	The levels of IgG against diphtheria toxoid vaccine were not affected in children sensitized by filariasis.
				Sensitized (n = 167)	NI		
				Unexposed (n = 110)	NI		
Malaria	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *P. falciparum*	Sensitized (n = 188)	NI	NS	In children sensitized by *P. falciparum*, decreased levels of IgG against diphtheria toxoid vaccine were observed.
				Unexposed (n = 179)			
Schistosomosis	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *S. haematobium*	Sensitized (n = 238)	NI	NS	The levels of IgG against diphtheria toxoid vaccine were not affected in children sensitized by *S. haematobium.*
				Unexposed (n = 90)			
BCG							
Parasitic infection	**Author and place**	**Population Age range**	**Exposition factor**	**Average (CI)**		**p**	**Author's conclusion**
Geohelminthosis	Elias D *et al*., 2001 [51] Ethiopia	Students (18-24 years old)	Antihelmintic treatment	Study groups	IFNγ levels	**0.04**	The use of antihelmintics potentiated the immune response against BCG vaccine.
				Albendazole (n = 29)	170 pg/mL (136-204 pg/mL)		
				Placebo (n = 31)	70 pg/mL (56-84 pg/mL)		
	Lule *et al*., 2015 [52] Uganda	Children (1 – 5 years old)	Infection with hookworm	Study groups	IFNγ levels	NI	Geohelminth infection was associated with a decrease in IFNγ after stimulation with *M. tuberculosis in vitro*.
				Infected	179 pg/mL (143.5-214.8 pg/mL)		
				Uninfected	123 pg/mL (98.4-147.6 pg/mL)		
Malaria	Lule *et al*., 2015 [52] Uganda	Children (1 – 5 years old)	Asymptomatic malaria	Study groups	IFNγ levels	NI	Asymptomatic malaria was associated with decreased IFNγ after stimulation with *M. tuberculosis*
				Infected	174 pg/mL (139.2-208.8 pg/mL)		
				Uninfected	82 pg/mL (65.6-98.4 pg/mL)		
	Walther *et al*., 2012 [53] Gambia	Children (Newborn -12 months old)	Placental malaria	Study groups	T cells CD4+IFN+	**0.026**	Placental malaria generated a weak response of IFNγ to tuberculin at 12 months of age.
				Infected (n = 7)	0.007% (0.002-0.007%)		
				Uninfected (n = 28)	0.000% (0.000-0.002 %)		
Schistosomosis and Filarioidosis	Badawy *et al*. 2013 [54] Egypt	Children (6 months)	Infection by *S. mansoni* or *W. bancrofti*	Study groups	Tuberculin	**0.000**	The infection was associated with a lower response to tuberculin.
				Infected (n = 63)	< 5mm: 33 children		
				Uninfected (n = 187)	< 5mm: 22 children		

Table 1 (continued). Effect of parasitic infections on the immune response to vaccines.

