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, onchocercoidosis, 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**  |           |                      |                   |              |   |                     |
|                    | Cooper et al., 1999 [33] Ecuador | Subjects (5-70 years old) | Infection by *Oschocerca volvulus* | Study groups Antibody levels UI/mL |           |                   |
|                    |           |                      |                   | Infected                  | 1.32 (1.15-1.74) | NS | Infection by *O. volvulus* does not affect the generation of tetanus protection. |
|                    |           |                      |                   | Uninfected                | 1.41 (0.84-1.44) |    |                     |
|Filarioidosis        | Prost et al., 1983 [38] Burkina Faso | Subjects (9-34 years old) | Infection by *O. volvulus* | Study groups Antibody levels UI/mL |           |                   |
|                    |           |                      |                   | Infected (n = 28)         | 0.07 (0.056-0.084) | **0.001** | Infection by *O. volvulus* decreases humoral immunity. |
|                    |           |                      |                   | 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 |           |                   |
|                    |           |                      |                   | Infected (n = 40)         | 149 (73.5-583) | **0.0002** | Infection by *W. bancrofti* altered the immune response against tetanus toxoid. |
|                    |           |                      |                   | 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) |           |                   |
|                    |           |                      |                   | Unexposed (n = 110)       | NI | NS | The levels of IgG against tetanus toxoid were not affected in children sensitized by filariasis. |
|                    | Greenwood et al., [35] 1972 Nigeria | Children (6 months-6 years old) | Acute malaria by *Plasmodium falciparum* | Infected (n = 51) |           |                   |
|                    |           |                      |                   | Uninfected (N = 34)       | NI | < **0,02** | In children with acute *P. falciparum* malaria, a form of immunosuppression was demonstrated. |
|                    | 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) |           |                   |
|                    |           |                      |                   | Uninfected (N = 34)       | NI | > 0,1 | Malaria did not affect the immune response against tetanus toxoid. |
|Malaria             | Cumberland et al., 2007 [36] Kenya | Pregnant women (> 14 years old) | Placental malaria by *P. falciparum* | Study groups Antibody levels UI/mL |           |                   |
|                    |           |                      |                   | Infected (n = 312)        | 2.39 (1.46-4.12) | NI | IgG levels are significantly low in women with active-chronic or past placental malaria. |
|                    |           |                      |                   | 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) |           |                   |
|                    |           |                      |                   | Uninfected (n = 42)       | NI | NI | Acute *P. falciparum* infection did not affect the response against the boost of the tetanus toxoid vaccine. |
|                    | Malhotra et al., 2015 [40] Kenya | Mothers/children (> 14 years old/6-36 months old) | Exposed in utero to *P. falciparum* | Sensitized (n = 188) |           |                   |
|                    |           |                      |                   | Unexposed (n = 179)       | NI | NS | The levels of IgG against tetanus toxoid vaccine were not affected in children sensitized by *P. falciparum*. |
|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) |           |                   |
|                    |           |                      |                   | Unexposed (n = 90)        | NI | NS | The levels of IgG against tetanus toxoid vaccine were not affected in children sensitized by *S. haematobium*. |
Table 1 (continued). Effect of parasitic infections on the immune response to vaccines.

| Parasitic infection | Reference | Population age range | Exposition factor | Average (CI) | p | Author’s conclusion |
|---------------------|-----------|----------------------|-------------------|--------------|---|---------------------|
| Diphtheria toxoid    |           |                      |                   |              |   |                     |
| 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 (n = 167) Antibody levels |          | The levels of IgG against diphtheria toxoid vaccine were not affected in children sensitized by filariasis. |
|                     |           |                      |                   | Sensitized (n = 167) | NI | NS                  |
|                     |           |                      |                   | Unexposed (n = 110) | NI | NS                  |
| 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) |          | In children sensitized by *P. falciparum*, decreased levels of IgG against diphtheria toxoid vaccine were observed. |
|                     |           |                      |                   | Unexposed (n = 179) | NI | NS                  |
| 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) |          | The levels of IgG against diphtheria toxoid vaccine were not affected in children sensitized by *S. haematobium*. |
|                     |           |                      |                   | Unexposed (n = 90) | NI | NS                  |
| BCG                 |           |                      |                   |              |   |                     |
| Parasitic infection | Author and place | Population Age range | Exposition factor | Average (CI) | p | Author’s conclusion |
|                     |           |                      |                   |              |   |                     |
| Geohelminthos        | Elias D et al., 2001 [51] Ethiopia | Students (18-24 years old) | Antihelmintic treatment | Study groups IFNγ levels |          | The use of antihelmintics potentiated the immune response against BCG vaccine. |
|                     |           |                      |                   | Albendazole (n = 29) | 170 pg/mL (136-204 pg/mL) | 0.04 |
|                     |           |                      |                   | 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 |          | Geohelmint 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) |          |
|                     | Lule et al., 2015 [52] Uganda | Children (1 – 5 years old) | Asymptomatic malaria | Study groups IFNγ levels |          | 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+ |          | Placental malaria generated a weak response of IFNγ to tuberculin at 12 months of age. |
|                     |           |                      |                   | Infected (n = 7) | 0.007% (0.002-0.007%) | 0.026 |
|                     |           |                      |                   | 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 |          | The infection was associated with a lower response to tuberculin. |
|                     |           |                      |                   | Infected (n = 63) | < 5mm: 33 children | 0.000 |
|                     |           |                      |                   | Uninfected (n = 187) | < 5mm: 22 children |          |
### Table 1 (continued). Effect of parasitic infections on the immune response to vaccines.

