

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Helminth infections, atopy, asthma and allergic diseases: protocol for a systematic review of observational studies worldwide
<b>AUTHORS</b>	Arrais, Margarete; Maricoto, Tiago; Cooper, Philip; Gama, Jorge; Nwaru, Bright; Brito, Miguel; Taborda-Barata, Luís

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Jenna Patterson University of Cape Town, South Africa
<b>REVIEW RETURNED</b>	06-Mar-2020

<b>GENERAL COMMENTS</b>	<p>Search strategy: Why KoreMed and not other databases from Asia? Please also include European clinical trials registry.</p> <p>Data extraction: Please clarify the following line "If an article presents results from N different studies, then, N different forms will be created to collect data."</p> <p>Quantitative assessment: More details on the I2 statistic for reporting pooled analysis needs to be included. Additionally, how will forest plots help you identify publication bias?</p> <p>Data synthesis: Consider including sensitivity analyses for sample size of included studies.</p>
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<b>REVIEWER</b>	Eleftheria Vasileiou The University of Edinburgh, Usher Institute, UK
<b>REVIEW RETURNED</b>	09-Mar-2020

<b>GENERAL COMMENTS</b>	<p>This protocol aims to identify epidemiological evidence that assesses the association between helminth infections and allergic diseases. This will be achieved by identifying, extracting, appraising and synthesising relevant data that assesses the link between any type of helminth infection and various clinical outcomes related to allergic diseases, atopy and asthma. The broad selection criteria in this review protocol aim to give clearer answers (compared to older systematic reviews) on the effects of helminth infections on asthma symptoms and atopy.</p> <p>INTRODUCTION</p> <p>Page 7, Line 14-15:</p> <p>The recent systematic review was published in 2017, so I am assuming the most recent study in the review to have been published around 2016. Thus, are the authors certain that no new</p>
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	<p>studies on the effect of toxocariasis have been published from 2016 to 2020?</p> <p><b>METHODS AND ANALYSIS</b></p> <p>Search strategy Page 8, Lines 19-26:</p> <p>High prevalence of helminth infections is also seen in South Asia and Latin America. Did the authors consider searching for literature in region specific databases for the aforementioned regions?</p> <p>Inclusion criteria for study designs Page 8, Line 46:</p> <p>There is no age restriction; however, in page 13, lines 13-15 the authors state that this review will provide evidence for children. Can the authors clarify if the study is focused on children or not?</p> <p>Data extraction and management Page 9, Lines 50-59:</p> <p>Some of the participants' characteristics that authors may want to include in their data extraction form could be:</p> <ol style="list-style-type: none"> <li>1) Wheezing due to early-life respiratory viral infections (e.g. rhinovirus, RSV)</li> <li>2) Early childhood respiratory infections</li> <li>3) Family history of allergies</li> <li>4) Household smoking</li> </ol> <p>In addition, the duration of helminth infections may be important information to be extracted. I would expect longer exposure to the parasites to have a stronger effect on asthma symptoms and allergy.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

B) Reviewer: 1

Reviewer Name: Jenna Patterson

Institution and Country: University of Cape Town, South Africa

Please state any competing interests or state 'None declared': None

B1) Search strategy: Why KoreMed and not other databases from Asia? Please also include European clinical trials registry.

Reply: We would like to thank the reviewer for this comment. In fact, we have not only included KoreaMed, but also other relevant databases from Asia – IndMed, PakMediNet, and the others that are encompassed by WHO Global Health Library. We also tested two relevant Chinese databases which we had thought about including – Chinese Medical Current Contents (CMCC – [www.cmcc.org.cn](http://www.cmcc.org.cn)) and Chinese Biomedical Literature (CBM – <http://cbmwww.imicams.ac.cn/>) databases, but we encountered various difficulties namely no accessibility either directly on websites or indirectly.

Thus, we believe that it would be very useful to include these two Chinese databases but our capacity to actually search them is low and have not included them in our protocol.

Nevertheless, we have now included the Japanese "Ichushi" database, updated by the Japan Medical Abstracts Society (JAMAS).

All of the aforementioned changes are on page 7, lines 25-36.  
Finally, we have also included the European clinical trials registry in the same section, page 7, line 43.

B2) Data extraction: Please clarify the following line "If an article presents results from N different studies, then, N different forms will be created to collect data."