Bacterial polysaccharides							
Parasitic infection	**Reference**	**Population Age range**	**Exposition factor**	**Average (CI)[a]**		**p**	**Author's conclusion**
Malaria	Williamson *et al*., 1978 [55] Nigeria	Children (6 months - 6 years old)	Malaria by *P. falciparum*	Study groups	Antibody titers	*S. typhi* **< 0.01** Mening. **< 0.001**	Malaria was associated with decreased titers of antibodies against *S. typhi* and group C meningococcal polysaccharide when the vaccine was administered at the time of infection.
				Infected (n = 79)	*S. typhi*: 2.1 (log2) Meningococcal: 3.1 (log2)		
				Uninfected (n = 40)	*S. typhi*: 1.4 (log2) Meningococcal: .3.4 (log2)		
	Greenwood *et al.,* 1980 [56] Nigeria	Subjects (all ages)	Asymptomatic malaria by *P. falciparum*	Infected (n = 316)	NI	**< 0.02**	The antibody response against group C meningococcal polysaccharide was lower in cases with high parasitaemia within each age group
				Uninfected (n = 44)			
	Usen *et al*., 2000 [57] Gambia	Children (12-30 months old)	Malaria by *P. falciparum*	Study groups	Antibody levels	**< 0.001**	Infected children with *P. falciparum* had lower levels of antibodies against *Haemophilus influenzae* type B.
				Infected (n = 57	6.3 µg/mL (0.07-285 µg/mL)		
				Uninfected (n = 60)	23 µg/mL (0.36-555 µg/mL)		
	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *P. falciparum*	Sensitized (n = 188)	NI	**0.005**	Children sensitized by *P. falciparum* had significantly lower *Haemophilus influenzae* type B specific IgG levels.
				Unexposed (n = 179)			
Filarioidosis	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *B. malayi* or *W. bancrofti*	Sensitized (n = 167)	NI	**0.007**	Children sensitized by filarioidosis had significantly lower *Haemophilus influenzae* type B specific IgG levels.
				Unexposed (n = 110)			
Schistosomosis	Malhotra *et al*., 2015 [40] Kenya	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *S. haematobium*	Sensitized (n = 238)	NI	**0.034**	Children sensitized by S. *haematobium* had significantly lower *Haemophilus influenzae* type B specific IgG levels.
				Unexposed (n = 90)			

Table 1 (continued). Effect of parasitic infections on the immune response to vaccines.

Others vaccines							
Malaria	Simondon *et al*., 1999 [58] Senegal **Pertussis toxin**	Children (1-2 months old)	Exposed to *P. falciparum*	Study groups	Antibody titres (GMT)	**< 0.05**	The antibody response to pertussis toxin was lower in infants infected with malaria than in a group of healthy infants.
				Infected (n = 66)	81.1 (72.4-91.2)		
				Uninfected (n = 115)	97.3 (87.1-107.1)		
	Malhotra *et al*., 2015 [40] Kenya **Hepatitis B**	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *P. falciparum*	Sensitized (n = 188)	NI	NS	The levels of IgG specific against Hepatitis B were not affected in children sensitized by *P. falciparum*
				Unexposed (n = 179)			
	Brown *et al*., 2014 [59] Tanzania **human papillomavirus-16/18 AS04-adjuvanted**	Women (10-25 years old)	Infection by *S. haematobium; S. mansoni; Strongyloides stercolaris; Ascaris lumbricoides; Trichuris trichiura; Taenia spp.*	Study groups	Antibody titres EU/mL		High HPV immunogenicity regardless of the presence of malaria and helminth infections among young girls and women in Tanzania. There was some evidence of enhanced antibody titres to HPV vaccine genotypes in participants with malaria parasitaemia.
				Malaria (n = 20)	HPV16 4335(2890-6502) HPV18 1109(764-1609)	**0.05** 0.59	
				Helminth (n = 59)	HPV16 2843 (2171-3723) HPV18 1038 (802-1344)	0.64 0.71	
				Uninfected (n = 129)	HPV16 2613 (2124-3215) HPV18 970 (781-1205)		
Schistosomosis	Malhotra *et al*., 2015 [40] Kenya **Hepatitis B**	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *S. haematobium*	Sensitized (n = 238)	NI	NS	Sensitization by S. *haematobium* was not associated with significantly lower Hepatitis B -specific IgG.
				Unexposed (n = 90)			
Filarioidosis	Malhotra *et al*., 2015 [40] Kenya **Hepatitis B**	Mothers/children (> 14 years old/ 6-36 months old)	Exposed in utero to *B. malayi* or *W. bancrofti*	Sensitized (n = 167)	NI	NS	Sensitization by filarioidosis was not associated with significantly lower Hepatitis B -specific IgG.
				Unexposed (n = 110)			
Helminthosiss	Brückner *et al*., 2015 [60] Gabon **Seasonal influenza**	Children (6-10 years old)	Infection by *A. lumbricoides; Ancylostoma duodenale; Fasciola hepatica; T. trichiura*	Study groups	Antibody HI titres	NS	There was no significant difference in the HI titers against the influenza vaccine between the two study groups.
				Antihelminthic (n = 44)	AH1N1 320(35-960) AH3N2 320(280-640) B/Brisbone 320 (280-640)		
				Placebo (n = 38)	AH1N1 320 (20-480) AH3N2 320 (240-600) B/Brisbone 160 (80-800)		
	Cooper *et al*., 2001 [34] Ecuador **Live oral cholera vaccine CVD 103-HgR**	Subjects (12-32 years old)	*A. lumbricoides*	Study groups	Cytokines levels pg/mL	**IL2 0.03** INFγ NS	*A. lumbricoides*-infected subjects who received placebo treatment before vaccination demonstrated a depressed IL-2 response.
				Anthelminthic (n = 15)	IL2: 21,8 (0-74) INFγ: 7,7 (0-209,7)		
				Placebo (n = 13)	IL2: 0 (0-252,9) INFγ: 7,9 (0-298,2)		

