

Mass deworming for soil-transmitted helminths and schistosomiasis among pregnant women: a systematic review and individual participant data meta-analysis

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TITLE OF THE REVIEW

Mass deworming for soil-transmitted helminths and schistosomiasis among pregnant women: a systematic review and individual participant data meta-analysis

BACKGROUND

The term 'helminth' means parasitic worms. Soil transmitted helminthiasis (STH) are a group of diseases caused by infection with four intestinal parasites: *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whip worm), *Necator americanus* (hookworm) and *Ancylostoma duodenale* (hookworm) (WHO, 2015). In the 1990s around 25% of the world's population (roughly about 1.5 billion people) were estimated to be infected with one or more of STH with a disproportionately higher burden in low- and middle- income countries (LMICs) (Chan, Medley, Jamison, & Bundy, 1994). A more recent analysis suggests that globally, an estimated 438.9 million people were infected with hookworm in 2010, 819.0 million with roundworms and 464.6 million with whipworm. STH altogether, contributed to a total of 4.98 million years lived with disability (YLDs). Of these YLDs, 65% were attributable to hookworm, 22% to roundworm and the remaining 13% to whipworm. In terms of geographical distribution, around 67% of STH occurred in Asia contributing to 68% of the YLDs (Pullan, Smith, Jasrasaria, & Brooker, 2014).

Even within LMICs, the disease disproportionately affects the most marginalised population groups and appears to be predominantly affecting the poorest populations with lack of clean water, hygiene and sanitation facilities (Pullan et al., 2014). Over 270 million preschool-age children and over 600 million school-age children live in STH endemic areas and an estimated 4 million pregnancies a year are complicated by maternal hookworm infection alone (Bundy, Chan, & Savioli, 1995). Women in LMICs are especially prone since they may be pregnant or lactating for as much as half of their reproductive lives (WHO, 1994) and estimates indicate that over 50% of the pregnant women have iron-deficiency anaemia (Mason, 2000; Organization, 1997). The association between anaemia during pregnancy and adverse pregnancy outcomes, including low birth weight (LBW), preterm birth, perinatal mortality and infant survival have already been documented (Rahman et al., 2016; Sifakis & Pharmakides, 2000). Furthermore, the chances of favourable pregnancy outcomes are reduced by 30% to 45% in anaemic mothers, with their infants having less than one half of normal iron reserves (Rahman et al., 2016). According to the World Health Organization (WHO), mass drug administration (MDA) of antihelminthics for high risk population groups is recommended and treatment frequency varies depending on the STH prevalence in the given community (Crompton, 2006; Montresor, Crompton, Gyorkos, & Savioli, 2002).

While water, sanitation and hygiene (WASH) and MDA are generally accepted as effective interventions to disrupt STH and schistosomiasis transmission, there is a great deal of heterogeneity in reported effect estimates from the existing systematic reviews.

Furthermore, the effectiveness of MDA in improving various maternal and child health outcomes is a current source of debate (Turner et al., 2015).

A recent Cochrane systematic review evaluating deworming among children concluded that there is insufficient evidence supporting the benefit of deworming for children (Taylor-Robinson, Maayan, Soares-Weiser, Donegan, & Garner, 2012). A recent Campbell review assessing the effects of mass deworming for soil transmitted helminths on growth, educational achievement, cognition, school attendance, quality of life and adverse effects in children, suggests that there is a need to reconsider mass deworming programmes in their current form and consider additional policy options to improve child health and nutrition in worm-endemic areas (Welch, Awasthi, Cumberbatch, & Fletcher, 2016). Similarly, the most recent Cochrane review of deworming in the second trimester of pregnancy (as discussed in the above section) concludes that there was insufficient evidence to recommend deworming in pregnancy (Salam, Maredia, Das, Lassi, & Bhutta, 2014).

