Validity of studies on the association between soil-transmitted helminths and the incidence of malaria: Should it impact health policies?

Validez de los estudios de asociación entre geohelmintos e incidencia de malaria: ¿Debería impactar las políticas de salud?

Abstract

Introduction: The global distribution of malaria and soil-transmitted helminths is widely overlapped. Some studies suggest a possible association between helminth infection and incidence of malaria. Objectives: To identify the available epidemiologic evidence and to assess the validity of these studies. **Methods:** A systematic review was carried out in specialized databases. The studies identified were critically analyzed and ranked according to the U.S. Preventive Services Task Force's classification. The major methodological limitations of each study were identified. **Results:** Six studies on the topic were found. Only two studies had a high evidence level (level I), three had level II-2, and one had level III-3. There are important methodological limitations for clarifying the association between soil-transmitted helminths and the incidence of malaria. **Conclusion:** It is too early to discuss the potential public health implications of these findings, given the lack of studies and limited validity of the evidence available. Further studies with new methodological considerations could improve the knowledge on the association. However, it is more important to carry out actions on structural determinants to control and prevent the occurrence of both diseases.

Keywords: Helminths. Malaria. Comorbidity. Bias (epidemiology). Communicable disease control.

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Resumen

Introducción: La distribución mundial de las geohelmintiasis y la malaria se encuentra ampliamente sobrepuesta. Algunos estudios sugieren una asociación entre las infecciones con geohelmintos y la incidencia de malaria. **Objetivos:** Identificar la evidencia epidemiológica disponible y evaluar la validez de estos estudios. **Metodología:** Una revisión sistemática fue realizada en bases de datos especializadas. Los estudios identificados fueron analizados críticamente y ordenados según clasificación de la U.S. Preventive Services Task Force. Se identificaron las principales limitaciones metodológicas de cada estudio. **Resultados:** Se encontraron seis estudios publicados sobre el tema. Solo dos estudios tienen un alto nivel de evidencia (nivel I), tres de nivel II-2, y uno de nivel III-3. Existen importantes limitaciones metodológicas para aclarar la asociación entre geohelmintos e incidencia de malaria. **Conclusiones:** Es apresurado discutir las potenciales implicaciones en salud pública de estos hallazgos dada la escasez de estudios y la validez limitada de la evidencia existente. Futuros estudios con nuevas consideraciones metodológicas podrían mejorar el conocimiento acerca de esta asociación. Sin embargo, es más importante realizar acciones sobre los determinantes estructurales para controlar y prevenir la ocurrencia de ambas enfermedades.

Palabras clave: Helmintos. Malaria. Comorbilidad. Sesgo (epidemiología). Control de enfermedades transmisibles.

Introduction

More than 2 billion people around the world are estimated to be infected by geohelminths[1,2], most of them live in developing countries where there is a high incidence of malaria. Around 300 to 500 million cases of malaria are presented each year, and it is responsible for more than two million deaths during similar periods[3].

Geohelminth and malaria distributions overlap in wide areas due to their transmission characteristics and a high percentage of the world population suffers from co-infection by these parasites causing important effects on co-morbidity, especially multifactor anemia[4].

An association between geohelminth infection and the incidence of clinical malaria (as well as co-morbidity) was suggested for the first time in 1978[5]. However, most studies concerning such associations have only been carried out during the past 10 years. Such work has also explored the potential protective effect of geohelminths in the development of complicated malaria[6]. In spite of the renewed interest in this topic, few investigations have been carried out, and they have reached different results. Several evolutionary and immunological hypotheses have been suggested but the mechanisms supporting such potential associations still remain unknown[7].

Some authors have drawn attention to the methodological limitations and the confounding factors present in such investigations.[7,8] Even though geohelminths and malaria have different transmission mechanisms, they share the host's environmental, cultural, socioeconomic, behavioral and biological determinants which could thereby act as potentially confounding variables. The probable influence of selection bias and the limitations of these investigations' intrinsic validity have also been pointed out, being partly explained by a large amount of data being taken from studies carried out with other objectives in mind[9]. Most reviews focus on describing potential biological mechanisms supporting the association and listing the epidemiological evidence sustaining such relationship. Critical and systematic epidemiological analyses of existing studies is thus indispensable, due to the important repercussions which these results may have on public health policies, especially on malaria control programs and on determining priority public health interventions[10].