CI: Confidence interval; NI: No information; NS: The probability value is not reported but is said to be non-significant; IU/mL: International Units per milliliter; pg/mL: picograms per milliliter; mm: millimeter; Log2: logarithm base 2; µg/mL: micrograms per milliliter; GMT: geometric mean titres; EU/mL: equivalent units per milliliter; HI: hemagglutinin-inhibition; p values were considered significant considering a 95% confidence interval.

Table 2. Effect of chemoprophylaxis for malaria on the immune response to vaccines.

Reference	Population age range	Exposition factor	Average (CI)		p	Authors' conclusion
Tetanus toxoid						
McGregor *et al.,*1962 [61] Gambia	Subjects (5-70 years old)	Chloroquine (CQ) Pyrimethamine (PT)	Study groups CQ (n = 16) PT (n = 14) No-chemoproph. (n = 36)	Antibody levels 0.19 IU/mL 0.18 IU/mL	NS	There were significantly more patients who did not respond to the vaccine in the group without chemoprophylaxis. However, no differences were observed in antibody levels between the groups.
Greenwood *et al*., 1981 [62] Nigeria	Children (3-17 months old)	Chloroquine	Study groups CQ (n = 93) no-CQ (n = 91)	Antibody levels 5.7 log2 (3.1- 8.6 log2) 5.9 log2 (5.5- 6.3 log2)	NS	No difference in antibody levels against the tetanus toxoid vaccine was observed in the groups with or without CQ administration.
Monjour *et al*., 1982 [63] Burkina Faso	Children (11 months-3 years old)	Amodiaquine (AQ)	Study groups AQ (n = 159) no-AQ (n = 126)	Antibody levels NI	> 0.05	There were no differences in the levels of protection between the groups.
Gilles *et al*., 1983 [64] Nigeria	Children (1-5 years old)	CQ Asymtomatic malaria	Study groups CQ (n = 123) no-CQ (n = 119)	Antibody levels 1.31 IU/mL (1.06-1.56) 1.25 IU/mL (0.94-1.56)	NS	Malaria chemoprophylaxis was not necessary in the first year of life to achieve protection of infants against tetanus.
Brabin *et al*., 1984 [65] Kenya	Pregnant women	CQ	CQ: (n = 107) no-CQ (n = 73)	NI	NS	No difference was found in IgG titers against tetanus toxoid vaccine. All women responded appropriately to the vaccine.
Schellenberg *et al*., 2001 [66] Tanzania	Children (2 months old)	Sulfadoxine–Pyrimethamine (SP)	SP (n = 351) No-SP (n = 351)	NI	NS	No differences in the rate of seroconversion for tetanus.
Massaga *et al*., 2003 [67] Tanzania	Children (12-16 weeks)	AQ	Study group AQ (n = 77) Placebo (63)	Antibody levels 12.7 IU/mL (7.6-18.7) 10.4 IU/mL (6.1-13.7)	0.28	The administration of AQ together with the vaccination against tetanus toxoid did not change the antibody levels generated by the vaccination.
Rosen *et al*., 2005 [68] Burkina Faso	Children (4 months-6 years old)	AQ	Study group AQ (n = 134) no-AQ (n = 138)	Seroconversion 104/134 (77%) 126/138 (91%)	0.08	Chemoprophylaxis of malaria before vaccination in endemic areas of malaria does not improve or deteriorate the immunogenicity of tetanus toxoid vaccine.
Measles						
Reference	**Population age range**	**Exposition factor**	**Average (CI)**		**p**	**Author's conclusion**
Greenwood *et al*., 1981 [62] Nigeria	Children (3-17 month old)	CQ	Study group CQ (n = 93) no-CQ (n = 91)	Antibody levels 3.5 log2 (3.1-3.9 log2) 2.9 log2 (2.6-3.2 log2)	NS	No difference in antibody levels against measles was observed in the groups with or without CQ administration.
Gilles *et al*., 1983 [64] Nigeria	Children (1-5 years old)	CQ Asymptomatic malaria	Study group CQ (n = 121) no-CP (n = 116)	Antibody levels 5.15 IU/mL (2.34-7.96) 5.57 IU/mL (3.21-7.93)	NS	Malaria chemoprophylaxis is not necessary in the first year of life to achieve the infant protection against measles.
Cénac *et al*., 1988 [69] Niger	Children (9- 48 months old)	CQ	Study group CQ (n = 289) no-CQ (n = 291)	Seroconversion 218/289 (76%) 238/291 (82&)	NS	The seroconversion was not significantly different between the groups.
Rosen *et al*., 2005 [68] Burkina Faso	Children (4 months-6 years old)	AQ	Study group AQ (n = 137) no-AQ (n = 187)	Seroconversion 127/137 (93%) 180/187 (96%)	0.16	Chemoprophylaxis of malaria before vaccination in endemic areas of malaria does not improve or deteriorate the immunogenicity of measles vaccine.