Critical appraisal of suggests that the studies included in these reviews fail to account for various factors that modify the effectiveness of deworming (Barry, Simon, Mistry, & Hotez, 2013; Turner et al., 2015). These factors include baseline nutritional status (including anaemia and stunting), type of STH infection, treatment protocol, worm burden (particularly intensity of infection) and concomitant interventions (such as iron, vitamin A, feeding and other drugs such as praziquantel for schistosomiasis) (Barry et al., 2013; Turner et al., 2015). Importantly, there has been no comprehensive study of these potential sources of heterogeneity in the effects of WASH and MDA on transmission of STH. Additionally, STH infections are not always symptomatic and not all who receive MDA will benefit equally. Hence there is a need to understand potential targeting of such programs for the age groups at risk, for example pregnant women, adolescents and women of reproductive age (Anderson, Turner, Truscott, Hollingsworth, & Brooker, 2015). A recent systematic review has also highlighted the scarcity of cost related data for STH programs, which is of prime importance in planning treatment frequency and targeting for STH and schistosomiasis interventions (Turner et al., 2015).

Therefore, an objective assessment of sources of heterogeneity in existing studies, as well as subsets of subjects with varied risks and responses, is required to move the field forward. Despite the availability of more recent global estimates on the burden and interventions for STH and schistosomiasis, additional research is needed to understand the factors that explain the variation in the effect estimates of recommended interventions to prevent transmission. Specifically, a critical knowledge gap is how the effectiveness of MDA and WASH are affected by both individual and community-level factors, and by each other.

Existing evidence suggests that recommended, routine, repeated deworming public health programmes on a large scale have little or no benefit with significant heterogeneity in reported effect estimates (Salam, Haider, Humayun, & Bhutta, 2015; Taylor-Robinson et al., 2012; Welch et al., 2016). Furthermore, studies on interventions other than deworming lack

rigorous evaluation, standardization in assessing and reporting outcomes and methodological limitations. Existing studies fail to account for various factors that modify the effectiveness of deworming including underlying host and environment factors (including baseline nutritional status, type of STH infection, treatment protocol, worm burden and concomitant interventions). Moreover, it is important to contextualise that all intestinal worms are not the same; not all intestinal worms respond to the same deworming medication; and not all infested individuals exhibit the disease. Based on the above mentioned reasons, it is important to characterise factors that modify the effect of maternal deworming and WASH interventions on STH and schistosomiasis transmission and to quantify the effect of deworming efforts in this specific sub-population.

OBJECTIVES

We will undertake a global systematic review of existing studies, using individual participants data (IPD) meta-analysis approaches. IPD will provide an added advantage of evaluating variation in effect estimates by various individual, sociodemographic and environmental factors in pregnant women, which is not possible through systematic review and meta-analysis. IPD will also lead to improved power and standardisation of analyses across studies with a longer follow-up time, more participants, and more outcomes. The objective(s) of the review are:

1. What is the effectiveness of deworming for STH and schistosomiasis in pregnant women?
2. What factors explain the variation in the effectiveness of deworming for STH and schistosomiasis in pregnant women?

EXISTING REVIEWS

Salam RA, Haider BA, Humayun Q, Bhutta ZA. Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy. *The Cochrane Library*. 2015 Jan 1.

Strunz EC, Addiss DG, Stocks ME, Ogden S, Utzinger J, Freeman MC: Water, sanitation, hygiene, and soil-transmitted helminth infection: a systematic review and meta-analysis. *PLoS Med* 2014, 11(3):e1001620.

Ziegelbauer K, Speich B, Mäusezahl D, Bos R, Keiser J, Utzinger J: Effect of sanitation on soil-transmitted helminth infection: systematic review and meta-analysis. *PLoS medicine* 2012, 9(1):81.

Salam RA, Maredia H, Das JK, Lassi ZS, Bhutta ZA: Community-based interventions for the prevention and control of helminthic neglected tropical diseases. *Infectious diseases of poverty* 2014, 3(1):23.

A concurrent IPD review of the effects of deworming in children is also being registered with the Campbell Collaboration (Welch et al., 2017). The present review will additionally examine the effectiveness of maternal deworming for schistosomiasis, and it will investigate potential modifiers of the effectiveness of deworming for both soil-transmitted helminths and schistosomiasis.

