Chapter 7

The effect of helminth infections on cellular immune response of malaria infected subjects: A systematic review and meta-analysis of observational studies

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Abstract

Background

It has been postulated that helminths can influence the immune responses of malaria infected subjects. However, immuno-epidemiological studies report contradictory results. To summarize current available data and factors that may explain the differences observed we conducted a meta-analysis.

Methods

Articles were searched in 12 online databases. A random effect model was computed. Standardized mean difference and their 95% CIs were estimated using a "Restricted maximum likelihood estimator". The results were grouped to reflect the different arms of the cellular immune response. A moderator analysis was performed to understand the variations among the different studies.

Results

Of 1256 articles retrieved, 19 were eligible. Our main finding is that none of the immune parameters assessed in malaria infected subjects were influenced by helminth. Nonetheless, the results of the moderator analysis suggested that helminth species, past exposure to helminths, co-endemicity with multiple helminths and the type of immunological assays might explain this result.

Discussion and conclusion

This meta-analysis shows that a concurrent helminth infection does not influence the immune response of individuals co-infected with *P. falciparum*. However the moderator analysis also highlights the need for more standardized study designs and protocols to assess the interaction between helminths and malaria in immuno-epidemiological studies.

Introduction

Over the last decades, the question has arisen as to whether chronic helminth infections could have an impact on responses to a concurrent *Plasmodium spp.* infection. This question is important because helminths and malaria parasites share the same geographical distribution and frequently co-infect the same human host (1,2). From an immunological point of view, it has been demonstrated that helminths can exert potent modulatory effects on the immune system. A chronic helminth infection is usually marked by a Th2 polarized immune response (3) and by the induction of a regulatory network that can dampen the host immune response to the helminth itself (4–6), to other parasites (7,8) as well as to bystander antigens (9,10). A number of studies have examined the consequence of such immunological changes on malaria co-infection, but these have yielded variable results. In an attempt to determine the effect of helminths on immune responses during malaria infection in subjects living in areas endemic for both malaria and helminthiasis, we have performed a meta-analysis of the available observational studies. To our knowledge this is the first of its kind. Our objectives were firstly to specifically investigate the effect of helminths on response to infection with *Plasmodium spp.* and secondly to identify the factors that could explain the variability observed.

Methods

Literature search and selection of published articles

Literature search was carried out by an experienced librarian on the 13th of February 2014. Articles reporting on helminth and malaria co-infection in humans were searched in 12 different online databases. Databases included PubMed, MEDLINE, Embase, Web of Science, ScienceDirect as well as regional databases (See Appendix 1). The subject query was applied in all databases taking into account the terminological and technical differences between these databases. The query consisted of the combination of three subjects: helminths, malaria, and cellular immune response. Various synonyms and related terms for all subjects were used. Results were limited to human studies (see Appendix 2 for full details of the search queries). We did not

include any restriction on date of publication nor on language. Once identified, all articles were imported and stored into Reference Manager 12. Title and abstract of the identified articles were first screened for their relevance. Full texts of articles that passed this screening step were then consulted to check whether they were eligible for the meta-analysis. We considered eligible articles those that 1) reported results of a cross sectional, longitudinal or case control study, 2) were conducted in humans living in countries where helminth and malaria are endemic, 3) compared helminth and *Plasmodium spp.* co-infected subjects to subjects with single *Plasmodium spp.* infection 4) assessed the cellular immune response of the included participants. We excluded animal studies and case report studies in human. Studies were included regardless of their sample size, or whether or not they reported a randomization procedure for the selection of the participants.

Data extraction

Data were extracted from the eligible articles and saved in an electronic database. The type of data extracted were related to publication identification (author names, journal and year of publication) or to the study (objectives, study site, age group, type of helminths, Plasmodium species, type of immunological assays and the type of readouts for those assays as well as the statistical test used). In cases where multiple groups were assessed, we only extracted the data pertaining to the two groups of interest for our analysis. The mean and the standard deviation were extracted in order to calculate the effect size. When this information was not available in the text, they were calculated based on analysis of raw data provided by the authors or estimated from the available statistics. Authors were contacted when data were not available or when additional information was needed.

Statistical analysis

The statistical analysis was performed using R statistical software version 3.0.1 with his package metafor (version 1.9.2) and the integrated development environment Rstudio version 0.97.551. We used a random effect model for our meta-analysis since we assumed a within study random error as well as variation in effect size from one

study to the next that could lead to heterogeneity among the measured true effect.

Standardized mean difference (SMD) and their 95% CIs were estimated using a "Restricted maximum likelihood estimator" (REML). For a more comprehensible and systematic approach results reported in the selected articles were grouped in categories reflecting the Th1, Th2 or Th17 arm of the cellular immune response. Additional groups included results reporting on regulatory cytokines and regulatory T cells. Authors usually report results of more than one cytokine, for example TNF and IFN-γ for the Th1 cytokine group. Therefore our data were not considered independent and a multiple treatment meta-analysis was performed to take into account the dependency of the data. The unit of analysis was the article identification number.

A sensitivity analysis was conducted to assess the influence of moderators on the robustness of the results. The following moderator variables were considered 1) the type of helminth assessed (Schistosoma only, intestinal helminths only, filaria only or Schistosoma plus intestinal helminths), 2) the source of the cytokines (serum or plasma, intracellular or supernatants of stimulated cells) and 3) the type of stimuli used for stimulated cells (iRBCs, Malaria antigens, MSP1-19, LPS, LPS + Zymozan, PHA or PMA + ionomycin).

Results

Description of the selected articles

Figure 1 describes the selection process of the articles included in the meta-analysis. A description of the 19 eligible articles is given in table 1. The majority of studies (n = 17) were conducted in Africa (Nigeria:2 (22,25), Senegal:3 (26–28), Mali:7(11,13–15,19,21,23), Ghana:3 (8,18,20), Kenya: 2(16,17)) and two in Asia (India:1 (12), Indonesia:1(24)). Twelve studies were cross-sectional (8,14,16–20,22,24,25,27,28), 3 used case-control design (12,15,21), 1 was longitudinal (26) and 3 studies from the same authors combined a longitudinal and a case control design (11,13,23). The age range varied but majority of the studies (17 in total) included school aged children, whereas 1 focused on children aged from 3 to 6 (22) and two were

conducted in adults (12,28). When added together the total sample size was 2501 subjects (table 1).

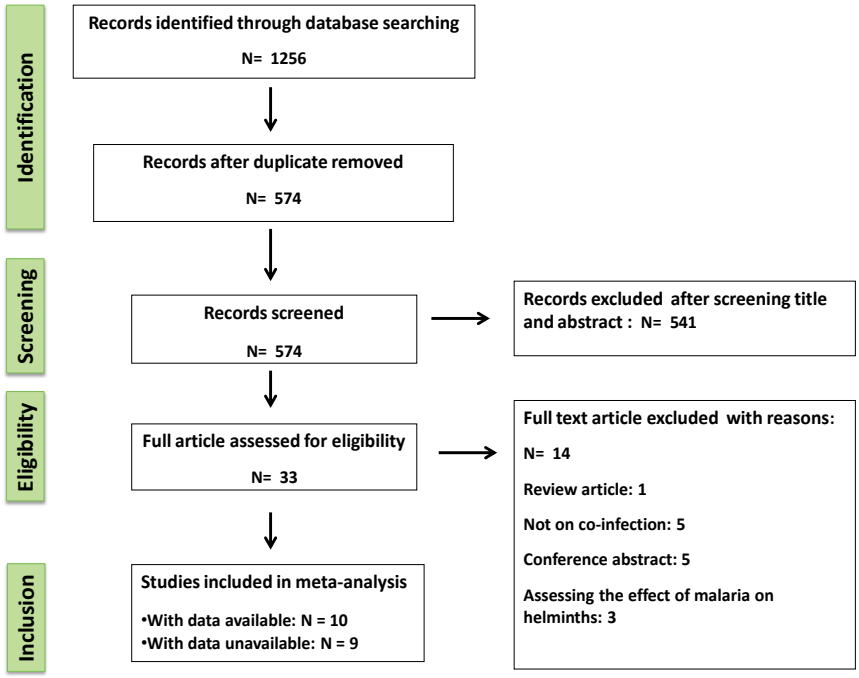

Figure 1: Flow chart showing the selection process of the articles included in the meta-analysis

Th1 and pro-inflammatory response

A total of 18 articles assessed the effect of helminths on the Th1/pro-inflammatory immune response of malaria co-infected subjects (8,12–28). Eight of the articles were not included in the meta-analysis because no raw data were available (12,15,17–19,24,26,28). From the 10 articles that were used, the Th1/pro-inflammatory responses were characterized based on the levels of IFN-γ (8,13,14,16,20–22,25,27), TNF (8,13,14,16,20–22,25), IL-12 (27), IL-12p40 (16), IL12-p70 (13,21), IL-2 (11,13,22), IL-8 (13,25), IL-1b (13), sTNFr (16). These analytes were measured either in the plasma/serum of the study

participants (13,16,22,25) or in supernatants obtained after stimulation of whole blood or PBMC (8,14,18,21,27). Intracellular cytokines in T cells were also taken along (14). The result of our meta-analysis is displayed in figure 2. Results indicate variation on the standardized mean difference of the cytokine of interest. For example in the case of TNF, 2 out of the 12 effect sizes reported showed a decrease in its level in helminth/malaria co-infected subjects in comparison with subjects with malaria only. In one study an increase of the effect size was observed in co-infected subjects whereas in 8 cases no significant difference was observed between malaria single infected and co-infected subjects. The pooled standardized mean difference was not significantly different between co-infected and single *P. falciparum* infected subjects (TNF SMD =-0.44 (95%CI [-1.33, 0.45], p = 0.33). This implies that helminth infections are not associated with a significant impairment of TNF response in malaria infected subjects although a trend toward a decrease was seen. IFN-γ another important Th1 cytokine was assessed in 9 studies that reported 16 different results. As shown in Figure 2, 2/16 results were in line with an increase of IFN-γ levels in co-infected subjects and 1/16 showed a decrease of this cytokines in the coinfected group by comparison to *P. falciparum* single infected subjects. In 13/16 studies no significant effect of helminths on IFN-γ response was seen in subjects with malaria. The pooled estimate of the effect size showed no overall effect of helminths on IFN-γ response (IFN-γ SMD = 0, 95%CI [-1.36, 1.36], p = 1). Similarly no effect of helminths was observed on the levels of IL-2, IL-8 or IL-12. When data of all the Th1/Pro-inflammatory cytokines were pooled, we failed to find a significant difference between helminth and malaria co-infected subjects in comparison to subjects with single *P. falciparum* infection (Overall SMD =0.02, 95% CI[-0.46, 0.49], p = 0.9).