Studying co-morbidity as part of epidemiology has rapidly gained importance during the past few years; it has been especially associated with aging and its important repercussions on health expenditures[11]. Co-morbidity refers to the presence of one or more diseases in an individual who has an "index disease"[12]. In our case, Geohelminthiasis could be considered as the index disease, since, according to the suggested hypothesis, it is present before malaria. The relationship between geohelminth infection and malarial incidence is a type of co-morbidity which has not been frequently studied for many reasons: a) there are two infectious diseases involved; b) it occurs predominantly in children[11]; and c) the relationship between malnutrition and malaria is not clear (in spite of contradictory studies postulating that malnutrition protects against malaria)[13]. Nutritional status has thus become an intermediate variable in the relationship, which must be treated as such during statistical analysis.

Due to the topic's complexity, the present study explored the validity of investigating the association of geohelminths with the incidence of malaria, and discusses whether the topic deserves further investigation or whether it would be more profitable to take direct measures to prevent its occurrence.

Methods

A search in the *Pubmed* database was performed for original articles exploring the association between geohelminths and malarial incidence. The following combinations were used as search words: "*helminths"* and *"malaria," "Ascaris" and "malaria," "Trichuris" and "malaria," "hookworm" and "malaria," "helminths" and "severe malaria," "Ascaris" and "severe malaria," "Trichuris" and "severe malaria" and "hookworm" and "cerebral malaria."* An additional search was performed within the references of the review articles on the topic which had been published during the three previous years (n=15).

Two observers independently reviewed the titles and (when necessary) the summary of all publications obtained from the search. Original studies directly related to the question of interest were included in this analysis. Studies on the association of geohelminths with severe anaemia, multiple infection or mixed infections were excluded. Investigations carried out with groups of pregnant females or those with other helminths such as schistosomes were also excluded.

The US Preventive Services' Task Force classification was used for classifying the studies according to level of evidence. It contains the following categories: I) evidence obtained from a randomized clinical trial, II-1) evidence obtained from a well-designed study without randomization, II-2) evidence obtained from a well-designed cohort or case-control study (preferably from more than one center or research group), II-3) evidence obtained from multiple time series or without intervention and III) experience-based opinion from respected authorities, descriptive studies and case reports or reports from committees of experts[14].

Results

Only six studies have been published evaluating the association between geohelminth infection and incidence of malaria. Table 1 summarizes their designs.

Level of evidence I

Brutus *et al.*,'s 2003 study[15] was the first to use a randomized design. Their work explored the interaction between reduced *Ascaris lumbricoides* prevalence and its

Table 1. Studies regarding the association between soil-transmitted helminths and malarial incidence

Author/ year	Place	Type of design	Measurement of exposure	Measurement of outcome*	Controlled co-variables	Control by localization	Sense of association	Strength of association with geohelminths *
Shapiro, 2003	4 provinces from the Kabala district in Uganda	Case-control	Kato Katz at the time of the study	At the time of the study: weekly active detection, house by house of feverish people for 3 months	Gender, age, living conditions	No	Null	AOR: 1.08; 0.59-1.95 95%CI
Spiegel, 2003	Dielmo, Senegal	Bidirectional cohorts	Direct O&P examination half way through the study	Based on the Malaria Surveillance Program. Cases detected 6 months before and 6 months after	Age, gender, using mosquito netting	No	Positive	RR: 1.54 p: 0.003
Nacher, 2002	5 provinces from Rathchaburi in Thailand	Prospective cohorts	Direct O&P examination and Kato Katz at the start of the study	Ongoing follow-up of the case detection program for 1 year	Age, protozoa, gender	No	Positive	ARR: 2.24; 1.4-3.6 95%CI
Murray, 1977	Comoro Islands	Ecological study plus intervention with levamisole	Direct O&P examination and fecal concentration once	Thick smear 20 days after administering levamisole on one of the islands	None	No	Protective potential only evaluated for *A. lumbricoides*	Not applicable
Brutus, 2006	Anbohimea, Madagascar	Controlled trial: antihelminthics *cf* vitamins	Direct O&P examination and fecal every 2 months over an 18 month period	Thick smear every 2 months over an 18 month period after assignment to levamisole or vitamins	Random assignment to exposure	N-A	Protective in the group aged more than 5 Only *A. lumbricoides*	Not applicable
Brutus, 2007	Fenoarivo, Madagascar	Controlled trial: antihelminthics *cf* vitamins	Direct O&P examination and fecal every 2 months over an 18 month period	Thick smear every 2 months for 18 months, following assignment to levamisole or vitamins	Random assignment to exposure	N-A	Protective in the 5 -15 age group Only *A. lumbricoides*	Not applicable