Table 2. Effect of chemoprophylaxis for malaria on the immune response to vaccines.

Reference	Population age range	Exposition factor	Average (CI)		p	Authors' conclusion
Others						
Gilles *et al*., 1983 [64] Nigeria **Polio 1,2 and 3**	Children (1-5 years old)	CQ Asymptomatic malaria	Study group CQ (n = 29) no-CP (n = 19)	Antibody levels GMT Polio 1: 379 (± 609) Polio 2: 134 (± 217) Polio 3: 210 (± 363) Polio 1: 1344 (± 2320) Polio 2: 145 (± 193) Polio 3: 190 (± 311)	NS	Malaria chemoprophylaxis is not necessary in the first year of life to achieve the infant protection against poliovirus vaccine.
Faucher *et al*., 2002 [70] Gabon **Live Oral Typhoid and Cholera vaccines**	School children (4-16 years old)	Atovaquone/ Proguanil (AP)	Study group AP (n = 165) Placebo (n = 165)	Antibody levels GMT IgG S. typhi:2.99(± 1.21) IgA S. typhi:0.97(± 1.13) IgG cholera :5.4 (± 1.0) IgG S. typhi:2.99(± 1.27) IgA S. typhi:0.88(± 1.12) IgG cholera :5.3 (± 1.0)	IgG *S. typhi* 0.958 IgA *S. typhi*: 0.072 IgG cholera 0.637	The two treatment groups did not differ significantly with respect to changes in antibody titers after vaccination.
Rosen *et al*., 2005 [68] Burkina Faso **Diphtheria toxoid**	Children (4 months-6 years old)	AQ	Study group AQ (n = 147) no-AQ (n = 135)	Seroconversion 108/147 (73%) 116/135 (86%)	0.26	Chemoprophylaxis of malaria before vaccination in endemic areas of malaria did not improve or deteriorate the immunogenicity of diphtheria toxoid vaccine.