Table 1: Characteristics of the studies included in the meta-analysis

N°	Authors (year of publication)	Study design	Country	Age range (in years)	Sample size *n*	Helminth species	Plasmodium species	Clinical malaria or asymptomatic carriage of *P. falciparum*	Immunological assay performed	Stimuli used if cells were stimulated	Read out
1	Noone et al. (2013)	Cross-sectionnal	Nigeria	3 to 6	231	*Ascaris Lumbricoides*	*P. falciparum*	Clinical malaria	Plasma cytokine	NA	Plasma cytokines
2	Courtin et al. (2011)	Longitudinal (but immunological assays done at one time point)	Senegal	6 to 19	305	*S. haematobium*	*P. falciparum*	Both	Plasma cytokine	NA	Plasma cytokines
3	Diallo et al. (2010)	Cross-sectional	Senegal	7 to 15	79	*S. haematobium*	*P. falciparum*	Asymptomatic carriage	Whole blood culture	MSP1 antigens and *P. falciparum* schizont lysate	Cytokines measured in the cell culture supernatant
4	Dolo et al. (2012)	Case control	Mali	4 to 20	24	*Wuchereria brancofti* and *Mansonella perstans*	*P. falciparum*	Clinical malaria	Plasma cytokine	NA	Plasma cytokine
5	Hartgers et al. (2009)	Cross-sectional	Ghana	6 to 12	117	*S. haematobium* and *intestinal helminths*	*P. falciparum*	Asymptomatic carriage	Whole blood culture	*P. falciparum* iRBCs	Cytokines measured in the cell culture supernatant

Abbreviations used: iRBC: infected Red Blood cells, PBMC: Peripheral Blood Mononuclear Cells, SEA: Soluble Eggs Antigens, SWA: Soluble Worm Antigen, SWAP: Soluble Worm Antigen Protein, AMA1: Apical membrane antigen 1, MSP1: Merozoite Surface Protein 1, PHA: Phytohaemagglutinin, NA: Not Applicable

Table 1 (*contd*): Characteristics of the studies included in the meta-analysis

N°	Authors (year of publicatio)	Study design	Country	Age range (in year)	Sample size *n*	Helminth species	Plasmodium species	Clinical malaria or asymptomatic carriage of *P. falciparum*	Immunological assay performed	Stimuli used if cells were stimulated	Read out
6	Lyke et al. (2006)	Nested case control	Mali	4 to 14	505	*S. haematobium*	*P. falciparum*	Clinical malaria	Serum cytokine	NA	Serum cytokine
7	Metenou et al. (2009)	Case-control	Mali	11 to 20	38	*Wuchereria brancofti* and *Mansonella perstans*	*P. falciparum*	No current plasmodium infection	Whole blood culture	iRBCs	Cytokines measured in cell culture supernatant
8	Metenou et al. (2011)	Cross-sectional	Mali	11 to 18	28	*Wuchereria brancofti* and *Mansonella perstans*	*P. falciparum*	Asymptomatic carriage	Whole blood culture	iRBCs	Intracellular cytokines
9	Muok et al. (2009)	Cross-sectional	Kenya	8 to 10	153	*Schistosoma mansoni*	*P. falciparum*	Not clear	Whole blood collected and stained withouth stimulation	NA	T cells characterized by surface markers
10	Nmorsi (2009)	Cross-sectional	Nigeria	1 to 15	160	*S. haematobium*	*P. falciparum*	Clinical malaria	Plasma cytokines	NA	Plasma cytokines
11	Wilson et al. (2009)	Cross-sectional	Kenya	4 to 17	228	*S. mansoni*	*P. falciparum*	Asymptomatic carriage	Plasma cytokines	NA	Plasma cytokines

Abbreviations used: iRBC: infected Red Blood cells, PBMC: Peripheral Blood Mononuclear Cells, SEA: Soluble Eggs Antigens, SWA: Soluble Worm Antigen, SWAP: Soluble Worm Antigen Protein, AMA1: Apical membrane antigen 1, MSP1: Merozoite Surface Protein 1, PHA: Phytohaemagglutinin, NA: Not Applicable

Table 1 (contd): Characteristics of the studies included in the meta-analysis

N°	Authors (year of publication)	Study design	Country	Age range (in years)	Sample size *n*	Helminth species	Plasmodium species	Clinical malaria or asymptomatic carriage of *P. falciparum*	Immunological assay performed	Stimuli used if cells were stimulated	Read out
12	Lyke et al. (2012)	Case control/longitudinal	Mali	4 to 14	38	*S. haematobium*	*P. falciparum*	Clinical malaria	Surface staining of PBMC	NA	T cells characterized by surface markers
13	Metenou et al. (2012)	Cross-sectional	Mali	11 to 18	35	*Wuchereria brancofti* and *Mansonella perstans*	*P. falciparum*	No current plasmodium infection	1.Whole blood culture 2.Gene expression 3.cDNA synthesis 4.RT-PCR	iRBCs	1.RNA 2.mDCs, pDCs
14	Panda et al. (2013)	Case control	India	Not determined but seems to be adult	234	Filaria (genus and species not specified in the text)	*P. falciparum*	Clinical malaria	1.Plasma cytokine 2.Whole blood	NA	1. Plasma cytokine 2.Regulatory T cells characterized by surface markers
15	Wammes et al. (2010)	Cross-sectionnal	Indonesia	School age children	20	Geo helminths	*P. falciparum*	No current plasmodium infection	1.Cell isolation, depletion and phenotyping 2.Proliferation assay	iRBCs	1.T cells characterization2.T cells proliferation 3.Cytokines in cell culture supernatatant

Abbreviations used: iRBC: infected Red Blood cells, PBMC: Peripheral Blood Mononuclear Cells, SEA: Soluble Eggs Antigens, SWA: Soluble Worm Antigen, SWAP: Soluble Worm Antigen Protein, AMA1: Apical membrane antigen 1, MSP1: Merozoite Surface Protein 1, PHA: Phytohaemagglutinin, NA: Not Applicable

Table 1 (contd): Characteristics of the studies included in the meta-analysis

N°	Authors (year of publication)	Study design	Country	Age range (in years)	Sample size *n*	Helminth species	Plasmodium species	Clinical malaria or asymptomatic carriage of *P. falciparum*	Immunological assay performed	Stimuli used if cells were stimulated	Read out
16	Wilson et al. (2009)	Cross-sectionnal	Kenya	4 to 17	79	*S. mansoni*	*P. falciparum*	Asymptomatic carriage	Whole blood culture	SEA, SWA and PHA	Cytokines in cell culture supernatatant
17	Hartgers et al. (2008)	Cross-sectional	Ghana	6 to 13	16	*S. haematobium and intestinal helminths*	*P. falciparum*	Asymptomatic carriage	Whole blood culture	iRBCs	Cytokines measured in the cell culture supernatant
18	Lyke et al. (2012)	Case control/ longitudinal	Mali	4 to 14	84	*S. haematobium*	*P. falciparum*	Clinical malaria	1.PBMC culture.2.Memory B cells assays 3.ELISA.4.Flow cytometry staining.5.EIISPOT	SEA, SWA, AMA1, MSP1	1.Antibodies, 2.Memory B cells response to malaria or schistosoma antigens
19	Diallo et al. (2004)	Cross-sectional	Sénégal	Children from 7 to 15 and adult more than 30 years old	Children: 79 Adult: 48	*S. haematobium*	*P. falciparum*	Asymptmatic carriage	Plasma cytokines	NA	Plasma cytokines

Abbreviations used: iRBC: infected Red Blood cells, PBMC: Peripheral Blood Mononuclear Cells, SEA: Soluble Eggs Antigens, SWA: Soluble Worm Antigen, SWAP: Soluble Worm Antigen Protein, AMA1: Apical membrane antigen 1, MSP1: Merozoite Surface Protein 1, PHA: Phytohaemagglutinin, NA: Not Applicable