* Defined as being an infection caused by any geohelminth
AOR: adjusted odds ratio. CI: confidence interval. RR: relative risk. ARR: adjusted relative risk

parasite load with the density of *Plasmodium falciparum* infection in an endemic area in Madagascar. The authors used data from a clinical trial comparing levamisole treatment with multivitamin treatment. A 16-month follow-up period led to simultaneously revealing geohelminth infection-reinfection cycles and the incidence of cases of malaria. The results revealed that *P. falciparum* density progressively increased in the group assigned to levamisole treatment compared to the control group (even though only among people aged over 5), as well as showing that levamisole was very effective against *A. lumbricoides*[15].

This study's results indirectly suggested that *A. lumbricoides* may have a protective effect against the development of malaria. The fact that malaria is mesoendemic in Madagascar could explain why an association has not been found in the age group under 5 years; several years are required for acquiring immunity against malaria as well as potential equilibrium between the parasites[15]. Results are unlikely to have been affected by confusion, as this was a randomized clinical trial. This study's findings only reproduced those found by Murray in 1978 and were not consistent with any of the other analytical studies on the topic. However, the fact that results could have been affected by localization bias cannot be ruled out (discussed later on), in spite of the study being carried out in the same place.

Moreover, considering that levamisole is an antihelminthic drug with an important immunomodulating effect when used to treat cancer and autoimmune diseases[16], one could question if the findings obtained in this study are directly related to *A. lumbricoides* infection or to a secondary effect of levamisole, in that different results could have been obtained if another antihelminthic drug had been used. Some authors have suggested that levamisole has an effect on *Plasmodium spp* sequestration and thus can be used in complicated malaria[17], thereby suggesting that this drug could affect malarial incidence by this other route.

A more recent study, also published by Brutus *et al.*[18], compared the effect of providing levamisole or multivitamin treatment on non-complicated malaria by using a randomized clinical trial with a very similar design to that previously used by this group. The work was carried out in an area with *Schistosoma mansoni* transmission where houses were frequently sprayed with DDT from 1993 to 1998; the area was located 1,250 meters above sea-level (MASL), very close to the one studied in the previously described randomized study[15]. The results, after 18 months (obtained by modeling fixed and random effects), showed that those who had been treated with levamisole and managed to reduce their *A. lumbricoides* egg load presented increased *P. falciparum* density; this effect was only observed among subjects aged 5-14 years. It is clear that the results were very similar to those described previously and the limitations of the evidence provided by this work were similar to foregoing ones.

Level of evidence II

Nacher *et al.*[19] carried out a prospective cohort study in five of Thailand's rural areas in 1998. This study consisted of an intestinal parasite survey and a one-year follow-up for evaluating malarial incidence. Based on an already implemented educational program on malaria, the authors sought to ensure that all symptomatic cases were referred to the region's only diagnosis and treatment distribution center. This work found a positive association between geohelminth infection and *P. falciparum* malarial incidence. The authors presented the results adjusted by gender and age. However, socioeconomic strata, educational level and housing conditions were not taken into account, meaning that they could have acted as potentially confounding variables. The study subjects' location and where they came from were not taken into account; the study could have incurred in localization bias as the study subjects came from five different localities.

Shapiro *et al.*, conducted a case-control study in four rural provinces from the Kabala district in Uganda in 2003[20]. Cases (defined as individuals having a confirmed thick smear result for *Plasmodium sp.*) were selected by the weekly malaria surveillance program in which health agents visited each house, searching for symptomatic individuals. Controls were non-symptomatic inhabitants from the same districts. A detail which might have gone unnoticed in this work was that only cases from the Kikuto and Rwandamira provinces were included while controls came from the Kabirizi and Kigara provinces; the authors justified this design by blaming the difficulty in recruiting cases on migration in the Kabirizi and Kigara provinces. According to the same article's results, both populations from which the cases came had significantly higher prevalence of Geohelminthiases than the two other populations. This meant that cases would have had a greater probability of being exposed to geohelminths than controls (selection bias).