CI: Confidence interval; NI: no information; NS: The probability value is not reported but is said to be non-significant; CQ: Chloroquine; AQ: Amodiaquine; PT: Pyrimethamine; SP: Sulfadoxine/pyrimethamine; AP: Atovaquone/proguanil; IU/mL: International Units per milliliter; GMT: geometric mean titres; p values were considered significant considering a 95% confidence interval.

In addition, for antigens such as the Bacillus Calmette-Guérin (BCG) vaccine and *Mycobacterium tuberculosis*, the cellular immune response is important; $CD4^+$ T cells exert their effect by producing gamma interferon (IFN-γ), primarily, after stimulation with mycobacterial antigens [27]. Parasitic infections can limit the amplification of the IFN-γ response necessary for the immune response against this pathogen.

On the other hand, it is important to emphasize that polyparasitism affects a large number of people residing in tropical and subtropical regions. Simultaneous parasitic infections enhance and promote the persistence of the regulatory immune profile in infected subjects, which exacerbates the problem. All this has been revealed by studies that associate the modulation caused by parasites with the increased virulence of lethal pathogens such as the human immunodeficiency virus (HIV) [28,29] and *Mycobacterium tuberculosis* [30-31].

The Expanded Immunization Program (EIP) aims to control, eliminate, and eradicate several immunopreventable diseases. The EIP is the result of joint actions by nations to achieve the technical capacity and political support necessary to improve universality in vaccination coverage [32]. Since the implementation of this program, a reduction in morbidity and mortality of those diseases has been clearly observed. In addition to high vaccine coverage as a primary objective, the effectiveness of vaccines must also be ensured. This effectiveness is understood as the conservation of the quantity and quality of the immune response obtained in a parasitized population compared to a non-parasitized population (control).

The objective of this review was to compile, summarize and analyze information about immunomodulation by parasitic infections and its effects on the immune response to vaccines. We also identified the parasites most associated with immunomodulation of vaccine responses and those vaccines most affected.

Methodology

A search was carried out in the PubMed, Scopus, and Web of science (WOS) databases. Several search strategies were employed using combinations of MeSH [Majr] terms such as "tetanus toxoid", "BCG vaccine", "Bacterial vaccines", "Malaria", "Helminths", among others; and not MeSH terms such as "parasitic infections", "vaccination efficacy", "impairment vaccination efficacy" and "parasites". The central subject of the search was the influence of parasitic infections on the human immune response to bacterial and viral vaccines; however, studies that evaluated the effect of chemoprophylaxis for malaria on the response to bacterial and viral vaccines were also included. First, the papers were selected based on the title, and then based on the abstract. The inclusion criteria were: 1) Original studies or systematic reviews about the effect of parasitic infections or chemoprophylaxis for malaria on the immune response to vaccines. 2) Studies carried out in humans. There were no date or language

restrictions. The search deadline was July 10, 2018. A total of 19 papers that evaluated the effect of parasitic infections on the immune response against different vaccines, and 10 papers that evaluated the effect of chemoprophylaxis for malaria on the response to vaccines were included.

Results

Effect of parasitic infections on the immune response to vaccination

The relevant parasitic infections were: filarioidosis, schistosomosis, malaria and geohelminthosis. In these studies, the vaccines evaluated were tetanus toxoid, diphtheria toxoid, BCG, bacterial polysaccharides vaccines, hepatitis B, pertusis toxin, human papillomavirus, seasonal influenza and live oral cholera (Table 1). Chemoprophylaxis for malaria with chloroquine, amodiaquina, sulfadoxine/pyrimethamine and atovaquone/proguanil were evaluated; in these studies, the vaccines evaluated were tetanus toxoid, measles, poliovirus, live oral cholera and diphtheria toxoid (Table 2).

Discussion

The influence of parasitic infections on the efficacy of bacterial and viral vaccines has been scarcely studied and there are conflicting results. Most of the studies found in this review, with the exception of Cooper's work in 1999 and 2001 [33,34], were carried out in Africa and some countries in Asia.