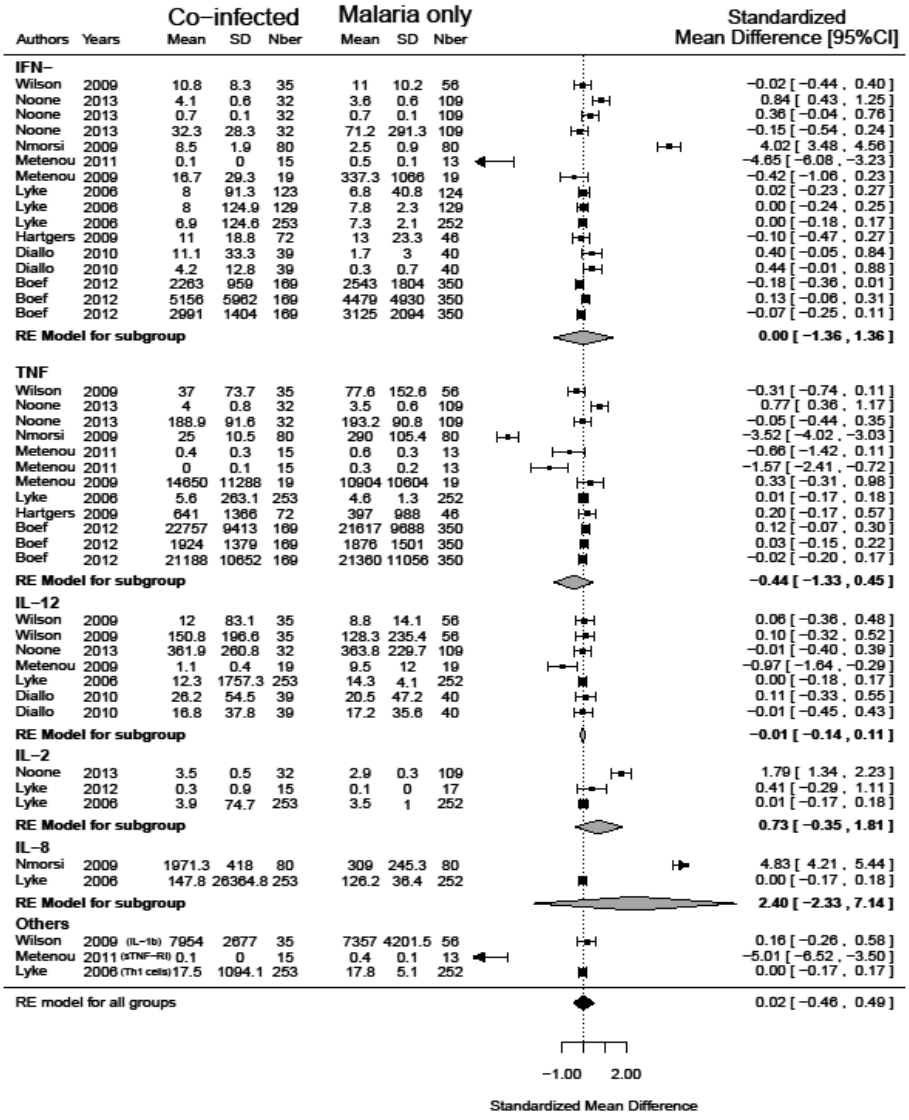

Figure 2: Forest plot of meta-analysis investigating the effect of helminth co-infection on the Th1/pro-inflammatory cytokines of *P. falciparum* infected subjects. The standardized mean difference (SMD) for each experiment is shown as a black square with 95% confidence intervals (CIs). The blue diamond represents the pooled estimate of the SMD for subgroup while the pooled estimate for all groups is shown at the bottom of the figure. Positive SMD indicates an increase of the Th1/pro-inflammatory cytokines in helminth and *P. falciparum* co-infected subjects by comparison to subjects with *P. falciparum* infection only.

Th2 cytokines

From the articles reporting on Th2 immune response that were eligible for the meta-analysis, 8 reported results on IL-4, IL-5, IL-13 cytokines that are known to be part of the Th2 response(8,13,14,16,20,22,25,27). In addition Metenou *et al.* assessed the Th2 immune response by characterizing multifunctional T cells that express IL-4, IL-5 and/or IL-10 (14). As depicted in figure 3 not much variation was observed in the reported effect of helminths on malaria regarding the Th2 cytokine responses assessed. Regardless of the cytokine, no difference was observed between the helminth and malaria co-infected compared to those subjects with *P. falciparum* only. The only exception to this observation was an increase of IL-4 and IL-5 in co-infected subjects reported by Nmorsi *et al.*(25) and an increase of IL-13 as indicated by the data from by Boef *et al.* (20).The overall pooled effect size did not reveal any difference between the two groups compared (Overall SMD = 0.24, 95% CI [-0.22, 0.69], p = 0.3).

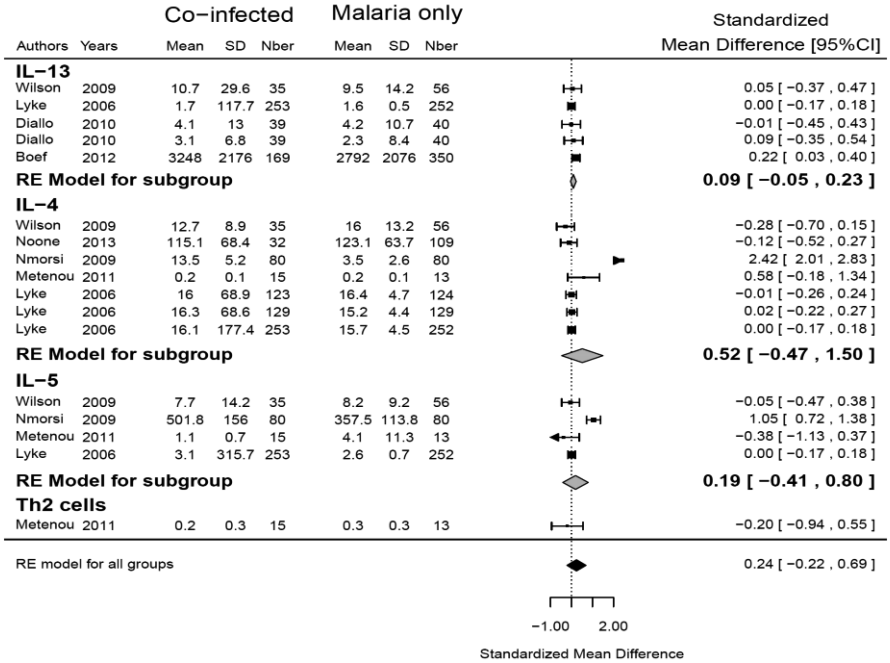

Figure 3: Forest plot of meta-analysis investigating the effect of helminth co-infection on the Th2 cytokines cytokines of *P. falciparum* infected subjects. The standardized mean difference (SMD) for each experiment is shown as a black square with 95% confidence intervals (CIs). The blue diamond represents the pooled estimate of the SMD for subgroup while the pooled estimate for all groups is shown at the bottom of the figure. Positive SMD indicates an increase of the Th2 cytokines in helminth and *P. falciparum* co-infected subjects by comparison to subjects with *P. falciparum* infection only.

Regulatory cytokines

IL-10 and TGF-β were the two regulatory cytokines studied (figure 4). The effect sizes of these cytokines were reported in 10 different articles that had generated 20 different results (8,13,14,16,18,20–22,25,27). A total of 16 different results obtained from 9 articles (8,13,14,16,20–22,25,27) reported on IL-10 which was found to be significantly higher in co-infected subjects for 4/16 studies (8,14,21,27). Conversely 1/16 showed a significant decrease of this cytokine in the co-infected group by comparison to subjects with *P. falciparum* only (13). Overall the meta-analysis revealed no significant effect of helminths on the IL-10 levels of malaria infected subjects despite a tendency for an increase in co-infected group (IL-10 SMD = 0.22, 95% CI [-0.12, 0.55], p =0.21). On the other hand data on the TGF-β were available from 3 articles which reported 4 results (16,22,27). Overall no differences were observed between co-infected and the malaria only group (TGF-β SMD= -0.12, 95% CI [-0.33, 0.09], p = 0.26). Finally the overall pooled estimate was not significantly different between the two groups that we compared (Overall SMD = 0.18, 95% CI [-0.14, 0.49], p =0.26).

Th17 cytokines

Data on the Th17 cytokines were available from 4 articles (14,20–22). They reported 7 different results that were included in the meta-analysis shown in Figure 5. A significant decrease of IL-17 was observed in 2 of the results in the helminth and malaria coinfected group (14,21). The remaining five available results did not show a significant effect of helminths on Th-17 response to *P. falciparum* infected subjects. Finally the pooled effect size did not differ significantly between the groups (Overall SMD =-0.17, 95% CI [-0.59, 0.24], p = 0.41)

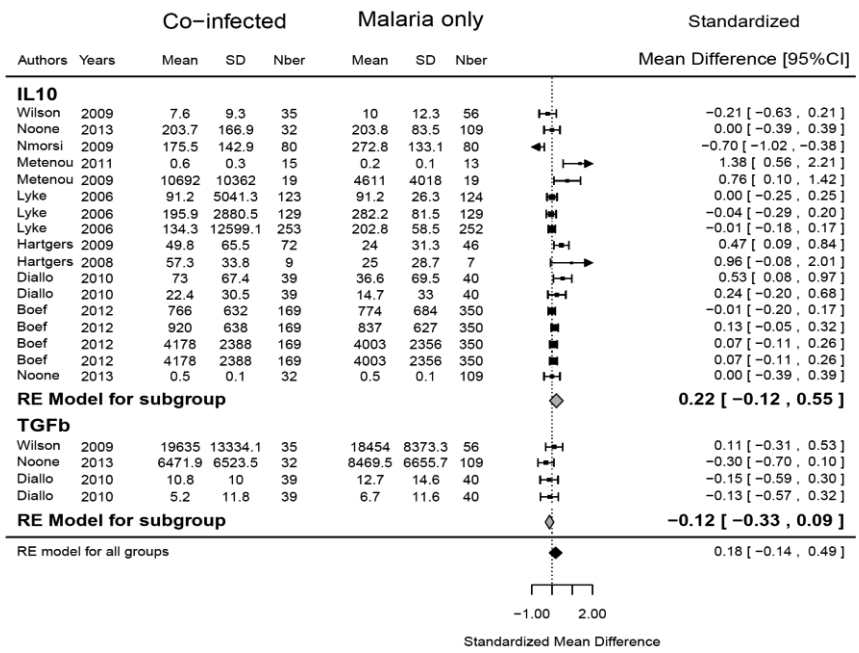

Figure 4: Forest plot of meta-analysis investigating the effect of helminth co-infection on the regulatory cytokines of *P. falciparum* infected subjects. The standardized mean difference (SMD) for each experiment is shown as a black square with 95% confidence intervals (CIs). The blue diamond represents the pooled estimate of the SMD for subgroup while the pooled estimate for all groups is shown at the bottom of the figure. Positive SMD indicates an increase of the regulatory cytokines in helminth and *P. falciparum* co-infected subjects by comparison to subjects with *P. falciparum* infection only.