The results would thus tend to be an overestimation of the association and could explain the association not being detected. Unfortunately, the article's analysis did not deal exclusively with controls from the two provinces where the cases were recruited. One of this study's advantages was that covariables such as socioeconomic strata and housing conditions (floor, roof, sanitation) were controlled by using Filmer's compound index[21]. The authors did not present the crude odds ratio (OR). However, once calculated (OR 0.87; OR; 95% confidence interval or CI: 0.58-1.29), it did not significantly differ from the adjusted odds ratio presented by the investigators (OR 1.08; 95% CI: 0.59-1.95).

The above findings could be explained by three different reasons. First, housing conditions and socioeconomic strata are not confounding variables for the association between geohelminths and malaria. Secondly, it may be residual confounding, and the role of strange non-measured co-variables was not detected (i.e. lack of schooling, malnutrition or localization). Thirdly, the influence of confounding variables measured in the study was not suitably detected. For example, Filmer's index, because it is a compound and complex indicator that consolidates numerically many poor housing conditions, may not have the necessary specificity for detecting some specific patterns for the housing's infrastructure (e.g. earth flooring without windows, a frequent risk factor for geohelminths and malaria). Another limitation to the findings of this study is that it was not possible to differentiate the *Plasmodium* species. The authors claim that *P. falciparum* was the predominant species in the district according to prior data.

Another bidirectional cohort was studied in Dielmo, Senegal, in 1998 by Spiegel *et al*[22]. The investigators submitted 80 children from this population to coprological tests. The study population's covariables and their comparison with those from the reference population were not presented in the paper. As in previous studies, Spiegel based his study on a malaria surveillance program, determining the occurrence of cases of malaria during the six months prior to and after measuring exposure, and found a higher incidence in the cases infected with geohelminths. This work took into account age, gender and the use of mosquito nets as adjustment covariables, but not as socioeconomic variables.

Level of evidence III

Murray[5], while studying malaria in two of the islands from the Comoro complex in 1977, observed lower malarial prevalence (1.7%) in the island with higher *A. lumbricoides* prevalence (93%) while malarial prevalence was higher (23%) on the other island which had a much lower prevalence of this geohelminth (24%). Murray thus suggested that there was a negative relationship between *A. lumbricoides* prevalence and *P. falciparum*, making a protection-inducing association between geohelminth infection and malaria for the first time.

Murray completed his observations in the following year by carrying out a controlled clinical trial on the same populations, and found that the population assigned to antihelminthic treatment presented a significant increase in malarial incidence 20 days after the intervention when compared to the control (placebo) group. The main limitations for these observations consisted in the limited number of observations and the short follow-up of the outcome, given that changes in malarial incidence in less than a month could be explained by short outbreaks introduced or by a seasonal nature.

With the exception of age, no other covariable was taken into account. It is well known that malnutrition, which is more prevalent in people infected with geohelminths, can act as an important confounding variable, even when relationships between malaria and malnutrition are controversial. Murray's work did not take into account that the distribution pattern for both parasites could obey ecological conditions and that there is no direct biological relationship between them. However, even with all the aforementioned limitations, it is interesting that Murray's results were consistent with those found in the only controlled trial published on the topic. Some authors also seem to suggest that Murray' results were consistent with those suggesting a protection-inducing effect by geohelminths against developing complicated malaria[6].

Discussion

Only six studies on the association between geohelminth infection and malarial incidence could be found and their results were highly divergent. Two closed cohort analytical studies found a positive association between geohelminth infection and malaria[19,22], a case-control study found no association[20], and the other three (an ecological[5] and two randomized clinical trials[15,18]) found a protection-inducing association. The fact that the results found in Brutus *et al.*'s controlled trials were not consistent with any of the analytical studies could be explained by these studies' methodological limitations, especially by the powerful influence of confounding variables.