| 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 | 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) | < 0.01 Mening. | < 0.001 |
|                     |           |                      |                   | 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 |
|                     |           |                      |                   | Uninfected (n = 44) | |
| Usen et al., 2000 [57] Gambia | Children (12-30 months old) | Malaria by *P. falciparum* | | Study groups | Antibody levels | 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) | < 0.001 |
|                     |           |                      |                   | 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 |
|                     |           |                      |                   | Unexposed (n = 179) | |
| Filaroidosis        | 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) | Children sensitized by filarioidosis had significantly lower *Haemophilus influenzae* type B specific IgG levels. |
|                     |           |                      |                   | Unexposed (n = 110) | NI | 0.007 |
| 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) | Children sensitized by *S. haematobium* had significantly lower *Haemophilus influenzae* type B specific IgG levels. |
|                     |           |                      |                   | Unexposed (n = 90) | NI | 0.034 |
### Table 1 (continued). Effect of parasitic infections on the immune response to vaccines.

**Others vaccines**

| Study groups          | Antibody titres (GMT) | The antibody response to pertussis toxin was lower in infants infected with malaria than in a group of healthy infants. | The levels of IgG specific against Hepatitis B were not affected in children sensitized by *P. falciparum* |
|-----------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Simondon *et al.*, 1999 [58] Senegal Pertussis toxin | Infected (n = 66) 81.1 (72.4-91.2) Uninfected (n = 115) 97.3 (87.1-107.1) | (>) 05 | 0.59 |
| Malhotra *et al.*, 2015 [40] Kenya Hepatitis B | Infected (n = 188) 91.2 (82.0-101.2) Uninfected (n = 179) 91.2 (82.0-101.2) | NI | NS |
| Malaria | 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. |
| Brown *et al.*, 2014 [59] Tanzania human papillomavirus-16/18 AS04-adjuvanted | Malaria (n = 20) HPV16 4335 (2890-6502) HPV18 1109 (764-1609) Strongyloides stercoralis; Ascaris lumbricoides; Trichuris trichiura; Taenia spp. Uninfected (n = 129) HPV16 2843 (2171-3723) HPV18 1038 (802-1344) | 0.05 | 0.64 |
| Schistosomiasis | Study groups | Antibody titres EU/mL | Sensitization by *S. haematobium* was not associated with significantly lower Hepatitis B-specific IgG. |
| Malhotra *et al.*, 2015 [40] Kenya Hepatitis B | Sensitized (n = 238) 91.2 (82.0-101.2) Unexposed (n = 90) 91.2 (82.0-101.2) | NI | NS |
| Filariosis | Study groups | Antibody H1 titres | Sensitization by filarioidosis was not associated with significantly lower Hepatitis B-specific IgG. |
| Malhotra *et al.*, 2015 [40] Kenya Hepatitis B | Sensitized (n = 167) | A. lumbricoides-infected subjects who received placebo treatment before vaccination demonstrated a depressed IL-2 response. |
| Brückner *et al.*, 2015 [60] Gabon Seasonal influenza | Placebo (n = 38) | NS | NS |
| Helminthiasis | Study groups | Cytokines levels pg/mL | There was no significant difference in the H1 titers against the influenza vaccine between the two study groups. |
| Cooper *et al.*, 2001 [34] Ecuador Live oral cholera vaccine CVD 103-HgR | Anthelmintic (n = 15) IL2: 21.8 (6-74) INFγ: 7.7 (0-209) | IL2 0.03 | INFγ NS |