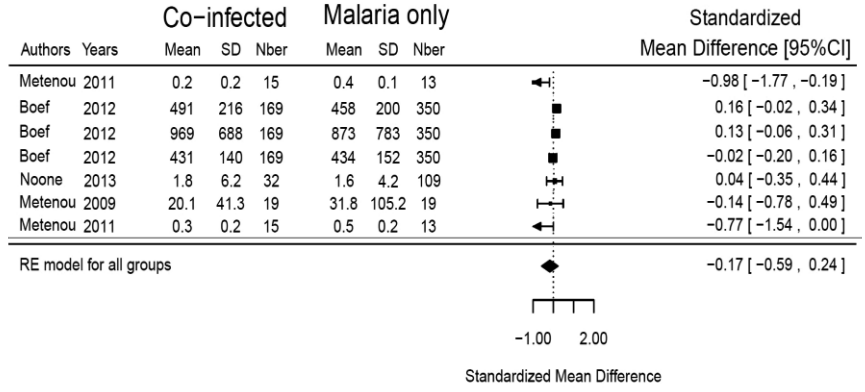

Figure 5: Forest plot of meta-analysis investigating the effect of helminth co-infection on the Th17 cytokines of *P. falciparum* infected subjects. The standardized mean difference (SMD) for each experiment is shown as a black square with 95% confidence intervals (CIs). The blue diamond represents the pooled estimate of the SMD for subgroup while the pooled estimate for all groups is shown at the bottom of the figure. Positive SMD indicates an increase of the Th17

cytokines in helminth and *P. falciparum* co-infected subjects by comparison to subjects with *P. falciparum* infection only.

Regulatory T cells

Data on the Regulatory T cells (Treg) were available from two different studies (11,14). They reported opposite effects. In one of these studies an increase in the frequency of Treg was reported (SMD= 0.86, 95%CI [0.09. 1.64]) (11) whereas in the other a lower frequency of Treg was observed (14) in co-infected subjects (SMD=-1.02, 95%CI [-1.69, -0.34]). The overall pooled effect was not significantly different between the groups (Overall SMD = -0.09, 95%CI [-1.93, 1.76], p = 0.9).

Publication bias

The presence of publication bias was assessed for the pooled effect size of the Th1, Th2 and the regulatory cytokine responses by scrutinizing their respective funnel plot. As shown in figure 6 funnel plots of the Th1 and regulatory cytokine responses show a roughly symmetrical structure indicating the absence of publication bias. Funnel plot for Th2 showed a slight asymmetry. Presence of publication bias was not assessed for the Th17 response nor for the regulatory T cells due to the small number of studies (less than 10).

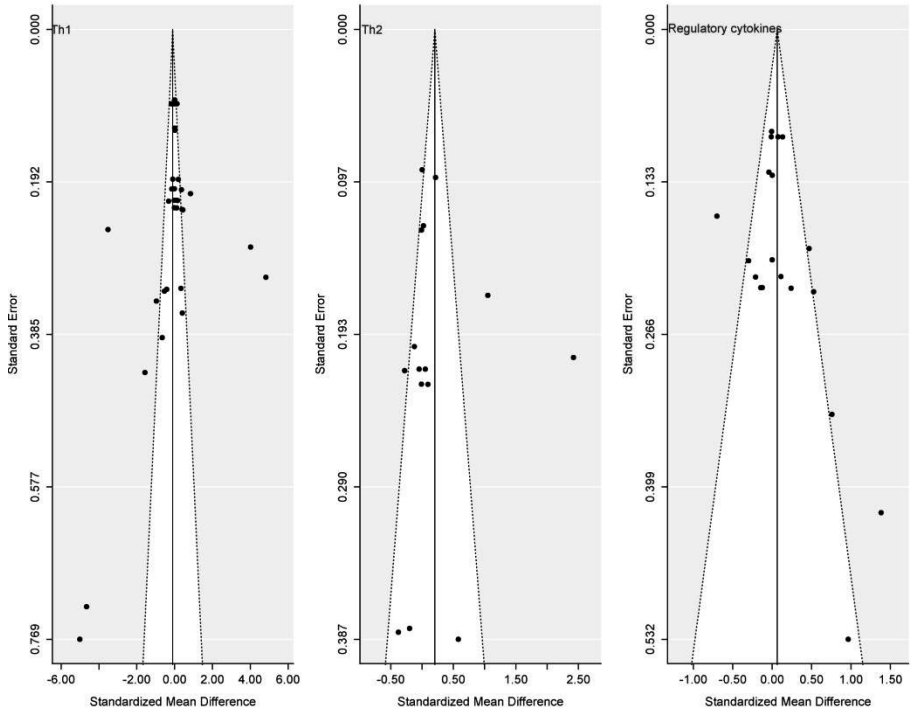

Figure 6: Funnel plot analysis to detect publication bias. The left panel shows funnel plot performed on the results published for the Th1/Pro-inflammatory cytokines whereas the middle and the right panels show funnel plots for the Th2 and the Regulatory cytokines. Each point represents a single result.

Moderator analysis

We conducted a moderator analysis to determine to what extent differences in methodologies or the characteristics of the populations assessed could have influenced the outcome of our meta-analysis. The moderator analysis was performed on the pooled estimate of the Th1, Th2, Th17 and regulatory cytokines effect size. The moderator analysis was not conducted on the effect size of the Regulatory T cells since only two results were available. As shown in Table 2 we observed that of the helminths studied filaria infection was associated with a significant decrease of the Th1 and the Th17 response in subjects with malaria (respectively Th1 SMD = -1.1, 95%CI [-2, -0.2], p =0.01 and Th17 SMD = -0.5, 95%CI[-1,-0.1], p = 0.008) along with a significant increase of the regulatory cytokines in the same group (Regulatory cytokines SMD = 1.02, 95%CI [0.4, 1.7], p = 0.001) suggesting a filaria

specific effect. It was noted that studies on filarial infection utilised an IgG diagnostic test that could also exclude past exposure to filarial infection. An increase of the regulatory cytokines was also observed when subjects with malaria were co-infected with both schistosoma and intestinal helminths (Regulatory cytokines SMD = 0.6, 95%CI [0.02, 1.1], p=0.04). This might indicate that not only the species of helminths but also the number of helminths species infecting the human host might influence the effect on the host immune system. When considering the second moderator variable (type of cytokines measurement) we noted that the pooled estimate of the Th17 response was higher in the co-infected group when this cytokine was measured intracellularly (Th17 SMD = -0.9, 95%CI[-1.4, -0.3], p = 0.002). Finally we observed that the use of PHA as a stimulus resulted in a significantly higher effect size of the Th2 response in the co-infected group (Th2 SMD = 0.2, 95%CI [0.09, 0.4], p = 0.008) whereas the use of iRBCs led to a significant increase in the regulatory cytokines in the same group (Regulatory cytokines SMD = 0.6, 95%CI [0.2, 1.01], p = 0.002).

Table 2: Result of the moderator analysis

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Moderators variables	Levels	Th1			Th2			Regulatory cytokines			Th17		
		N° of studies	SMD [95%CI]	p	N° of studies	SMD [95%CI]	p	N° of studies	SMD [95%CI]	p	N° of studies	SMD [95%CI]	p
Type of helminths	Intestinal helminths	13	0.2 [-0.6, 1.1]	0.6	3	0.05 [-0.8, 0.9]	0.9	6	-0.01 [-0.4, 0.3]	1	4	0.1 [-0.01, 0.2]	0.1
	Filaria*	7	1.1 [-2, -0.2]	0.01	4	0.02 [-0.9, 1]	1	3	1.02 [0.4, 1.7]	0.001	3	-0.5 [-1, -0.1]	0.008
	Schistosoma	21	0.3 [-0.2, 0.9]	0.2	16	0.4 [-0.2, 1.02]	0.2	10	-0.14 [-0.4, 0.14]	0.3	-	-	-
	Schistosoma and intestinal helminths	2	0.04 [-1.2, 1.3]	0.9	1	0.3 [-0.9, 1.6]	0.6	2	0.6 [0.02, 1.1]	0.04	-	-	-
Type of cytokine measurement	Plasma and serum Cytokines	19	-0.4 [-1.2, 0.5]	0.4	15	0.4 [-0.2, 0.9]	0.2	9	-0.1 [-0.5, 0.2]	0.5	1	0.04 [-0.4, 0.4]	0.8
	Cytokines measured after cells stimulation	15	-0.01 [-1.03, 1.01]	1	6	0.2 [-0.4, 0.8]	0.5	10	0.4 [-0.01, 0.7]	0.06	4	0.08 [-0.02, 0.2]	0.1
	Intracellular cytokines	9	0.5 [-0.3, 1.4]	0.2	3	-0.005 [-1.2, 1.2]	1	2	0.3 [-0.2, 0.8]	0.3	2	-0.9 [-1.4, -0.3]	0.002

SMD: Standardized mean difference

Table 2 *(contd)*: Result of the moderator analysis

Moderators variables	Levels	Th1			Th2			Regulatory cytokines			Th17		
		N° of studies	SMD [95%CI]	p	N° of studies	SMD [95%CI]	p	N° of studies	SMD [95%CI]	p	N° of studies	SMD [95%CI]	p
Type of stimuli used in case cytokines were measured after cells stimulation	iRBCs	11	-0.4 [-1.4, 0.4]	0.3	6	0.1 [-0.1, 0.3]	0.3	6	0.6 [0.2, 1.01]	0.002	3	-0.5 [-1.2, 0.2]	0.1
	Malaria antigens	1	0.4 [-1.6, 2.4]	0.7	-	-	-	-	-	-	-	-	-
	MSP1-19	2	-0.5 [-1.5, 0.5]	0.3	1	0.09 [-0.3, 0.5]	0.7	2	0.4 [-0.9, 0.1]	0.1	-	-	-
	LPS	2	-0.04 [-1.9, 1.8]	1	-	-	-	1	0.07 [-0.6, 0.7]	0.8	1	0.2 [-0.7, 1]	0.7
	LPS+Zymozan	2	-0.03 [-1.9, 1.8]	1	-	-	-	1	-0.01 [-0.7, 0.7]	1	1	-0.02 [-0.9, 0.8]	1
	PHA	2	0.08 [-1.8, 2]	0.9	2	0.2 [0.09, 0.4]	0.008	1	0.13 [-0.6, 0.8]	0.7	1	0.1 [-0.7, 1]	0.8
	PMA/Ionomycin	4	0.9 [-1, 3]	0.3		-	-	1	0 [-0.8, 0.8]	1	-	-	-

SMD: Standardized mean difference

Discussion

The Th1 response has been shown to be important for control of *Plasmodium spp*. infection. Experimental animal studies have indicated that mice that lack the ability to produce IFN-γ were unable to control the malaria parasites and died (29). In humans, Th1 type and pro inflammatory responses are also important for *P. falciparum* specific immunity since increased levels of IFN-γ and TNF have repeatedly been observed in malaria infected subjects and have been linked with protection from infection (30,31). In Gabon, a longitudinal study showed that individuals with an IFN-γ response to *P. falciparum* liver stage antigens had a significantly delayed time to re-infection and a low rate of re-infection compared to their non–responders counterpart (32).