Although geohelminths and malaria have different transmission mechanisms, they share social and environmental determinants for their occurrence in such a way that the influence of the co-determinants for both diseases must be analyzed when faced with a real biological association between both parasites (Figure 1). The association found by Nacher and Spiegel[19,22] could be simply explained by the fact that populations infected by geohelminths have a greater risk of becoming ill due to structural determinants (poverty, malnutrition, poor schooling) than a population not infected by geohelminths. Put in another way, populations at greater risk of infection by geohelminths tend to be the same in terms of having a greater risk for malaria in the regions where both diseases are endemic. Evidence concerning this overlap of diseases has been well-known for several decades; but only recently it has begun to be explored, using spatial epidemiology's specific techniques which have shown the importance of knowing the contexts in which individuals at risk are found[23]. Some of these potential variables are now presented and discussed.

Housing conditions: Poor housing characteristics such as the lack of tools for containing the entry of insects (doors, grids or windows), the type of roofing or the material used for walls are well-known determinants of risk for malarial infection[24]. It has also been proved that living in poor physical infrastructure housing (wood or palm) leads to a greater risk of developing malaria than living in houses made of good construction materials[25]. This risk apparently increases if the housing is close to a source of water[26]. Housing conditions, such as having earthen flooring, have been associated with the presence of geohelminthiases[27]. Thus, living conditions in areas with poor socioeconomic conditions are risks for both diseases, thereby producing a higher incidence of both malaria and Geohelminthiases, regardless of a biological relationship between both parasites. This

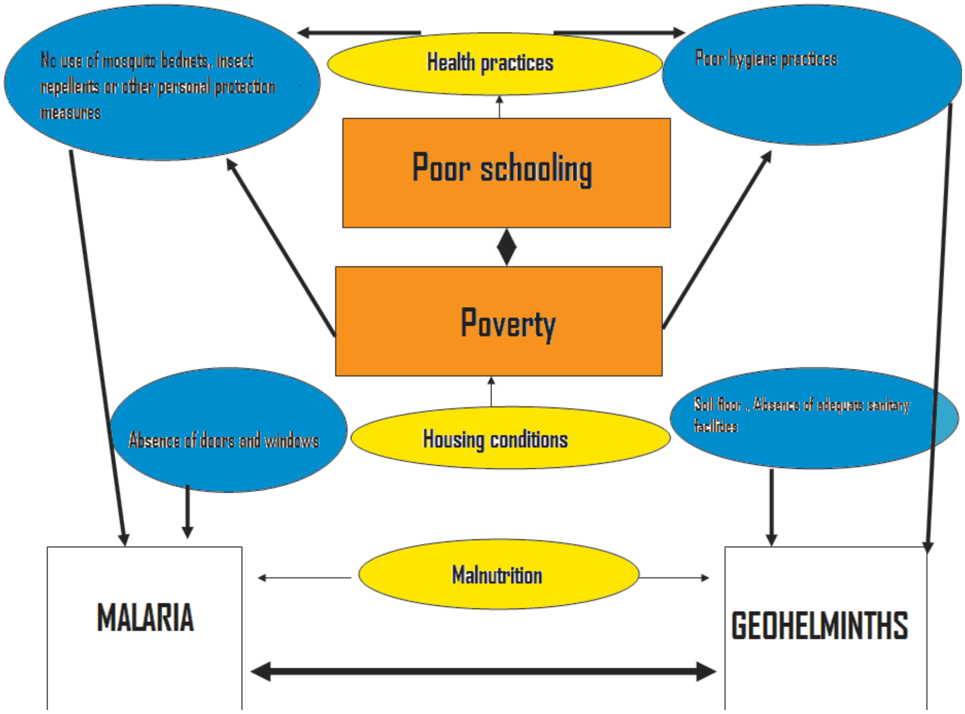

Figure 1. Causal webs linking soil-transmitted helminths and malarial occurrence. orange = structural determinants, yellow = anchorage determinants, blue = risk factors.

covariable must be considered in studies on the topic, but deconstructed in such a way that the characteristics of the roof, floor and walls of houses are measured for each study subject. Housing patterns could thus be identified as potentially confounding variables, and are common risk factors for geohelminths and malaria.

Malnutrition: Chronic malnutrition in children leads to alterations when the thymus is developing and therefore to a deficit in T-lymphocyte production and maturing, thereby causing serious immune defects, such as leucopenia, producing greater susceptibility to all types of infection[28,29]. Undernourished children are deficient in IgE, which protects against *A. lumbricodes*[30], and these children have been described to present an alteration in regulating immunity against helminths[31]. Some studies have found nutritional deficiencies and low weight to be associated with malarial incidence[32,33] (i.e. chronic malnutrition is also a common risk factor for both diseases).