Reply: We meant that each study would have its data extracted onto a specific form. However, given the reviewer's comment, we have now revised the section of the paper to make it clearer, as shown on page 8, lines 40,41 and lines 51-54.

B3) Quantitative assessment: More details on the I2 statistic for reporting pooled analysis needs to be included. Additionally, how will forest plots help you identify publication bias?

Reply: We thank the reviewer for these important comments. We have now added further information on I2 and clarified our initial descriptions of the forest and funnel plots. This new information is on page 10, lines 15-22.

B4) Data synthesis: Consider including sensitivity analyses for sample size of included studies.

Reply: We have done as requested and such information is on page 11, lines 21-24.

C) Reviewer: 2

Reviewer Name: Eleftheria Vasileiou

Institution and Country: The University of Edinburgh, Usher Institute, UK

Please state any competing interests or state 'None declared': None

This protocol aims to identify epidemiological evidence that assesses the association between helminth infections and allergic diseases. This will be achieved by identifying, extracting, appraising and synthesising relevant data that assesses the link between any type of helminth infection and various clinical outcomes related to allergic diseases, atopy and asthma. The broad selection criteria in this review protocol aim to give clearer answers (compared to older systematic reviews) on the effects of helminth infections on asthma symptoms and atopy.

## INTRODUCTION

C1) Page 7, Line 14-15:

The recent systematic review was published in 2017, so I am assuming the most recent study in the review to have been published around 2016. Thus, are the authors certain that no new studies on the effect of toxocariasis have been published from 2016 to 2020?

Reply: We thank the reviewer for this important question. Although we search in many different databases, the most recent systematic review on Toxocara and allergic diseases is, in fact, the one by Mohammadzadeh et al, published in December 2018, included articles published until May 2018. Our preliminary search did not find any subsequent article on Toxocara and allergic diseases. However, given that the review by Mohammadzadeh et al only focused on the relationship between Toxocara infection and allergic cutaneous diseases but not respiratory allergic diseases, we believe that our systematic review, by including not only Toxocara but a whole array of different helminths, and also focusing on broader range of allergic diseases, and not just skin diseases, will thus be very relevant.

## METHODS AND ANALYSIS

C2) Search strategy

Page 8, Lines 19-26:

High prevalence of helminth infections is also seen in South Asia and Latin America. Did the authors

consider searching for literature in region specific databases for the aforementioned regions?

Reply: We agree with the aspect raised by this question. We have now expanded on the section on database searches and the relevant databases across the world, including those from South Asia and Latin America, as the reviewer suggested, are now included, on page 7, lines 24-30.

### C3) Inclusion criteria for study designs

Page 8, Line 46:

There is no age restriction; however, in page 13, lines 13-15 the authors state that this review will provide evidence for children. Can the authors clarify if the study is focused on children or not?

Reply: We thank the reviewer for highlighting this important oversight. Yes, we will include both children and adults and have changed the text accordingly, on page 12, which now reads "...associations in children and adults." (line 24) and also "...and allergic diseases in children and adults,..." (line 42).

### C4) Data extraction and management

Page 9, Lines 50-59:

Some of the participants' characteristics that authors may want to include in their data extraction form could be:

- 1) Wheezing due to early-life respiratory viral infections (e.g. rhinovirus, RSV)
- 2) Early childhood respiratory infections
- 3) Family history of allergies
- 4) Household smoking

Reply: We thank the reviewer for these suggestions and we have included them in the text, on page 8, lines 56-68, and page 9, lines 3-4.

C5) In addition, the duration of helminth infections may be important information to be extracted. I would expect longer exposure to the parasites to have a stronger effect on asthma symptoms and allergy.

Reply: We thank the reviewer for this suggestion and have included it in the text, on page 9, line 5.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Jenna Patterson University of Cape Town
<b>REVIEW RETURNED</b>	10-Apr-2020
<b>GENERAL COMMENTS</b>	Authors have revised according to previous comments. Well done and should be published.
<b>REVIEWER</b>	Eleftheria Vasileiou The University of Edinburgh, Usher Institute, UK
<b>REVIEW RETURNED</b>	20-Apr-2020
<b>GENERAL COMMENTS</b>	The protocol is now improved and the authors have clearly responded to and addressed (where possible) all comments and suggestions by the reviewers. I am happy for this protocol to be accepted for publication in BMJ Open.