Helminths known as strong inducers of the Th2 response have been shown to increase (15,22,25,27,28), decrease (13,14,21,25) or have no effect (8,12–16,19,20,22,27,28) on Th1 response in *P. falciparum* infected individuals. These studies have been included in the current meta-analysis and when pooled together yielded an effect size that suggests no significant impact of helminths on Th1 response to malaria.

In humans, IL-4 (31,33) and IL-13 (31) have been reported to be increased in individuals with uncomplicated malaria and might be further expanded in helminth co-infected subjects. Here out of the 23 results included in the meta-analysis only two showed an increase of IL-4 and IL-5 respectively in the co-infected groups. Furthermore the pooled effect did not yield any significant difference between the two groups despite a tendency for an increase in subjects co-infected with helminth and malaria. Similarly the results of the regulatory response and Th17 which has been shown to be expanded during *P. falciparum* infection did not show any change as a result of helminth co-infection.

People are usually exposed to helminth antigens already in utero (34), they get infected early in life (35) and most of the time they are infected with more than one helminth species (36). In this context it would be difficult to identify individuals that are truly free of helminths not only for current but also for past infections. It is most likely that the helminth free subjects included in the majority of the studies were

infected with more than one type of helminths, or had been exposed to helminths antigens prior to their participation in the studies. This is of particular interest for the interpretation of our results since; i) past exposure to helminth antigens could imprint the host immune system in lasting manner (37) and ii) host immune system could be modulated by antigens from different helminths species (38). One major limitation of the studies included in this meta-analysis is that most of them were cross sectional in design thus could not provide information on past exposure to helminths. Moreover as already alluded to, the studies mainly focused on one helminth species and therefore were not able to assess the confounding effect of other helminth infections.

This is supported by the moderator analysis we conducted to assess whether the effect of helminths on the cytokine response of *P. falciparum* infected subjects was dependent on the species of helminths assessed. Of the different helminth species examined in the studies included we noted that malaria co-infection with filaria in an area where no other helminths were endemic was associated with a significant decrease in the Th1/Pro-inflammatory as well as the Th17 response and with an increase of regulatory cytokines. However only two studies assessed the effect of filarial parasites on the immune response of malaria infected subjects and these were both reported by the same authors. Furthermore microscopic examination was used to determine current filarial infection whereas past infection with/exposure to filaria was ascertained by the detection of IgG to filarial antigens (14,21). With such a methodology it was possible to identify subjects that were truly free of filarial infection and therefore possible to show an effect of this helminth on the Th1 response of *P. falciparum* infected subjects.

The moderator analysis we performed was of particular importance in determining the factors that could influence the result of our meta-analysis. In addition to the type of helminths the details of the immunological assays used were important. For example the Th2 response was more pronounced in individuals coinfected with helminths and *P. falciparum* if PHA was used as stimulus. Similarly regulatory cytokine were more pronounced in subjects from the co-infected group if their cells were cultured with iRBCs rather than any other stimulus. Taken together these observations might indicate that

heterogeneity is mainly created by the various study designs and methodologies used. However this should not be seen as an obstacle for conducting a meta-analysis since the first aim of such an approach is to summarize studies that have inherent differences. Furthermore, it is possible, to use a random effect model (as we did here), to take into account the observed heterogeneity. Limitations of this meta-analysis are related to the fact that in the majority of the articles included, the selection of participants was not randomized, studies were cross sectional or sample sizes were small. These situations are well known and well described for meta-analyses conducted on observational studies that are by definition less strict than meta-analysis of randomized controlled trials in design (39–41). However due to the importance of such an analysis for summarizing results and informing researchers, meta-analysis is preferred to narrative review (40). It could be misleading to extend our results to all the components of the immune system. Indeed with the advances in technologies, the immune system appears more and more complex and this meta-analysis has only considered a fraction of this complexity. For example, due to the paucity of data, we were not able to assess whether the B cells or antibody responses of malaria infected subjects were affected by a concurrent helminth infection. Similarly neither cells involved in innate immunity nor the distribution of the different T cells subsets was assessed.

In conclusion this meta-analysis summarizes the results of immuno-epidemiological studies that assessed the effect of helminths on the cellular immune response of *P. falciparum* infected subjects. Our results indicate that current helminth infections do not affect *P. falciparum* associated immune response. However it is not clear whether this is due to the fact that individuals considered as free of helminths could have been exposed earlier in their life or could have harboured other helminth species also capable of modulating their immune response. Further studies will be needed to address this. Moreover this meta-analysis also highlights the need for more standardized study design and methodologies to assess the effect of helminths on *P. falciparum* specific immune response.

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Appendix

Appendix 1: List and links of the 12 consulted online databases

Database	*URL*
PubMed	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?otool=leiden
MEDLINE (OVID-version)	http://gateway.ovid.com/ovidweb.cgi?T=JS&MODE=ovid&NEWS=n&PAGE=main&D=prmz
Embase (OVID-version)	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=main&MODE=ovid&D=oemezd
Web of Science	http://isiknowledge.com/wos
ScienceDirect	http://www.sciencedirect.com/
AIM (African Index Medicus)	http://indexmedicus.afro.who.int/
IMEMR (Index Medicus for the Eastern Mediterranean Region)	http://applications.emro.who.int/library/Databases/wxis.exe/Library/Databases/iah/?IsisScript=iah/iah.xic&base=imemr&lang=i

IMSEAR (Index Medicus for South-East Asia Region)	http://imsear.hellis.org/
IndMED	http://indmed.nic.in/
KoreaMED	http://koreamed.org/SearchBasic.php
LILACS (Latin America and the Caribbean)	http://lilacs.bvsalud.org/en/
WPRIM (Western Pacific Region Index Medicus)	http://www.wprim.org/

Appendix 2: keywords used for the search strategy

Database	*Query*
PubMed	("Helminthiasis"[Mesh] OR "helminthiasis"[all fields] OR "helminthiases"[all fields] OR "Nematomorpha Infection"[all fields] OR "Nematomorpha Infections"[all fields] OR "Cestode Infections"[all fields] OR "Diphyllobothriasis"[all fields] OR "Echinococcosis"[all fields] OR "Hymenolepiasis"[all fields] OR "Monieziasis"[all fields] OR "Taeniasis"[all fields] OR "Dictyocaulus Infections"[all fields] OR "Dirofilariasis"[all fields] OR "Fascioloidiasis"[all fields] OR "Monieziasis"[all fields] OR "Setariasis"[all fields] OR "Equine Strongyle Infections"[all fields] OR "Toxocariasis"[all fields] OR "Nematode Infections"[all fields] OR "Adenophorea Infections"[all fields] OR "Larva Migrans"[all fields] OR "Secernentea Infections"[all fields] OR "Trematode Infections"[all fields] OR "Clonorchiasis"[all fields] OR "Dicrocoeliasis"[all fields] OR "Echinostomiasis"[all fields] OR "Fascioliasis"[all fields] OR "Fascioloidiasis"[all fields] OR "Opisthorchiasis"[all fields] OR "Paragonimiasis"[all fields] OR "Schistosomiasis"[all fields] OR "Cestode Infection"[all fields] OR "Dictyocaulus Infection"[all fields] OR "Equine Strongyle

	Infection"[all fields] OR "Nematode Infection"[all fields] OR "Adenophorea Infection"[all fields] OR "Secernentea Infection"[all fields] OR "Trematode Infection"[all fields] OR "Sparganosis"[all fields] OR "Cysticercosis"[all fields] OR "Neurocysticercosis"[all fields] OR "Enoplida Infections"[all fields] OR "Enoplida Infection"[all fields] OR "Trichinellosis"[all fields] OR "Trichuriasis"[all fields] OR "Ascaridida Infections"[all fields] OR "Ascaridida Infection"[all fields] OR "Anisakiasis"[all fields] OR "Ascariasis"[all fields] OR "Ascaridiasis"[all fields] OR "Toxascariasis"[all fields] OR "Toxocariasis"[all fields] OR "Oxyurida Infections"[all fields] OR "Oxyurida Infection"[all fields] OR "Oxyuriasis"[all fields] OR "Enterobiasis"[all fields] OR "Rhabditida Infections"[all fields] OR "Rhabditida Infection"[all fields] OR "Strongyloidiasis"[all fields] OR "Spirurida Infections"[all fields] OR "Spirurida Infection"[all fields] OR "Dracunculiasis"[all fields] OR "Filariasis"[all fields] OR "Acanthocheilonemiasis"[all fields] OR "Dipetalonema Infections"[all fields] OR "Dipetalonema Infection"[all fields] OR "Dirofilariasis"[all fields] OR "Filarial Elephantiasis"[all fields] OR "Loiasis"[all fields] OR "Mansonelliasis"[all fields] OR "Onchocerciasis"[all fields] OR "Setariasis"[all fields] OR "Gnathostomiasis"[all fields] OR "Strongylida Infections"[all fields] OR "Hookworm Infections"[all fields] OR "Strongylida Infection"[all fields] OR "Hookworm Infection"[all fields] OR "Ancylostomiasis"[all fields] OR "Necatoriasis"[all fields] OR "Oesophagostomiasis"[all fields] OR "Strongyle Infections"[all fields] OR "Strongyle Infection"[all fields] OR "Trichostrongyloidiasis"[all fields] OR "Dictyocaulus Infections"[all fields] OR "Dictyocaulus Infection"[all fields] OR "Haemonchiasis"[all fields] OR "Ostertagiasis"[all fields] OR "Trichostrongylosis"[all fields] OR "Neuroschistosomiasis"[all fields] OR "Helminths"[Mesh] OR "Helminths"[all fields] OR "Helminth"[all fields] OR "Parasitic Worms"[all fields] OR "Parasitic Worm"[all fields] OR "Aschelminthes"[all fields] OR "Aschelminthe"[all fields] OR "Gordius"[all fields] OR "Nematomorpha"[all fields] OR "Nematomorphas"[all fields] OR "Acanthocephala"[all fields] OR "Moniliformis"[all fields] OR "Nematoda"[all fields] OR "Adenophorea"[all fields] OR "Secernentea"[all fields] OR "Platyhelminths"[all fields] OR "Cestoda"[all fields] OR "Trematoda"[all fields] OR "Turbellaria"[all fields] OR "Rotifera"[all fields] OR "Enoplida"[all fields] OR "Dioctophymatoidea"[all fields] OR "Mermithoidea"[all fields] OR "Trichuroidea"[all fields] OR "Capillaria"[all fields] OR "Trichinella"[all fields] OR "Trichinella spiralis"[all fields] OR "Trichuris"[all fields] OR "Ascaridida"[all fields] OR "Ascaridia"[all fields] OR "Ascaridoidea"[all fields] OR "Anisakis"[all fields] OR "Ascaris"[all fields] OR "Ascaris

