Supplementation with micronutrients and schistosomiasis: systematic review and meta-analysis

María Morales-Suarez-Varela^{a,b}, Isabel Peraita-Costa^{a,b}, Agustín Llopis-Morales^a and Agustín Llopis-González^{a,b}

^aÁrea de Medicina Preventiva y Salud Pública, Departamento de Medicina Preventiva y Salud Pública, Ciencias de la Alimentación, Toxicología y Medicina Legal, Facultad de Farmacia, Universitat de Valencia, Burjassot, Valencia, Spain; ^bCIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

ABSTRACT

Schistosomiasis is a parasitic disease caused by helminths of the genus *Schistosoma* with two presentations; one intestinal and another urinary; which depend on the specie of *Schistosoma*. One of the species that can produce intestinal schistosomiasis is *Schistosoma mansoni*, and the specie that produces urinary schistosomiasis is *Schistosoma haematobium*. Infection can be aggravated by a deficient nutritional status, which negatively impacts the immune system and increases susceptibility to infection. The main objective of this meta-analysis is to determine if a relationship exists between multimicronutrient supplementation and the reduction of infestation with *Schistosoma mansoni* and *Schistosoma haematobium* in children and adolescents. A search was conducted through a scientific literature database, and articles that complied with the pre-established requirements were retrieved. The Review Manager (Rev Man) 5.3 computer program was used for data processing and analysis was carried out with the objective of testing whether the addition of micronutrient supplementation to treatment with broad-spectrum antiparasitic anthelmintic medication has an impact on schistosomiasis infection. Of the 257 initial articles retrieved, eight were included both quantitatively and qualitatively in the meta-analysis. Supplementation reduces infestation with *Schistosoma spp* 1.33 times more than placebo. In individuals infested with *Schistosoma, mansoni* supplementation is 1.30 times more effective than placebo and for individuals infested with *Schistosoma haematobium*, supplementation is 1.62 times more effective than the placebo. The results show a clear relationship between supplementation and reduction of infestation. The supplementation with micronutrients decreases the presence of *Schistosoma spp* in children and adolescents.

KEYWORDS

Children; adolescents; schistosomiasis; schistosoma mansoni; schistosoma haematobium; supplementation; meta-analysis

Introduction

Schistosomiasis is a disease that belongs to the group known as “Neglected Tropical Diseases” or “NTDs” [1], which affects around 260 million people worldwide. Of those 260 million affected, 46% are children aged between 5 and 14 years old. The most affected populations are the inhabitants of tropical and subtropical countries. Generally, the infestation affects poor communities with inadequate health care and/or without access to safe drinking water [2]. This disease affects the entire population but has a special effect in children and adolescents, as it compromises their ability to learn, school attendance and physical development [3].

Malnutrition is defined as “an insufficient intake or absorption of energy, proteins or micronutrients, which in turn causes a nutritional deficiency” [4] and is one of the main problems in developing countries. Worldwide, malnutrition affects 793 million people [5] and of these, around 200 million are children under 5 years of age suffering from chronic malnutrition, while around 13% of children under 5 years suffer from acute malnutrition [6].

Infectious diseases can negatively impact the nutritional status of children and adolescents [7]. Parasitic infestations can increase the loss of nutrients and this may cause a deficient nutritional status, which in turn causes an increase in susceptibility to infection, thus creating a vicious cycle [8]. The causes of this negative impact on nutritional status have been studied on numerous occasions, as shown by the study carried out by Cunningham-Rundles et al. [9] which shows that an inadequate contribution of certain micronutrients can cause an immune deficiency that increases susceptibility to infection. This same study states that vitamin B12, vitamin A, vitamin C, vitamin B2, selenium, iron and zinc have immunomodulatory functions that can influence the state of infection [9]. Other studies such as that of Nga et al. [10] show that the lack of certain micronutrients can reduce the immune response of the host and therefore decrease the resistance of the body to a possible infection. The study by Ayoya et al. [11] states that inadequate iron intake through diet and infection

with *Schistosoma spp* could be reversed through the administration of iron and praziquantel and that multimicronutrient supplementation promoted the best utilization of available iron.