However, a nutritional defect produced by Geohelminthiases could produce a greater risk of malarial episodes, thereby configuring a non-immunological association between both parasites which has not been discussed to date (i.e. Geohelminthiases-associated malnutrition produces less immune ability and thus greater risk of infection). The host's nutritional state thus determines response to infection, but infection could equally be caused by malnutrition.

Nevertheless, the association between Geohelminthiases and malaria could also become confounding in the opposite sense, given that the former parasites are associated with chronic malnutrition and certain controversial evidence suggests that malnutrition could protect against malaria[5,13].

Economic activity: Working in malaria-endemic areas (i.e. agriculture) has been associated with greater risk of contracting malaria, especially in rural areas[34]. Studies have shown a greater risk of Geohelminthiases in people carrying out agricultural activities due to their constant contact with the soil[35].

Using protection against malaria: Practices such as using mosquito netting, impregnated hammocks[33], and the type of roof used on the housing are some of the most important protection measures for preventing malaria[36]; such practices are directly related to education, culture and availability. It may be that people making little use of these means of protection are the same ones with inadequate sanitary practices and very limited availability of basic services, thereby leading to risk for Geohelminthiases.

Location bias

Ignoring study subjects' origin (as has been done up to now) could lead to false inferences[37]. Participants can come from different environmental and social micro-ecosystems and present different risks for malaria and Geohelminthiases; these are determined by the location of sources of ecological risk for both diseases more than by a true immune interaction between parasites. It is known that variations of less than 200 MASL between different dwellings in the same rural area have been related to significant differences in the risk for acquiring malaria[33]. Geohelminthiases prevalence could be related to distribution patterns with areas of greater concentration according to changes in the availability of domiciliary public utilities or sewage within the same locality. Location bias comes into view when study subjects' origin has not been taken into account and the probability of being coinfected with geohelminths and malaria may be influenced by this location, within the framework of a locality having heterogeneous distribution of sources of risk for both diseases. The problem becomes maximized in analysis with data from several locations; future studies could investigate the role of this covariable.

Biological plausibility of the helminth-malaria interaction

Some experimental evidence-based immunological theories (especially in murine models) may support the association of helminthiasis with malarial episodes. *P. falciparum* infection is known to induce a pro-inflammatory Th1-response, characterized by increased TNFα and INFλ, which is responsible for eliminating the parasite load in hepatocytes and erythrocytes, also limiting parasite replication[38]. Helminths elicit a Th2-polarised immune response, inducing IL-4, IL-5 and IL-7 cytokines[39]. The Th1 response seems to be regulated by Th2 with IgE and TGF β. It has thus been suggested that, in the presence of helminth infections, the Th2 response inhibits the anti-parasite role of the Th1-proinflammatory response and could thus produce greater susceptibility to malarial infection in the host. Such immuno-modulation of the inflammatory response by helminths could correspond to a form of host defense in the form of evolutionary adaptation between parasites and malaria[7].

Protective immunity in malaria is antibody-dependent; however, acquiring this type of immunity depends on the intensity and duration of exposure to the parasite. The IL-4 and IL-3 cytokine environment thus stimulates IgG4 and IgE production in the presence of a Th2-polarised response[40]; these are non-cytophylic antibodies, with reduced cytophylic antibodies (IgG1 and IgG3) which have been found to be the main effectors of acquired immunity in malaria[37].

It is interesting to note that some biological mechanisms could support a conflicting association (i.e. protection-induction arising from geohelminth infection and malarial incidence). Brutus *et al.*'s findings could thus be supported by some studies analyzing a possible immunomudulator effect of infection by *Plasmodium* and *Schistosoma* as a consequence of cross reactivity of antigens shared between both parasites; this could apparently produce a greater IgG3 response ability, thereby helping to eliminate *Plasmodium spp* in people infected with schistosomes[41,42]. Such findings are mainly related to *Schistosoma* (and are still preliminary) but show how it is possible to find biological mechanisms sustaining an association even though plausibility does not provide sufficient criteria.

