Interventions to improve water, sanitation, and hygiene for preventing soil-transmitted helminth infection

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Interventions to improve water, sanitation, and hygiene for preventing soil-transmitted helminth infection (Protocol)

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Interventions to improve water, sanitation, and hygiene for preventing soil-transmitted helminth infection

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of water, sanitation, and hygiene interventions to prevent soil-transmitted helminth infection.

Background

Description of the condition

Soil-transmitted helminths (STHs) are a group of parasitic worms that afflict over a billion people worldwide (Pullan 2014), with many more people who live in endemic areas at risk of infection (Bethony 2006). The most common STHs - roundworm (Ascaris lumbricoides), whipworm (Trichuris trichiura), and hookworms (Necator americanus and Ancylostoma duodenale) - that are endemic throughout Asia, Latin America, and Africa, live in the human gut for up to two years, and shed thousands of fertilized eggs per day through stools (Hotez 2006). STHs are transmitted to a new host through faecal exposure, either through ingestion of eggs (roundworm and whipworm) or through skin penetration by larvae (hookworm) (Hotez 2006).

Infection with hookworm and whipworm have been associated with anaemia (Crompton 2000). Whipworm is associated with undernutrition (Cappello 2004); roundworm may lead to impaired fat digestion and poor vitamin absorption (WHO 2002). Chronic and heavy infections with STHs can cause iron deficiency (Stolzfuß 1998; Gulani 2007), poor nutrition and stunting (Stolzfuß 1997; Crompton 2002), cognitive delays, and absence from school (Miguel 2004). Death from STH infection is uncommon, and the largest trial of deworming found no evidence of deworming on rates of mortality in a lightly infected population in northern India (Awasthi 2013). Polyparasitism, which is infection with more than one STH, is common and higher worm burden
leads to greater morbidity (Sanchez 2013; Al-Delaimy 2014). The global burden of disease due to STH infection is estimated to be 5.2 million disability adjusted life years (DALYs) (Murray 2013). The burden of disease is greatest among school-age children (five years to 15 years of age), though there is growing evidence of considerable morbidities among preschool-age children. The primary control effort for STH infection is deworming using one of the two benzimidazoles, either albendazole or mebendazole (Utzinger 2004), as part of either school-based mass drug administration (MDA) or community-based MDA for STH or community-based MDA as part of lymphatic filariasis control. It is well documented that the efficacy of these drugs is suboptimal and differs considerably between individual species of STH (Keiter 2008), and a recent Cochrane review found little convincing evidence of the impact of community-based MDA on children's growth, cognitive development, or school attendance (Taylor-Robinson 2015). Regardless, recent commitments by GlaxoSmithKline and Johnson & Johnson mean that nearly five billion doses of albendazole and mebendazole will be available for MDA to school-age children through 2020. This action is in response to World Health Assembly resolution WHA 54.19, which called for treatment of 75% and up to 100% of all school-age children at risk of STH by 2010, and more recent commitments by the international community for a dramatic scale-up of treatment and control (Hotz 2007; WHO 2012a). It is estimated that over 883 million school-age and pre-school age children will require preventive chemotherapy for STH (WHO 2012a; WHO 2013).

**Description of the intervention**

Even with high adherence to deworming, reinfection occurs rapidly after treatment (Jia 2012), and interruption of transmission is unlikely without complementary control efforts (Utzinger 2009; WaterAid 2012; WHO 2012a; Freeman 2013). STH is highly endemic among people who are poor, especially those with poor access to water and sanitation services. Improvements of water quantity for hygiene, water quality for drinking and cooking, basic sanitation, and hygienic behaviours can break transmission and lead to reductions in worm burden that complement deworming. The World Health Organization (WHO) Roadmap for Implementation for the control of NTDs (WHO 2012b) specifies the importance of water, sanitation, and hygiene (WASH) improvements for control efforts, but no targets have been set or strategy for integration of WASH and MDA. Control of trachoma, a blinding eye condition caused by repeated infection with the bacterium Chlamydia trachomatis, includes the SAFE strategy - consisting of surgery (S) to correct advanced stages of the disease; antibiotics (A) to treat active infection; facial cleanliness (F) to reduce disease transmission; and environmental change (E) to increase access to clean water and improved sanitation to eliminate disease altogether - entails two specific components for transmission control (the F and E) (Emerson 2012). However, no such strategy exists for STHs at present (Lancet 2012).