In addition to studying the possible causes of the impact on nutritional status, studies such as that of Reilly et al. [12] show that deficiency in vitamin A can reduce the response of specific anti-*Schistosoma* antibodies. The study by Ayoya et al. [13] shows that the treatment of a child population infested with *Schistosoma haematobium* using praziquantel and varying doses of iron has a greater positive effect on school attendance than that provided only by treatment with praziquantel.

Regarding the effect of micronutrient supplementation in reinfestations, studies such as the one by Friis et al. [14] show that zinc supplementation has no effect on the reinfestation rate of *Schistosoma mansoni* and *Schistosoma haematobium*, however, the intensity of reinfestation with *Schistosoma mansoni* was lower in the group that was supplemented with zinc than in the group taking the placebo. Other studies such as Mwanakasale et al. [15] demonstrate, however, that there is a reduction in the intensity and rate of reinfestation with *Schistosoma haematobium* in the group supplemented with iron when compared with the placebo group.

The main objective of this meta-analysis is to assess the presence of a relationship between the addition of multimicronutrient supplementation to treatment with broad-spectrum antiparasitic anthelmintic medication and the reduction of infestation with *Schistosoma mansoni* and *Schistosoma haematobium* in children and adolescents. Given that in some cases there is a coinfection between *Schistosoma mansoni* and *Schistosoma haematobium*, it is important to carry out a second analysis in which both species are studied individually, therefore, this meta-analysis has as a secondary objective to study whether there is a statistical relationship between supplementation with multimicronutrients and the reduction of the infestation with *Schistosoma mansoni* and *Schistosoma haematobium* separately.

Materials and methods

A meta-analysis is performed through recognized databases (PubMed, Embase and Cochrane). The search strategy used for this meta-analysis was conducted in English using the terms "schistosom *" and "iron". The asterisk of the term "schistosom *" is used so that articles that contain the word "schistosoma" and the word "schistosomiasis" appear in the search. After carrying out this search, a filter was applied so that only those articles with human subjects would be

shown. With this first search in the three databases, a total of 363 articles were obtained (15 articles from Cochrane, 203 from EMBASE and 145 from PubMed), which after being reviewed and eliminating duplicates, resulted in 257 articles.

Once the search was completed and after the duplicate articles were eliminated, a primary review of the articles was carried out based on the title and abstract of each article. Two independent and different reviewers selected the articles that met the proposed inclusion and exclusion criteria.

In the primary review of this meta-analysis those articles that spoke of *Schistosoma mansoni*, *Schistosoma haematobium*, co-occurrences coexisting with each other or with other parasites, were included. Articles in which the study population included pre-school children, schoolchildren, adolescents and young adults, were all included since despite the fact that most of the studies are focused on children and adolescents, many of them are made in a school population that includes a wide range of ages. Articles that studied iron supplementation, supplementation with multimicronutrients or zinc supplementation were included because despite the fact that the search is focused on iron, iron is often present within a multimicronutrient complex. With these criteria, and once the primary review was performed by each of the reviewers, the reviewers met to decide which articles met these criteria and, therefore, could move on to secondary review, which in this case was 33 articles.

In the secondary review, after reading the full text and based on the same proposed inclusion and exclusion criteria, the articles that make up this meta-analysis were selected. Once the articles were selected, the most relevant data were extracted from them: number of participants of each study, age range, number of individuals of each sex and ethnicity. As shown in Table 1, most of the studies are focused on children and adolescents, but some studies include older age ranges since, as mentioned above, in some cases studies are conducted in schoolchildren with participants of different ages.

In addition to the general characteristics of each of the articles, data on the infestation with *Schistosoma* (both *Schistosoma mansoni* and *Schistosoma haematobium*) in

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

Study	n	Age Range	Male/ Female	Ethnicity
Ayoya et al., 2009	406	7–12 years old	223/183	African
Friis et al., 2003	746	5–13 years old	359/387	African
Friis et al., 1997	313	11–17 years old	144/169	African
Mwanakasale et al., 2009	446	9–15 years old	215/231	African
Mwaniki et al., 2002	644	9–18 years old	304/360	African
Olsen et al., 2000	200	4–15 years old	114/62	African
Olsen et al., 2003	977	8–18 years old	477/500	African
Taylor et al., 2001	428	6–15 years old	214/214	African

Table 2. Relationship of placebo and supplements with schistosome infestation.