	lumbricoides"[all fields] OR "Ascaris suum"[all fields] OR "Toxascaris"[all fields] OR "Toxocara"[all fields] OR "Toxocara canis"[all fields] OR "Oxyurida"[all fields] OR "Oxyuroidea"[all fields] OR "Enterobius"[all fields] OR "Rhabditida"[all fields] OR "Rhabdiasoidea"[all fields] OR "Strongyloides"[all fields] OR "Rhabditoidea"[all fields] OR "Caenorhabditis"[all fields] OR "Spirurida"[all fields] OR "Camallanina"[all fields] OR "Dracunculoidea"[all fields] OR "Dracunculus Nematode"[all fields] OR "Spirurina"[all fields] OR "Filarioidea"[all fields] OR "Acanthocheilonema"[all fields] OR "Brugia "[all fields] OR "Dipetalonema"[all fields] OR "Dirofilaria "[all fields] OR "Loa"[all fields] OR "Mansonella"[all fields] OR "Microfilaria"[all fields] OR "Onchocerca "[all fields] OR "Setaria Nematode"[all fields] OR "Wuchereria"[all fields] OR "Spiruroidea"[all fields] OR "Thelazioidea"[all fields] OR "Gnathostoma"[all fields] OR "Strongylida"[all fields] OR "Ancylostomatoidea"[all fields] OR "Ancylostoma"[all fields] OR "Necator"[all fields] OR "Necator americanus"[all fields] OR "Heligmosomatoidea"[all fields] OR "Nematospiroides"[all fields] OR "Nematospiroides dubius"[all fields] OR "Nippostrongylus"[all fields] OR "Metastrongyloidea"[all fields] OR "Angiostrongylus"[all fields] OR "Molineoidae"[all fields] OR "Nematodirus"[all fields] OR "Strongyloidea"[all fields] OR "Oesophagostomum"[all fields] OR "Strongylus"[all fields] OR "Trichostrongyloidea"[all fields] OR "Dictyocaulus"[all fields] OR "Haemonchus"[all fields] OR "Ostertagia"[all fields] OR "Trichostrongylus"[all fields] OR "Tylenchida"[all fields] OR "Tylenchoidea"[all fields]) AND ("Malaria"[Mesh] OR malaria* OR "malaria"[all fields] OR "Paludism"[all fields] OR "Plasmodium Infections"[all fields] OR "Plasmodium Infection"[all fields]) AND ("Immunity, Cellular"[Mesh] OR "cellular immune response"[all fields] OR "cellular immune responses"[all fields] OR "Cellular Immunities"[all fields] OR "Cellular Immunity"[all fields] OR "Cell-Mediated Immunity"[all fields] OR "Cell Mediated Immunity"[all fields] OR "Cell-Mediated Immunities"[all fields] OR "Antigen Presentation"[all fields] OR "Immunologic Surveillance"[all fields] OR "Lymphocyte Activation"[all fields] OR "Cross-Priming"[all fields] OR "Cytokines"[mesh] OR "cytokines"[all fields] OR "cytokine"[all fields] OR "CD4-Positive T-Lymphocytes"[Mesh] OR "Antigens, CD4"[Mesh] OR "cd4"[all fields] OR "cd-4"[all fields] OR "t cell"[all fields] OR "t cells"[all fields] OR "T-Lymphocytes"[Mesh] OR "T-Lymphocyte"[all fields] OR "T-Lymphocytes"[all fields] OR "b cell" OR "b cells" OR "B-Lymphocytes"[Mesh] OR "B-Lymphocyte"[all fields] OR "B-Lymphocytes"[all fields] OR "Dendritic Cells"[Mesh] OR "Dendritic Cells"[all fields] OR "Dendritic Cell"[all fields] OR "Chemokines"[all fields] OR "Chemokine"[all fields] OR "beta-

	Thromboglobulin"[all fields] OR "Macrophage Inflammatory Proteins"[all fields] OR "Growth Differentiation Factor"[all fields] OR "Growth Differentiation Factors"[all fields] OR "Hematopoietic Cell Growth Factors"[all fields] OR "Hematopoietic Cell Growth Factor"[all fields] OR "Haematopoietic Cell Growth Factors"[all fields] OR "Haematopoietic Cell Growth Factor"[all fields] OR "Colony-Stimulating Factors"[all fields] OR "Colony-Stimulating Factor"[all fields] OR "Stem Cell Factor"[all fields] OR "Stem Cell Factors"[all fields] OR "Hepatocyte Growth Factor"[all fields] OR "Hepatocyte Growth Factors"[all fields] OR "Interferons"[all fields] OR "Interferon"[all fields] OR "Interleukin"[all fields] OR "Interleukins"[all fields] OR Interleukin*[all fields] OR "Leukemia Inhibitory Factor"[all fields] OR "Leukemia Inhibitory Factors"[all fields] OR "Lymphokines"[all fields] OR "Lymphokine"[all fields] OR "Leukocyte Migration-Inhibitory Factors"[all fields] OR "Leukocyte Migration-Inhibitory Factor"[all fields] OR "Lymphotoxin-alpha"[all fields] OR "Macrophage-Activating Factors"[all fields] OR "Macrophage Migration-Inhibitory Factors"[all fields] OR "Macrophage-Activating Factor"[all fields] OR "Macrophage Migration-Inhibitory Factor"[all fields] OR "Transfer Factor"[all fields] OR "Transfer Factors"[all fields] OR "Monokines"[all fields] OR "Monokine"[all fields] OR "Tumor Necrosis Factor"[all fields] OR "Tumor Necrosis Factors"[all fields] OR "Tumour Necrosis Factor"[all fields] OR "Tumour Necrosis Factors"[all fields] OR "Oncostatin M"[all fields] OR "Osteopontin"[all fields] OR "Transforming Growth Factor"[all fields] OR "Transforming Growth Factors"[all fields] OR "4-1BB Ligand"[all fields] OR "CD70"[all fields] OR "B-Cell Activating Factor"[all fields] OR "B-Cell Activating Factors"[all fields] OR "CD30"[all fields] OR "CD40"[all fields] OR "Ectodysplasins"[all fields] OR "Fas Ligand Protein"[all fields] OR "Fas Ligand Proteins"[all fields] OR "Lymphotoxin-alpha"[all fields] OR "Lymphotoxin-beta"[all fields] OR "OX40 Ligand"[all fields] OR "RANK Ligand"[all fields] OR "TNF"[all fields] OR "dendritic"[all fields]) NOT ("Animals"[mesh] NOT "Humans"[mesh])
MEDLINE (OVID-version)	(exp Helminthiasis/ OR "helminthiasis".af OR "helminthiases".af OR "Nematomorpha Infection".af OR "Nematomorpha Infections".af OR "Cestode Infections".af OR "Diphyllobothriasis".af OR "Echinococcosis".af OR "Hymenolepiasis".af OR "Monieziasis".af OR "Taeniasis".af OR "Dictyocaulus Infections".af OR "Dirofilariasis".af OR "Fascioloidiasis".af OR "Monieziasis".af OR "Setariasis".af OR "Equine Strongyle Infections".af OR "Toxocariasis".af OR "Nematode Infections".af OR "Adenophorea Infections".af OR "Larva Migrans".af OR "Secernentea Infections".af OR "Trematode

	Infections".af OR "Clonorchiasis".af OR "Dicrocoeliasis".af OR "Echinostomiasis".af OR "Fascioliasis".af OR "Fascioloidiasis".af OR "Opisthorchiasis".af OR "Paragonimiasis".af OR "Schistosomiasis".af OR "Cestode Infection".af OR "Dictyocaulus Infection".af OR "Equine Strongyle Infection".af OR "Nematode Infection".af OR "Adenophorea Infection".af OR "Secernentea Infection".af OR "Trematode Infection".af OR "Sparganosis".af OR "Cysticercosis".af OR "Neurocysticercosis".af OR "Enoplida Infections".af OR "Enoplida Infection".af OR "Trichinellosis".af OR "Trichuriasis".af OR "Ascaridida Infections".af OR "Ascaridida Infection".af OR "Anisakiasis".af OR "Ascariasis".af OR "Ascaridiasis".af OR "Toxascariasis".af OR "Toxocariasis".af OR "Oxyurida Infections".af OR "Oxyurida Infection".af OR "Oxyuriasis".af OR "Enterobiasis".af OR "Rhabditida Infections".af OR "Rhabditida Infection".af OR "Strongyloidiasis".af OR "Spirurida Infections".af OR "Spirurida Infection".af OR "Dracunculiasis".af OR "Filariasis".af OR "Acanthocheilonemiasis".af OR "Dipetalonema Infections".af OR "Dipetalonema Infection".af OR "Dirofilariasis".af OR "Filarial Elephantiasis".af OR "Loiasis".af OR "Mansonelliasis".af OR "Onchocerciasis".af OR "Setariasis".af OR "Gnathostomiasis".af OR "Strongylida Infections".af OR "Hookworm Infections".af OR "Strongylida Infection".af OR "Hookworm Infection".af OR "Ancylostomiasis".af OR "Necatoriasis".af OR "Oesophagostomiasis".af OR "Strongyle Infections".af OR "Strongyle Infection".af OR "Trichostrongyloidiasis".af OR "Dictyocaulus Infections".af OR "Dictyocaulus Infection".af OR "Haemonchiasis".af OR "Ostertagiasis".af OR "Trichostrongylosis".af OR "Neuroschistosomiasis".af OR exp Helminths/ OR "Helminths".af OR "Helminth".af OR "Parasitic Worms".af OR "Parasitic Worm".af OR "Aschelminthes".af OR "Aschelminthe".af OR "Gordius".af OR "Nematomorpha".af OR "Nematomorphas".af OR "Acanthocephala".af OR "Moniliformis".af OR "Nematoda".af OR "Adenophorea".af OR "Secernentea".af OR "Platyhelminths".af OR "Cestoda".af OR "Trematoda".af OR "Turbellaria".af OR "Rotifera".af OR "Enoplida".af OR "Dioctophymatoidea".af OR "Mermithoidea".af OR "Trichuroidea".af OR "Capillaria".af OR "Trichinella".af OR "Trichinella spiralis".af OR "Trichuris".af OR "Ascaridida".af OR "Ascaridia".af OR "Ascaridoidea".af OR "Anisakis".af OR "Ascaris".af OR "Ascaris lumbricoides".af OR "Ascaris suum".af OR "Toxascaris".af OR "Toxocara".af OR "Toxocara canis".af OR "Oxyurida".af OR "Oxyuroidea".af OR "Enterobius".af OR "Rhabditida".af OR "Rhabdiasoidea".af OR "Strongyloides".af OR "Rhabditoidea".af OR "Caenorhabditis".af OR "Spirurida".af OR "Camallanina".af OR "Dracunculoidea".af OR "Dracunculus Nematode".af OR "Spirurina".af OR "Filarioidea".af OR