**How the intervention might work**

The impact of WASH on health is well documented (Bartram 2010). Reviews have found considerable evidence for the role of WASH in reducing diarrhoeal disease (Fawell 2005; Prüss-Ustün 2014), limiting trachoma infection (Stocks 2014), reducing schistosomiasis transmission (Grimes 2014), and improving nutrition (Dangour 2013). However, in many cases few rigorous studies have been conducted. Water improvements could include improvements to water quality, such as point-of-use water treatment with filters or chlorine (Clasen 2007), which would prevent ingestion of STH ova, or safe water storage, given the known role of water handling in water contamination (Wright 2004). Improvements to water supply - typically a community-level intervention - can impact both water quality and water quantity, especially if the new source is closer to the house (Howard 2003). The WHO/UNICEF Joint Monitoring Programme for Water and Sanitation (JMP) defines “improved” water supply as any source protected from contamination, though evidence suggests that access to an improved source does not guarantee microbiological safety (Brown 2015). Sanitation improvements might include either demand-side promotion, such as community-led total sanitation (Kar 2008), or supply-side sanitation to promote increased access to, and use of, toilets. Hygiene improvements could include hygiene education, mass media campaigns, provision of educational materials to schools, or supply of soap. WASH interventions to control STH could include school- or community-based programmes and may be allocated by household, community, or school.

**Why it is important to do this review**

The Rockefeller Sanitation Commission Report in the early 1900s first documented the impact of sanitary improvements on STH infection (Horton 2003). Esrey 1991 first reviewed the associations between WASH and STHs, and more recently Strunz 2014 and Ziegelbauer 2012 although meta-analysis relied predominantly on observational studies. Other studies have attempted to model the attributable fraction of infections caused by poor access to and behaviours related to WASH (Soares Magalhães 2011). Understanding both the impact and costs of interventions are essential for establishing control policies for STH. While the cost and cost-effectiveness of MDA has been quantified (Holland 2001; Leslie 2011), and costing tools are currently available to estimate the life-cycle costs of WASH programmes (IRC 2014), we lack robust quantification of the effectiveness of WASH programmes on STH. WASH programmes may prove efficacious given long time horizons estimated for controlling STH through MDA alone, but more data are needed.
Here we investigate the rigorous evidence of the role of programmes to improve WASH either individually, in combination, or as a complement to deworming campaigns. A recent review found evidence of crude associations between sanitation access and STH prevalence (odds ratio (ORs) ranging between 0.46 and 0.58) and between sanitation use and individual STH infections (ORs ranging between 0.54 and 0.78) (Ziegelbauer 2012). A second review found similar results using adjusted estimates for the relationship between sanitation and STH, as well as strong associations between water supply, water treatment, and hygiene and individual and any STH infection (Strunz 2014). These reviews relied on observational studies, which may be subject to reporting bias and lack of causality. Though useful for policy guidance, a review of the gold-standard evidence is needed to assess the impact of WASH improvements on STH infection and perhaps to draw attention to the need for more robust evidence around effectiveness, and by extension, cost-effectiveness of these interventions.

**OBJECTIVES**

To assess the effectiveness of water, sanitation, and hygiene interventions to prevent soil-transmitted helminth infection.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include all randomized controlled trials (RCTs) and quasi-RCTs either individually allocated or assigned by cluster, such as household, village, school, or other group cluster. We will consider cluster RCTs for inclusion if they include at least two units per trial arm. We will exclude non-human animal studies and duplicate publications. For studies that pool multiple intestinal parasites into one outcome measure (for example, *Giardia intestinalis* plus soil-transmitted helminth (STH)), we will contact study authors to request disaggregated data. If information about STH outcomes alone is unavailable, we will exclude the study.

**Types of participants**

Trials must be conducted in environments where STHs are endemic and transmitted, and trial participants are those that reside in the trial site. We will include participants with or without STH infection at baseline. All types of participants will be considered, although we expect most trials to focus on school-age children.

We will include trials with preschool-age children, adolescent, or adult participants.