AUTHOR	YEAR	PLACEBO		SUPPLEMENTS	
		INFESTED	TOTAL	INFESTED	TOTAL
Ayoya et al., 2009	2009	51	97	53	105
Friis et al., 2003	2003	82	191	61	188
Friis et al., 1997	1997	105	130	104	131
Mwanakasale et al., 2009	2009	216	228	196	218
Mwaniki et al., 2002	2002	89	163	62	166
Olsen et al., 2000	2000	24	92	31	108
Olsen et al., 2003	2003	353	492	331	485
Taylor et al., 2001	2001	28	60	5	56

the placebo and supplementation groups were also extracted. Table 2 shows the data relating to individuals belonging to both the placebo and supplementation groups who were infested with any of the *Schistosoma* species.

Statistical methods

To carry out this meta-analysis, the Review Manager (Rev Man) 5.3 [16] computer program was used. The estimated effect of the data of each article was calculated using Odds Ratio (OR). If the Odds Ratio has a value equal to 1, it means that there is no association between the variables studied. If the value of the Odds Ratio is greater than 1, there is a positive association between the variables, while if the value is less than 1 the variables will have a negative association.

Heterogeneity was measured using the Chi-square test. To check whether the studies were homogeneous or not, a parameter known as I^2 that has significance up to 50%, and the Chi-square value that has significance up to a value of $P < 0.10$ were used. If the value of I^2 is less than 50% or the value of P is greater than 0.10, the study is considered homogeneous.

Measurement of the quality of the selected studies

The scale used to measure the quality of the selected studies is the SIGN scale [17], which consists of two parts. The first part measures the level of evidence and does so by assigning a number from 1 to 4 and the second part provides a grade of recommendation and for this assigns a letter from A to D.

Results

Description of the studies

Of the 257 initial articles that were analyzed, 8 (Friis et al., 1997, Olsen et al., 2000, Mwaniki et al., 2002; Taylor et al., 2001; Friis et al., 2003; Olsen et al., 2003; Ayoya et al., 2009; Mwanakasale et al., 2009) are part of this meta-analysis both quantitatively and qualitatively (Figure 1) [11,14,15,18–22]. All studies were

conducted in Africa and all participants are African, with an age range between 4 and 18 years old. All of the studies included reported on the combination of a broad spectrum antiparasitic anthelmintic medication (praziquantel at 40mg/kg) with placebo or micronutrient supplements.

Analysis of data

An analysis of the eight articles was carried out with the objective of evaluating the hypothesis proposed in this meta-analysis. The statistical analysis of the data gives rise to a statistical representation known as “Forest Plot”, which shows a central line or line of effect where the Odds Ratio has a value of 1. If the final diamond touches this line, the study does not have statistical significance.

Relationship between micronutrient supplementation and the presence of *Schistosoma* spp in children

The first statistical analysis carried out aims to demonstrate the hypothesis that multimicronutrient supplementation decreases infestation with *Schistosoma mansoni* and *Schistosoma haematobium* in children and adolescents. To demonstrate this, the data corresponding to the infestation with *Schistosoma* spp were extracted from each of the studies both for the placebo group and the supplementation group. Figure 2 is the “Forest Plot” that corresponds to this first analysis and shows the placebo group on one side and the supplementation group on the other.