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, Pyrimethamine (PT) | Study groups CQ (n = 16) | Antibody levels 0.19 IU/mL | NS |
|                    |                      |                                    | No-chemoproph. (n = 36) | Antibody levels 0.18 IU/mL |     |
| Greenwood et al., 1981 [62] Nigeria | Children (3-17 months old) | Chloroquine                        | Study groups CQ (n = 93) | Antibody levels 5.7 log2 (3.1-8.6 log2) | NS |
|                    |                      |                                    | no-CQ (n = 91) | Antibody levels 5.9 log2 (5.5-6.3 log2) |     |
| Monjour et al., 1982 [63] Burkina Faso | Children (11 months-3 years old) | Amodiaquine (AQ)                  | Study groups AQ (n = 159) | Antibody levels | NI |
|                    |                      |                                    | no-AQ (n = 126) | Antibody levels | > 0.05 |
| Gilles et al., 1983 [64] Nigeria | Children (1-5 years old) | CQ Asymptomatamic malaria         | Study groups CQ (n = 123) | Antibody levels 1.31 IU/mL (1.06-1.56) | NS |
|                    |                      |                                    | no-CQ (n = 119) | Antibody levels 1.25 IU/mL (0.94-1.56) |     |
| Brabin et al., 1984 [65] Kenya | Pregnant women | CQ                                 | CQ: (n = 107) | Antibody levels | NI |
|                    |                      |                                    | no-CQ (n = 73) | Antibody levels | NS |
| Schellenberg et al., 2001 [66] Tanzania | Children (2 months old) | Sulfadoxine-Pyrimethamine (SP)    | Study group AQ (n = 351) | Antibody levels 12.7 IU/mL (7.6-18.7) | 0.28 |
|                    |                      |                                    | No-SP (n = 351) | Antibody levels | NS |
| Massaga et al., 2003 [67] Tanzania | Children (12-16 weeks) | AQ                                 | Study group AQ (n = 77) | Antibody levels 10.4 IU/mL (6.1-13.7) |     |
|                    |                      |                                    | Placebo (63) | Antibody levels |     |
| Rosen et al., 2005 [68] Burkina Faso | Children (4 months-6 years old) | AQ                                | Study group AQ (n = 134) | Antibody levels 104/134 (77%) | 0.08 |
|                    |                      |                                    | no-AQ (n = 138) | Antibody levels 126/138 (91%) |     |

| **Measles**        |                      |                                    |              |     |                                                                                     |
| McGregor et al., 1981 [62] Nigeria | Children (3-17 month old) | CQ                                 | Study group CQ (n = 93) | Antibody levels 3.5 log2 (3.1-3.9 log2) | NS |
|                    |                      |                                    | no-CQ (n = 91) | Antibody levels 2.9 log2 (2.6-3.2 log2) |     |
| Gilles et al., 1983 [64] Nigeria | Children (1-5 years old) | CQ Asymptomatamic malaria         | Study group CQ (n = 121) | Antibody levels 5.15 IU/mL (2.34-7.96) | NS |
|                    |                      |                                    | no-CP (n = 116) | Antibody levels 5.57 IU/mL (3.21-7.93) |     |
| Cènac et al., 1988 [69] Niger | Children (9-48 months old) | CQ                                 | Study group CQ (n = 289) | Seropositivity 218/289 (76%) | NS |
|                    |                      |                                    | no-CQ (n = 291) | Seropositivity 238/291 (82%) |     |
| Rosen et al., 2005 [68] Burkina Faso | Children (4 months-6 years old) | AQ                                | Study group AQ (n = 137) | Seropositivity 127/137 (93%) | 0.16 |
|                    |                      |                                    | no-AQ (n = 187) | Seropositivity 180/187 (96%) |     |
| **Author’s conclusion** |                      |                                    |              |     |                                                                                     |
| McGregor et al., 1981 [62] Nigeria | Children (3-17 month old) | CQ                                 | Study group CQ (n = 93) | Antibody levels 3.5 log2 (3.1-3.9 log2) | NS |
|                    |                      |                                    | no-CQ (n = 91) | Antibody levels 2.9 log2 (2.6-3.2 log2) |     |
| Gilles et al., 1983 [64] Nigeria | Children (1-5 years old) | CQ Asymptomatamic malaria         | Study group CQ (n = 121) | Antibody levels 5.15 IU/mL (2.34-7.96) | NS |
|                    |                      |                                    | no-CP (n = 116) | Antibody levels 5.57 IU/mL (3.21-7.93) |     |
| Cènac et al., 1988 [69] Niger | Children (9-48 months old) | CQ                                 | Study group CQ (n = 289) | Seropositivity 218/289 (76%) | NS |
|                    |                      |                                    | no-CQ (n = 291) | Seropositivity 238/291 (82%) |     |
| Rosen et al., 2005 [68] Burkina Faso | Children (4 months-6 years old) | AQ                                | Study group AQ (n = 137) | Seropositivity 127/137 (93%) | 0.16 |
|                    |                      |                                    | no-AQ (n = 187) | Seropositivity 180/187 (96%) |     |
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.
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, pertussis 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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