In spite of the foregoing and the possibilities offered by biology for understanding geohelminth-malaria interactions, the epidemiological study of these biological mechanisms still remains a great challenge[43]. Two approaches were observed in the present work; one involved interaction between two or more risk factors and the other interaction between two events directly related to health. The former explicitly referred to concepts regarding a modifying effect and interaction in epidemiology[44], while the latter referred to comorbidity[12]. A direct consequence of geohelminth-malaria interactions is that an epidemiological approach must use explicit techniques for such purpose. Using measurements of comorbidity such as the *rho* obtained from bivariate probit regression models[10] or adapting already known indexes such as the Cumulative Illness Rating Scale, Kaplan–Feinstein classification, Charlson's comorbidity index or the co-existent disease index[45] is recommendable since these could control the treatment selection bias described in 1974 by Kaplan and Feinstein[46] in both prospective and retrospective studies.

Bearing in mind the difficulties around this topic, another option lies in incorporating models based on a theory with the required complexity or analyzing multiple levels. The latter approach represents a response to a frequent problem in epidemiological studies, which results from considering that all variables must be measured at the individual level, ignoring that many belong to higher levels of aggregation (dwelling, neighborhood, municipality)[47,48]. New and better methodological considerations ensuring the reproducibility of studies on the topic lead to discovering this association's true sense and strength.

Potential implications for public health

Geohelminthiasis is a highly prevalent infection in the developing world, especially affecting the school aged population (5-15)[1]. After malaria, it accounts for more than 40% of the burden of tropical diseases, and is responsible for the loss of more than 39 million disability adjusted life years (DALYs) annually[2]. Infected individuals can suffer from disorders such as anemia, malnutrition, poor school performance, and growth and development disorders[49]. In spite of the foregoing, geohelminthiases are currently considered to be neglected diseases as interest in investigating and controlling them has declined (in spite of their high prevalence and associated morbidity) [50]. Interest in studying the potential effects of geohelminthiases on other infections such as malaria, tuberculosis and HIV (with an enormous impact on disease burden) is partly motivated by the felt need for reprioritizing control of geohelminthiases. If it can be convincingly demonstrated that geohelminths can increase the risk for malarial incidence, then this would have repercussions on the control policy in developing countries since antihelminthic distribution and environmental sanitation would also become considered as part of transverse malaria control strategies.

Considering the clear lack of evidence on the association between geohelminths and malarial incidence and the serious methodological limitations in existing material, it is disturbing that a start should be hurriedly made on serious estimations regarding the impact on public health of such relationship. Controlling geohelminthiases should not depend on the establishment of its association with malarial incidence, since low cost and highly effective control strategies are available and are known to have a major impact on the disease load of the affected populations.

Certain studies have also suggested a protection-inducing association between geohelminth infection (especially *A. lumbricoides*) against developing brain malaria[51, 52] and acute renal failure secondary to malaria[53]. However, a more recent study has found a totally different association[54].

Evidence on this topic (the same as that related to malarial incidence) is even more scarce and there are divergent and broad limitations regarding its validity. Whether geohelminthiases have an influence on the development of clinical malaria must not cast doubt on controlling such parasitoses, since there are many more well-known determinants of its clinical course and of malaria mortality other than geohelminthiases. Far from casting doubt on controlling geohelminthiases, demonstrating the potential effect of geohelminths on developing complicated malaria will reinforce the need for simultaneously controlling both diseases.

It is important to clarify the relationship between geohelminthiases and malarial incidence for epidemiology, given these diseases' relevance, and since several of their proximal and distal determinants are already known; however, the continuation of this type of study should not be exaggerated (a phenomenon called "circular epidemiology"[55]), but investigation in prevention and control actions regarding their determinants should rather be emphasized. It should be remembered that knowledge is only one of the components of the "triangle which moves mountains"[56] and social movements and political participation also influence the scope of populations' wellbeing. They should be brought into effect as soon as possible, given the solid evidence available for preventing and controlling geohelminthiases and malaria without waiting for more refinements in knowledge. On the other hand, deeper investigations into transverse strategies for cost-effective and socially healthy control of diseases with common determinants (such as Geohelminthiases and malaria) are desirable while the scientific community's efforts are directed towards boosting social mobilization and political willingness. Our commitment seems to be more complicated but also, perhaps, more important.

Conflicts of interest: The authors state that they have no conflict of interest whatsoever.

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