As shown in Figure 2, the results indicate that supplementation with multimicronutrients reduces infestation with *Schistosoma* spp 1.33 times more than placebo [Odds Ratio: 1.33 (1.13–1.58); $p = 0.0009$]. The Taylor 2001 study [21] has been excluded from this first analysis. This is because this study is very heterogeneous, and was ruled out after conducting a sensitivity study (Figure 3 and Figure 4). To carry out the sensitivity study, a funnel plot was used, showing the studies that are more heterogeneous. Figure 3 shows how the Taylor 2001 study [21] goes outside the 95% confidence interval lines (95% CI), indicating that it is a heterogeneous study. When this study is eliminated from the statistical analysis, it can be seen how all the studies are within the 95% CI lines and the statistics are homogeneous ($I^2 = 30\%$, $P = 0.20$) (Figure 3).

Relationship between micronutrient supplementation and the presence of *Schistosoma mansoni* and *Schistosoma haematobium* individually in children

As explained, the previous statistical analysis takes into account the infestation with *Schistosoma* spp. The

Figure 1. Flow diagram of the search strategy.

Figure 2. "Forest Plot" of the first statistical analysis. "Forest Plot" showing the relationship between multimicronutrient supplementation and infestation with *Schistosoma* spp.

population may be infested with *Schistosoma mansoni*, *Schistosoma haematobium* or both. In this second statistical analysis, the hypothesis is raised whether multimicronutrient supplementation has more effect in the population infected with *Schistosoma mansoni* alone or in the infestation only with *Schistosoma haematobium* or if there is no difference between them. Two subgroup analysis were carried out; in one of them the relationship between multimicronutrient supplementation and infestation only with *Schistosoma mansoni* was studied, and in the other, the relationship between multimicronutrient supplementation and infestation only with *Schistosoma haematobium* was studied (Figure 5).

The results show that supplementation with multimicronutrients in individuals infested with *Schistosoma mansoni* is 1.30 times more effective than placebo [OR: 1.30 (1.08–1.57); $p = 0.005$]. It should be taken into account that despite being technically heterogeneous ($I^2 = 52\%$, $P = 0.08$), χ^2 test has significance up to a value of $I^2 = 50\%$ and a χ^2 value of $P < 0.10$, the test values in this case are very close to the reference values. This heterogeneity is due to the fact that very few studies are available to perform this statistical analysis on.

In the case of individuals infested only with *Schistosoma haematobium*, the results of the statistical analysis indicate that multimicronutrient

Figure 3. “Funnel Plot” of the first statistical analysis A. “Funnel Plot” or funnel plot that indicates the homogeneity of the studies included in the statistical analysis.

Figure 4. “Funnel Plot” of the first statistical analysis B. “Funnel Plot” or Graph of funnel that shows the homogeneity of the articles included in the statistical study once the article that is more heterogeneous has been eliminated.

supplementation is 1.62 times more effective than the placebo [OR: 1.62 (1.19–2.22); $p = 0.002$]. In this case, the study is more heterogeneous than the previous one, since there is an even smaller number of articles available for statistical analysis. As can be seen in Figure 6, the Taylor 2001 article [21] is very heterogeneous, but due to the small number of articles available for this second statistical analysis, it was decided to include it, although it also influences the heterogeneity of the result.

Quality of articles

As indicated previously, the quality of the studies selected for this meta-analysis has been evaluated using the criteria of the SIGN [17] and Table 3 shows the results obtained.

Discussion

This meta-analysis provides an analysis and quantitative evaluation of the relationship between multimicronutrient supplementation and decreased infestation with *Schistosoma mansoni* and *Schistosoma haematobium* in children and adolescents treated with broad-spectrum antiparasitic anthelmintic medication, by integrating the data contained in eight studies.

The results show that the population receiving multi-micronutrient supplementation along with broad-spectrum antiparasitic anthelmintic treatment saw reduced infestation with *Schistosoma spp.* This result confirms what has been proposed by authors such as Long et al. [23], who affirm that in studies of vitamin supplementation, that an adequate level of vitamin A is required to maintain an adequate anthelmintic response since vitamin A regulates both the innate

Figure 5. "Forest Plot" of the subgroup analysis. Statistical analysis or "Forest Plot" of subgroups: infested only with *S. mansoni* and infested only with *S. haematobium*.

Figure 6. "Funnel Plot" del análisis de subgrupos. Gráfico de embudo o "Funnel Plot" del análisis correspondiente a los subgrupos.