**Types of interventions**

Potential interventions include provision of water supply, latrine construction or sanitation promotion, hygiene education, and water quality improvements (such as safe storage and handling or water treatment). We will include all interventions that improve WASH access or practices, or both, including those that employ multiple water, sanitation, and hygiene (WASH) strategies or an integrated approach that includes mass drug administration (MDA).

Control groups will be trial participants or groups that follow their typical WASH behaviours rather than the prescribed intervention or those that received a different type of intervention (such as MDA).

We will exclude interventions that include deworming (that is, treatment with anthelminthic drugs) in the experimental arm along with a WASH intervention, but not the control arm.

**Types of outcome measures**

**Primary outcomes**

1. Prevalence of infection with at least one STH species, as defined by at least one ovum of *A. lumbricoides*, *T. trichiura*, hookworm, or *Strongyloides stercoralis* found in the participant’s faeces.

**Secondary outcomes**

1. Prevalence and intensity of infection as measured by eggs per gram of faeces for specific STH type, including *A. lumbricoides* (ascariasis), *T. trichiura* (trichuriasis), hookworm (*A. duodenale* or *N. americanus*, or both), or *S. stercoralis* (strongyloidiasis).

2. Any adverse events resulting from WASH interventions and mass drug administration (MDA).

**Search methods for identification of studies**

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing).

**Electronic searches**

We will search the following databases using the search terms described in Appendix 1: Cochrane Infectious Diseases Group
Searching other resources

Conference proceedings
We will search conference proceedings of the American Society of Tropical Medicine & Hygiene, and the Water and Health Conference for the previous two years.

Grey literature
We will request unpublished research from the U.S. Centers for Disease Control and Prevention (CDC); The Carter Center; The Task Force for Global Health; the WHO regional offices; Water, Sanitation and Health Program of the WHO; World Bank Water and Sanitation Program; UNICEF Water, Environment and Sanitation (WES); Environmental Health Project (EHP); IRC International Water and Sanitation Centre; US Agency for International Development (USAID); and the UK Department for International Development (DFID).

Reference lists
We will also check the reference lists of all included trials for other potentially relevant research and review authors' personal collections.

Data collection and analysis

Selection of studies
Matthew C. Freeman (MCF) and Eric Strunz (ES) will independently review the titles and abstracts yielded by the search, and will identify all studies that potentially meet the inclusion criteria for this Cochrane review. After we obtain the full text articles of screened records that may meet the inclusion criteria, we will independently assess whether or not each study meets the inclusion criteria using an eligibility form. When MCF and ES do not initially reach a consensus, David G. Addiss (DGA) will make the final inclusion decision. If the eligibility is unclear, we will write to the study authors for clarification. We will scrutinize each trial report to ensure that we include multiple publications from the same trial only once. We will document all excluded studies with their reason for exclusion.

Data extraction and management
Two review authors, MCF and ES, will independently perform data extraction using a pre-designed data extraction form (Appendix 2). We will resolve any disagreements regarding the data extraction by discussion with a third review author (DGA or JU). If relevant data are unclear or unreported, we will contact trial authors for clarification. We will enter the extracted data into Review Manager (RevMan) (RevMan 2014). We will collect data about the trial population (including age and gender distribution) and setting (including country and urban status), inclusion and exclusion criteria, intervention description (including any non-WASH co-interventions), control details, diagnostic method, and statistical methods (including model covariates and modelling approach where applicable). We will also collect information about STH prevalence and intensity (point estimates with standard errors (SEs)) where trial authors report this information.

For each outcome, we will extract the number of participants randomized and analysed in each treatment group for each outcome. For dichotomous outcomes, we will extract the number of participants that experienced the event in each group and ratio measures with SEs if available. For count outcomes, we will extract the number of events (most likely eggs per gram of stool (EPG)) in the treatment and control group with the total person-time in each group and the rate ratio and SE if available. For time-until-event outcomes, we will extract hazard ratios (HRs) and SEs.

We will extract information on the number of clusters, type of clusters (for example, communities, households), average size of the cluster, unit of randomization, statistical methods used for correlated data, and estimates of the intra-cluster correlation coefficient (ICC) for each outcome.