This review shows that the immune response generated by bacterial polysaccharide vaccines and the BCG vaccine is affected by the presence of malaria, filarioidosis and schistosomosis. On the other hand, the effect of parasitic infections on the response to tetanus toxoid vaccine shows discordant results. Only two over six studies that evaluated the effect of malaria on the immune response against tetanus toxoid showed a decrease in IgG levels against the vaccine [35,36] (Table 1). However, it is important to note that each study includes different groups and different clinical presentation of malaria. In a recent study carried out in pregnant women, submicroscopic infection by *Plasmodium* was associated with a decrease in the levels of IgG against tetanus toxoid [37]. In the same way, of four studies that evaluated the effect of filarioidosis in the immune response against tetanus toxoid, two showed a decrease in IgG levels against tetanus toxoid vaccine [38,39], while two did not show differences between the groups [33,40] (Table 1). In general, those studies that reported changes in antibody levels after tetanus toxoid vaccination in the presence of parasitic infections had smaller sample sizes compared with the studies without differences between the groups, which included more than 100 subjects. In addition, the levels of antibodies generated by the diphtheria toxoid vaccine were not affected by the presence of parasitic infection.

It seems clear that vaccines such as tetanus toxoid and diphtheria toxoid, despite parasitic infections, continue to fulfill their protective function, as can be deduced from the drastic decline in morbidity observed after their use. However, a vaccine such as BCG is only partially effective because it provides some protection against severe forms of pediatric tuberculosis but is not completely protective against pulmonary disease in infants and is unreliable against adult pulmonary tuberculosis. In spite of nearly a century of use, BCG remains controversial, with known variations in vaccine efficacy across the world [41]. Nonetheless, it should be emphasized that parasitic infections can lead to lower antibody and INFγ levels, which represent a decrease in the quality of the humoral and cellular acquired immune responses. Moreover, this review shows that in all cases, the parasitic infections affected the immune response generated by bacterial polysaccharide vaccines. In general, the nature of polysaccharide antigens poses a challenge to the generation of long-term immunological memory [42]. Encapsulated bacteria are the main causes of bacteremia, pneumonia, and meningitis in childhood globally [43]. For this reason, the burden of parasitic infections in vaccinees should be considered with respect to the quality of the immune response generated by polysaccharide vaccines.

Parasitic infections can be chronic, and the persistence of the antigenic stimulus changes the expression of immune mediators and promotes constant immune regulation, including increases in regulatory T cell populations [44]. These alterations of the immune system could compromise the response to routine vaccination. Chronic infections are associated with exhausted T cells with less robust effector functions and with alterations in the differentiation of memory T cells [45]. The exhausted T cells manifest characteristic features including sustained up-regulation and co-expression of multiple inhibitory receptors and failure to produce antigen-independent memory T cells [46]. For this reason, the parasitic infections may induce impaired efficacy in the immunological processes in general, and until now, studies evaluating the immune response to vaccination are insufficient and with heterogeneous results.

Malaria and geohelminthosis are the parasitic infections most widely distributed in the world. It is important to explore if the general modulation of the immune system caused by these parasitic infections affects the immune response against different pathogens [29,47,48]. Parasitic co-infections can occur frequently, and more studies are needed to explore the effect of multiple parasitic infections on vaccine response and in the immune response against different pathogens.

In conclusion, individuals living in the tropical and subtropical areas of the world are most susceptible to alterations in the immune response, not only because of the large number of parasites they face on a daily basis, but also because these host-parasite interactions affect: 1) the generation of tolerance to parasitic infections; 2) the response efficacy against pathogens such as bacteria and viruses; 3) the ability to acquire protective immunity against vaccines and against pathogens. This situation would pose a serious challenge for the EIP and for other vaccines not included in the program. The available data, reviewed here, are insufficient but suggest that alteration of acquired protective immunity from vaccines does occur. From the point of view of public health, it is necessary to evaluate this subject in terms of the level of parasite prevalence in different populations and according to polyparasitism. This highlights the need for increasing studies on this subject, especially in the American continent, where millions of people are affected by multiple parasitic infections.

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