	"Acanthocheilonema".af OR "Brugia ".af OR "Dipetalonema".af OR "Dirofilaria ".af OR "Loa".af OR "Mansonella".af OR "Microfilaria".af OR "Onchocerca ".af OR "Setaria Nematode".af OR "Wuchereria".af OR "Spiruroidea".af OR "Thelazioidea".af OR "Gnathostoma".af OR "Strongylida".af OR "Ancylostomatoidea".af OR "Ancylostoma".af OR "Necator".af OR "Necator americanus".af OR "Heligmosomatoidea".af OR "Nematospiroides".af OR "Nematospiroides dubius".af OR "Nippostrongylus".af OR "Metastrongyloidea".af OR "Angiostrongylus".af OR "Molineoidae".af OR "Nematodirus".af OR "Strongyloidea".af OR "Oesophagostomum".af OR "Strongylus".af OR "Trichostrongyloidea".af OR "Dictyocaulus".af OR "Haemonchus".af OR "Ostertagia".af OR "Trichostrongylus".af OR "Tylenchida".af OR "Tylenchoidea".af) AND (exp Malaria/ OR malaria*.af OR "malaria".af OR "Paludism".af OR "Plasmodium Infections".af OR "Plasmodium Infection".af) AND (exp Immunity, Cellular/ OR cellular immune response.af OR cellular immune responses.af OR Cellular Immunities.af OR Cellular Immunity.af OR Cell-Mediated Immunity.af OR Cell Mediated Immunity.af OR Cell-Mediated Immunities.af OR Antigen Presentation.af OR Immunologic Surveillance.af OR Lymphocyte Activation.af OR Cross-Priming.af OR exp Cytokines/ OR cytokines.af OR cytokine.af OR exp CD4-Positive T-Lymphocytes/ OR exp Antigens, CD4/ OR cd4.af OR cd-4.af OR t cell.af OR t cells.af OR exp T-Lymphocytes/ OR T-Lymphocyte.af OR T-Lymphocytes.af OR b cell OR b cells OR exp B-Lymphocytes/ OR B-Lymphocyte.af OR B-Lymphocytes.af OR exp Dendritic Cells/ OR Dendritic Cells.af OR Dendritic Cell.af OR Chemokines.af OR Chemokine.af OR beta-Thromboglobulin.af OR Macrophage Inflammatory Proteins.af OR Growth Differentiation Factor.af OR Growth Differentiation Factors.af OR Hematopoietic Cell Growth Factors.af OR Hematopoietic Cell Growth Factor.af OR Haematopoietic Cell Growth Factors.af OR Haematopoietic Cell Growth Factor.af OR Colony-Stimulating Factors.af OR Colony-Stimulating Factor.af OR Stem Cell Factor.af OR Stem Cell Factors.af OR Hepatocyte Growth Factor.af OR Hepatocyte Growth Factors.af OR Interferons.af OR Interferon.af OR Interleukin.af OR Interleukins.af OR Interleukin*.af OR Leukemia Inhibitory Factor.af OR Leukemia Inhibitory Factors.af OR Lymphokines.af OR Lymphokine.af OR Leukocyte Migration-Inhibitory Factors.af OR Leukocyte Migration-Inhibitory Factor.af OR Lymphotoxin-alpha.af OR Macrophage-Activating Factors.af OR Macrophage Migration-Inhibitory Factors.af OR Macrophage-Activating Factor.af OR Macrophage Migration-Inhibitory Factor.af OR Transfer Factor.af OR Transfer Factors.af OR Monokines.af OR Monokine.af OR Tumor Necrosis Factor.af OR Tumor Necrosis Factors.af OR Tumour Necrosis Factor.af OR

	Tumour Necrosis Factors.af OR Oncostatin M.af OR Osteopontin.af OR Transforming Growth Factor.af OR Transforming Growth Factors.af OR 4-1BB Ligand.af OR CD70.af OR B-Cell Activating Factor.af OR B-Cell Activating Factors.af OR CD30.af OR CD40.af OR Ectodysplasins.af OR Fas Ligand Protein.af OR Fas Ligand Proteins.af OR Lymphotoxin-alpha.af OR Lymphotoxin-beta.af OR OX40 Ligand.af OR RANK Ligand.af OR TNF.af OR dendritic.af) NOT (exp Animals/ NOT exp Humans/)
Embase (OVID-version)	(exp Helminthiasis/ OR "helminthiasis".af OR "helminthiases".af OR "Nematomorpha Infection".af OR "Nematomorpha Infections".af OR "Cestode Infections".af OR "Diphyllobothriasis".af OR "Echinococcosis".af OR "Hymenolepiasis".af OR "Monieziasis".af OR "Taeniasis".af OR "Dictyocaulus Infections".af OR "Dirofilariasis".af OR "Fascioloidiasis".af OR "Monieziasis".af OR "Setariasis".af OR "Equine Strongyle Infections".af OR "Toxocariasis".af OR "Nematode Infections".af OR "Adenophorea Infections".af OR "Larva Migrans".af OR "Secernentea Infections".af OR "Trematode Infections".af OR "Clonorchiasis".af OR "Dicrocoeliasis".af OR "Echinostomiasis".af OR "Fascioliasis".af OR "Fascioloidiasis".af OR "Opisthorchiasis".af OR "Paragonimiasis".af OR "Schistosomiasis".af OR "Cestode Infection".af OR "Dictyocaulus Infection".af OR "Equine Strongyle Infection".af OR "Nematode Infection".af OR "Adenophorea Infection".af OR "Secernentea Infection".af OR "Trematode Infection".af OR "Sparganosis".af OR "Cysticercosis".af OR "Neurocysticercosis".af OR "Enoplida Infections".af OR "Enoplida Infection".af OR "Trichinellosis".af OR "Trichuriasis".af OR "Ascaridida Infections".af OR "Ascaridida Infection".af OR "Anisakiasis".af OR "Ascariasis".af OR "Ascaridiasis".af OR "Toxascariasis".af OR "Toxocariasis".af OR "Oxyurida Infections".af OR "Oxyurida Infection".af OR "Oxyuriasis".af OR "Enterobiasis".af OR "Rhabditida Infections".af OR "Rhabditida Infection".af OR "Strongyloidiasis".af OR "Spirurida Infections".af OR "Spirurida Infection".af OR "Dracunculiasis".af OR "Filariasis".af OR "Acanthocheilonemiasis".af OR "Dipetalonema Infections".af OR "Dipetalonema Infection".af OR "Dirofilariasis".af OR "Filarial Elephantiasis".af OR "Loiasis".af OR "Mansonelliasis".af OR "Onchocerciasis".af OR "Setariasis".af OR "Gnathostomiasis".af OR "Strongylida Infections".af OR "Hookworm Infections".af OR "Strongylida Infection".af OR "Hookworm Infection".af OR "Ancylostomiasis".af OR "Necatoriasis".af OR "Oesophagostomiasis".af OR "Strongyle Infections".af OR "Strongyle Infection".af OR "Trichostrongyloidiasis".af OR