INTERVENTION

Any deworming drugs versus placebo or no treatment. In case of co-interventions other than deworming, both groups should receive the same co-intervention.

POPULATION

Pregnant women receiving preventive or therapeutic deworming in low- and middle-income countries.

OUTCOMES

Primary outcomes:

- Maternal anaemia (haemoglobin less than 11 g/dL)
- Worm burden/prevalence/intensity/parasite density (as reported by the study authors).

Secondary outcomes:

- Haemoglobin
- Ferritin
- Maternal anthropometric measures (height, weight)
- Body mass index (BMI)
- Birth weight
- Low birth weight (LBW) (less than 2500 g)
- Preterm birth (birth before 37 weeks of gestation)
- Perinatal mortality (includes fetal death after 28 weeks of gestation and infant death that occurs at less than seven days of life)
- Stillbirth
- Congenital abnormalities
- Infant survival at six months
- Mortality.

STUDY DESIGNS

For systematic review and meta-analysis, all studies assessing the effects of deworming during pregnancy will be considered. Types of studies will include individually randomised controlled trials, cluster randomised controlled trials, quasi randomised studies, controlled before-after studies, case-control studies and cohort studies. Incorporating non-randomised studies will provide evidence on adverse outcomes, uncommon outcomes and outcomes where randomised assignment may be unethical. No language or date restrictions will be applied.

For IPD analysis, we will include only randomised controlled trials and cluster randomised controlled trials.

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REVIEW AUTHORS

Lead review author: The lead author is the person who develops and co-ordinates the review team, discusses and assigns roles for individual members of the review team, liaises with the editorial base and takes responsibility for the on-going updates of the review.

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ROLES AND RESPONSIBILITIES

Please give a brief description of content and methodological expertise within the review team. It is recommended to have at least one person on the review team who has content expertise, at least one person who has methodological expertise and at least one person who has statistical expertise. It is also recommended to have one person with information retrieval expertise. Please note that this is the *recommended optimal* review team composition.

- Content: Zulfiqar Bhutta, Rehana Salam, Michelle Gaffey, Philippa Middleton, and Maria Makrides have maternal health and nutritional expertise.
- Systematic review methods: Rehana Salam, Philippa Middleton and Maria Makrides have methodological expertise.
- Statistical analysis: Simon Cousens has statistical expertise.
- Information retrieval: Rehana Salam and Michelle Gaffey have information retrieval expertise.

FUNDING

We have funding from the Bill and Melinda Gates Foundation.

The review timeline is as follows:

	Jul 2017	Aug	Sep	Oct	Nov	Dec	Jan 2018	Feb	Mar
Title registered	X								
Protocol development	X	X							
Protocol submission		X							
Searching and screening		X	X						
Data extraction			X	X	X				
Synthesis				X	X	X			
Interpretation and write up						X	X		
Publication								X	X

POTENTIAL CONFLICTS OF INTEREST

Vivian Welch is an author of a prior aggregate-level Campbell Deworming review.

No other potential conflict of interest for any of the other authors.

Comments on the protocol and report will be sought from the funders as part of the review process, however the peer review is led by the IDCG editorial team which is independent of the funders and ultimately responsible for ensuring the quality of the analysis conducted.

PRELIMINARY TIMEFRAME

Note, if the protocol or review are not submitted within 6 months and 18 months of title registration, respectively, the review area is opened up for other authors.

- Date you plan to submit a draft protocol: August 2017
- Date you plan to submit a draft review: January 2018

AUTHOR DECLARATION

Authors' responsibilities

By completing this form, you accept responsibility for preparing, maintaining, and updating the review in accordance with Campbell Collaboration policy. The Coordinating Group will provide as much support as possible to assist with the preparation of the review.

A draft protocol must be submitted to the Coordinating Group within one year of title acceptance. If drafts are not submitted before the agreed deadlines, or if we are unable to contact you for an extended period, the Coordinating Group has the right to de-register the title or transfer the title to alternative authors. The Coordinating Group also has the right to de-register or transfer the title if it does not meet the standards of the Coordinating Group and/or the Campbell Collaboration.

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Date: 9 March 2017