Table 3. Quality study table. Results of the evaluation of the quality of the selected studies.

ARTICLES	QUALITY
Ayoya et al., 2009	A1++
Friis et al., 2003	A1+
Friis et al., 1997	A1-
Mwanakasale et al., 2009	B2++
Mwaniki et al., 2002	A1++
Olsen et al., 2000	A1++
Olsen et al., 2003	A1++
Taylor et al., 2001	A1++

and adaptive immune responses. Some studies like that proposed by Parent et al. [24] demonstrated experimentally that vitamin A deficiency reduces the response of *Schistosoma*-specific antibodies, suggesting that deficiency of this vitamin may increase the susceptibility to have an infestation by *Schistosoma mansoni*. Other authors such as Cook & Linch [25] affirm that iron

deficiency anemia increases morbidity and mortality due to infections, and others such as Stephenson et al. [26], state that the lack of iron and other micronutrients worsen the infestation by *Schistosoma spp* and other parasitic infections that occur with blood loss. As stated by studies such as Friis et al. [18], it is also important to take into account the existence of possible interactions between the various micronutrients, for example, zinc is related to the conversion of β -carotene to vitamin A (Dijkhuizen & Wieringa, 2001) [27].

These results are also confirmed in those cases in which the population is infested only with *Schistosoma mansoni* or only with *Schistosoma haematobium*. Some studies such as that of Mwaniki et al. [20], showed that reducing the infestation intensity of *Schistosoma mansoni* increased serum retinol, and this is because vitamin A deficiency reduces the humoral immune response to

schistosome antigens (Parent et al., 1984) [24] and increases the parasitic load (Krakower et al., 1940) [28]. Vitamin A concentrations depend on the inflammatory response, therefore, when infection intensity goes down, the acute phase response will go down, and retinol concentrations go up [29]. The study proposed by Mwanakasale et al. [15] shows that the reinfestation rate of *Schistosoma haematobium* was significantly higher in the control group compared to the group that took iron supplementation at six months.

Another aspect to consider is how micronutrients influence the rate of reinfestation of *Schistosoma spp.* Authors such as Olsen et al. [19] showed that iron supplementation significantly reduces the rate of reinfestation, but has no effect on the intensity of the reinfestation, and they did so by counting eggs, although this study was conducted in adults. Other studies, such as the one proposed by Olsen et al. [22], however, affirm that micronutrient supplementation decreases the intensity of reinfestation with *Schistosoma mansoni*. This is also affirmed by the study by Friis et al. [14], in which supplementation with zinc reduced the intensity of reinfestation with *Schistosoma mansoni*, but had no effect on the rate of reinfestation.

One of the limitations when carrying out this study is the lack of information available within the articles, since some articles could have possibly been included due to their characteristics in this meta-analysis, but did not provide sufficient information. Due to this, the analysis relative to the infestation only with *Schistosoma mansoni* has only been carried out on five articles, and the one related to the infestation only with *Schistosoma haematobium* only includes four articles, which negatively influences homogeneity.

In relation to the quality of the articles, most of the articles are of good quality, they are randomized clinical trials and therefore very useful when performing this meta-analysis.

Conclusions

Schistosomiasis is an important disease especially in children, given that they are a very vulnerable part of the population, therefore it is important to study its causes, consequences and how its prevalence can be reduced. After the completion of this meta-analysis, a series of conclusions have been reached:

1. The combination of broad-spectrum antiparasitic anthelmintic medication with micronutrient supplementation reduces infestation with *Schistosoma spp.* in children and adolescents. This is related to the fact that many of these micronutrients are involved in the immune system and participate in the immune response against the parasite.

2. The combination of broad-spectrum antiparasitic anthelmintic medication with micronutrient supplementation reduces the infestation with *Schistosoma mansoni* in children and adolescents, and iron is one of the most important micronutrients in this case.
3. The combination of broad-spectrum antiparasitic anthelmintic medication with micronutrient supplementation reduces the infestation with *Schistosoma haematobium* in children and adolescents.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

None.

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