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	OR exp B-Lymphocyte/ OR B Lymphocyte.af OR B Lymphocytes.af OR BLymphocyte.af OR BLymphocytes.af OR B-Lymphocyte.af OR B-Lymphocytes.af OR exp Dendritic Cell/ OR Dendritic Cells.af OR Dendritic Cell.af OR Chemokines.af OR Chemokine.af OR beta-Thromboglobulin.af OR Macrophage Inflammatory Proteins.af OR Growth Differentiation Factor.af OR Growth Differentiation Factors.af OR Hematopoietic Cell Growth Factors.af OR Hematopoietic Cell Growth Factor.af OR Haematopoietic Cell Growth Factors.af OR Haematopoietic Cell Growth Factor.af OR Colony-Stimulating Factors.af OR Colony-Stimulating Factor.af OR Stem Cell Factor.af OR Stem Cell Factors.af OR Hepatocyte Growth Factor.af OR Hepatocyte Growth Factors.af OR Interferons.af OR Interferon.af OR Interleukin.af OR Interleukins.af OR Interleukin*.af OR Leukemia Inhibitory Factor.af OR Leukemia Inhibitory Factors.af OR Lymphokines.af OR Lymphokine.af OR Leukocyte Migration-Inhibitory Factors.af OR Leukocyte Migration-Inhibitory Factor.af OR Lymphotoxin-alpha.af OR Macrophage-Activating Factors.af OR Macrophage Migration-Inhibitory Factors.af OR Macrophage-Activating Factor.af OR Macrophage Migration-Inhibitory Factor.af OR Transfer Factor.af OR Transfer Factors.af OR Monokines.af OR Monokine.af OR Tumor Necrosis Factor.af OR Tumor Necrosis Factors.af OR Tumour Necrosis Factor.af OR Tumour Necrosis Factors.af OR Oncostatin M.af OR Osteopontin.af OR Transforming Growth Factor.af OR Transforming Growth Factors.af OR 4-1BB Ligand.af OR CD70.af OR B-Cell Activating Factor.af OR B-Cell Activating Factors.af OR CD30.af OR CD40.af OR Ectodysplasins.af OR Fas Ligand Protein.af OR Fas Ligand Proteins.af OR Lymphotoxin-alpha.af OR Lymphotoxin-beta.af OR OX40 Ligand.af OR RANK Ligand.af OR TNF.af OR dendritic.af) NOT (exp Animals/ NOT exp Humans/)
Web of Science	TS=((Helminthiasis OR "helminthiasis" OR "helminthiases" OR "Nematomorpha Infection" OR "Nematomorpha Infections" OR "Cestode Infections" OR "Diphyllobothriasis" OR "Echinococcosis" OR "Hymenolepiasis" OR "Monieziasis" OR "Taeniasis" OR "Dictyocaulus Infections" OR "Dirofilariasis" OR "Fascioloidiasis" OR "Monieziasis" OR "Setariasis" OR "Equine Strongyle Infections" OR "Toxocariasis" OR "Nematode Infections" OR "Adenophorea Infections" OR "Larva Migrans" OR "Secernentea Infections" OR "Trematode Infections" OR "Clonorchiasis" OR "Dicrocoeliasis" OR "Echinostomiasis" OR "Fascioliasis" OR "Fascioloidiasis" OR "Opisthorchiasis" OR "Paragonimiasis" OR "Schistosomiasis" OR "Cestode Infection" OR "Dictyocaulus Infection" OR "Equine Strongyle Infection" OR

	"Nematode Infection" OR "Adenophorea Infection" OR "Secernentea Infection" OR "Trematode Infection" OR "Sparganosis" OR "Cysticercosis" OR "Neurocysticercosis" OR "Enoplida Infections" OR "Enoplida Infection" OR "Trichinellosis" OR "Trichuriasis" OR "Ascaridida Infections" OR "Ascaridida Infection" OR "Anisakiasis" OR "Ascariasis" OR "Ascaridiasis" OR "Toxascariasis" OR "Toxocariasis" OR "Oxyurida Infections" OR "Oxyurida Infection" OR "Oxyuriasis" OR "Enterobiasis" OR "Rhabditida Infections" OR "Rhabditida Infection" OR "Strongyloidiasis" OR "Spirurida Infections" OR "Spirurida Infection" OR "Dracunculiasis" OR "Filariasis" OR "Acanthocheilonemiasis" OR "Dipetalonema Infections" OR "Dipetalonema Infection" OR "Dirofilariasis" OR "Filarial Elephantiasis" OR "Loiasis" OR "Mansonelliasis" OR "Onchocerciasis" OR "Setariasis" OR "Gnathostomiasis" OR "Strongylida Infections" OR "Hookworm Infections" OR "Strongylida Infection" OR "Hookworm Infection" OR "Ancylostomiasis" OR "Necatoriasis" OR "Oesophagostomiasis" OR "Strongyle Infections" OR "Strongyle Infection" OR "Trichostrongyloidiasis" OR "Dictyocaulus Infections" OR "Dictyocaulus Infection" OR "Haemonchiasis" OR "Ostertagiasis" OR "Trichostrongylosis" OR "Neuroschistosomiasis" OR Helminth OR "Helminths" OR "Helminth" OR "Parasitic Worms" OR "Parasitic Worm" OR "Aschelminthes" OR "Aschelminthe" OR "Gordius" OR "Nematomorpha" OR "Nematomorphas" OR "Acanthocephala" OR "Moniliformis" OR "Nematoda" OR "Adenophorea" OR "Secernentea" OR "Platyhelminths" OR "Cestoda" OR "Trematoda" OR "Turbellaria" OR "Rotifera" OR "Enoplida" OR "Dioctophymatoidea" OR "Mermithoidea" OR "Trichuroidea" OR "Capillaria" OR "Trichinella" OR "Trichinella spiralis" OR "Trichuris" OR "Ascaridida" OR "Ascaridia" OR "Ascaridoidea" OR "Anisakis" OR "Ascaris" OR "Ascaris lumbricoides" OR "Ascaris suum" OR "Toxascaris" OR "Toxocara" OR "Toxocara canis" OR "Oxyurida" OR "Oxyuroidea" OR "Enterobius" OR "Rhabditida" OR "Rhabdiasoidea" OR "Strongyloides" OR "Rhabditoidea" OR "Caenorhabditis" OR "Spirurida" OR "Camallanina" OR "Dracunculoidea" OR "Dracunculus Nematode" OR "Spirurina" OR "Filarioidea" OR "Acanthocheilonema" OR "Brugia " OR "Dipetalonema" OR "Dirofilaria " OR "Loa" OR "Mansonella" OR "Microfilaria" OR "Onchocerca " OR "Setaria Nematode" OR "Wuchereria" OR "Spiruroidea" OR "Thelazioidea" OR "Gnathostoma" OR "Strongylida" OR "Ancylostomatoidea" OR "Ancylostoma" OR "Necator" OR "Necator americanus" OR "Heligmosomatoidea" OR "Nematospiroides" OR "Nematospiroides dubius" OR "Nippostrongylus" OR "Metastrongyloidea" OR "Angiostrongylus" OR "Molineoidae" OR "Nematodirus" OR "Strongyloidea" OR

	"Oesophagostomum" OR "Strongylus" OR "Trichostrongyloidea" OR "Dictyocaulus" OR "Haemonchus" OR "Ostertagia" OR "Trichostrongylus" OR "Tylenchida" OR "Tylenchoidea") AND (Malaria OR malaria* OR "malaria" OR "Paludism" OR "Plasmodium Infections" OR "Plasmodium Infection") AND (Cellular Immunity OR cellular immune response OR cellular immune responses OR Cellular Immunities OR Cellular Immunity OR Cell-Mediated Immunity OR Cell Mediated Immunity OR Cell-Mediated Immunities OR Antigen Presentation OR Immunologic Surveillance OR Lymphocyte Activation OR Cross-Priming OR Cytokine OR cytokines OR cytokine OR CD4 antigen OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocyte OR TLymphocyte OR TLymphocytes OR T Lymphocyte OR T Lymphocytes OR T-Lymphocyte OR T-Lymphocytes OR b cell OR b cells OR B-Lymphocyte OR B Lymphocyte OR B Lymphocytes OR BLymphocyte OR BLymphocytes OR B-Lymphocyte OR B-Lymphocytes OR Dendritic Cell OR Dendritic Cells OR Dendritic Cell OR Chemokines OR Chemokine OR beta-Thromboglobulin OR Macrophage Inflammatory Proteins OR Growth Differentiation Factor OR Growth Differentiation Factors OR Hematopoietic Cell Growth Factors OR Hematopoietic Cell Growth Factor OR Haematopoietic Cell Growth Factors OR Haematopoietic Cell Growth Factor OR Colony-Stimulating Factors OR Colony-Stimulating Factor OR Stem Cell Factor OR Stem Cell Factors OR Hepatocyte Growth Factor OR Hepatocyte Growth Factors OR Interferons OR Interferon OR Interleukin OR Interleukins OR Interleukin* OR Leukemia Inhibitory Factor OR Leukemia Inhibitory Factors OR Lymphokines OR Lymphokine OR Leukocyte Migration-Inhibitory Factors OR Leukocyte Migration-Inhibitory Factor OR Lymphotoxin-alpha OR Macrophage-Activating Factors OR Macrophage Migration-Inhibitory Factors OR Macrophage-Activating Factor OR Macrophage Migration-Inhibitory Factor OR Transfer Factor OR Transfer Factors OR Monokines OR Monokine OR Tumor Necrosis Factor OR Tumor Necrosis Factors OR Tumour Necrosis Factor OR Tumour Necrosis Factors OR Oncostatin M OR Osteopontin OR Transforming Growth Factor OR Transforming Growth Factors OR 4-1BB Ligand OR CD70 OR B-Cell Activating Factor OR B-Cell Activating Factors OR CD30 OR CD40 OR Ectodysplasins OR Fas Ligand Protein OR Fas Ligand Proteins OR Lymphotoxin-alpha OR Lymphotoxin-beta OR OX40 Ligand OR RANK Ligand OR TNF OR dendritic)) NOT TI=(Animal* OR mice OR mouse OR macaq* OR buffal*)
ScienceDirect	TITLE-ABSTR-KEY(((Helminthiasis OR Helminths OR Helminth) AND (Malaria) AND (immunity OR immune OR

	cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell)))
AIM (African Index Medicus)	Helminthiasis OR Helminths OR Helminth Malaria cellular immunity OR cellular immune response OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell Helminthiasis Malaria cellular immunity
IMEMR (Index Medicus for the Eastern Mediterranean Region)	(Helminthiasis OR Helminths OR Helminth) AND Malaria AND (cellular immunity OR cellular immune response OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell) Helminth Malaria immune
IMSEAR (Index Medicus for South-East Asia Region)	((Helminthiasis OR Helminths OR Helminth) AND (Malaria) AND (immunity OR immune OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell))
IndMED	((Helminthiasis OR Helminths OR Helminth) AND (Malaria) AND (immunity OR immune OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell))

KoreaMED	(Helminthiasis OR Helminths OR Helminth) AND Malaria AND (cellular immunity OR cellular immune response OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell) Helminth Malaria immune

LILACS (Latin America and the Caribbean)	Helminthiasis OR Helminths OR Helminth Malaria cellular immunity OR cellular immune response OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell Helminthiasis Malaria cellular immunity
WPRIM (Western Pacific Region Index Medicus)	Helminthiasis OR Helminths OR Helminth Malaria cellular immunity OR cellular immune response OR cytokine OR cytokines OR cd4 OR cd-4 OR t cell OR t cells OR T Lymphocytes OR T Lymphocyte OR b cell OR b cells OR B Lymphocytes OR B Lymphocyte OR Dendritic Cells OR Dendritic Cell Helminthiasis Malaria cellular immunity