Assessment of risk of bias in included studies
Two review authors, MCF and ES, will independently assess the methodological quality of each included trial using the Cochrane 'Risk of bias' assessment tool. This tool considers five quality domains within each study: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants/personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (other pre-specified, unique sources). If an included trial reports multiple relevant outcomes, we may need to assess blinding and incomplete outcome data more than once. Across all domains, we will rate a criterion as “unclear”
if we cannot acquire sufficient details or if the impact of specific methodological characteristics is unclear. We will summarize the risk of bias for each relevant outcome reported in each included trial. There are seven key potential sources of bias that authors will assess.

1. Sequence generation:
   i) low risk: the process used to generate the randomization list results in sequences that are unpredictable and statistically random (for example, computer-generated random number generator, unbiased coin toss, random number tables);
   ii) high risk: the sequences are generated using non-random techniques (for example, participant date of birth, alternation);
   iii) unclear risk: the methods were not described or there was insufficient information provided to allow judgment.

2. Allocation concealment:
   i) low risk: both the participants and the investigators enrolling participants cannot foresee or predict assignment (for example, central allocation or using sequential, sealed envelopes);
   ii) high risk: participants or investigators enrolling participants can foresee upcoming assignment (for example, a random number table is used for the sequence, but it is left open and in plain sight of investigators enrolling participants);
   iii) unclear risk: methods not described or insufficient information to allow judgment.

3. Blinding of participants and personnel:
   i) Low risk: blinding of participants and key personnel ensured, and unlikely that the blinding could have been broken; low risk will also be assigned if the outcome is judged by reviewers as unlikely to be influenced by lack of blinding.
   ii) High risk: no blinding, or incomplete blinding, and the outcome is likely to be influenced by blinding (for example, subjective outcomes like pain would likely be influenced by participant/personnel blinding, but physiological infection may be less readily impacted).
   iii) Unclear risk: methods not described or insufficient information to allow judgment.

4. Blinding of outcome assessment:
   i) low risk: blinding of outcome assessment ensured and unlikely that blinding could have been broken; low risk could also include rigorous quality control (for example, 10% of slides are reexamined by a senior technician) Speich 2015; low risk will also be assigned if the outcome is judged by reviewers as unlikely to be influenced by lack of blinding for outcome assessors;
   ii) high risk: outcome assessors not blinded, and this is likely to introduce bias (for example, diagnostics for STH infection often require stool examination, which could introduce confirmation bias if the laboratory technicians know from which group the stool originated);
   iii) unclear risk: methods not described or insufficient information to allow judgment.

5. Incomplete outcome data:
   i) low risk: no missing outcome data; reasons for missing data unlikely to be related to true outcome; missing outcome data balanced across intervention groups with similar reasons for missing data across groups. For dichotomous data, the proportion of missing outcomes compared with observed event risk not likely to be have a clinically relevant impact on the intervention effect estimate. For other data, plausible effect size among missing outcomes not likely to have a clinically relevant impact on the observed effect size;
   ii) high risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous data, proportion of missing outcomes compared with observed event risk likely to cause clinically relevant bias on the intervention effect estimate. For other data, plausible effect size among missing outcomes likely to cause a clinically relevant bias in observed effect size;
   iii) unclear risk: methods not described or insufficient information to allow judgment.

6. Selective outcome reporting:
   i) low risk: study protocol is available and all of the study's relevant pre-specified outcomes are reported in the originally specified way; study protocol is not available but published reports include all expected outcomes, including those that were pre-specified;
   ii) high risk: not all of the study's pre-specified primary outcomes are reported; one or more primary outcomes is reported using methods or data subsets that were not originally specified; one or more reported primary outcomes were not pre-specified (unless clear and compelling justification is provided); one or more outcomes of interest in the review are reported incompletely; failure to include a key outcome that would be expected to have been reported in such a study;
   iii) unclear risk: methods not described or insufficient information to allow judgment.

7. Other sources of bias:
   i) low risk: study appears free of other sources of bias;
   ii) high risk: study has a potential source of bias related to study design; study has been claimed to be fraudulent;
   iii) unclear risk: methods not described or insufficient information to allow judgment.

We anticipate that due to the nature of WASH interventions, the interventions will be allocated at a cluster level. As such, as part of our assessment of risk of bias, we will consider adjustment for baseline characteristics, loss to follow-up of clusters, and statistical adjustment for clustered data in the analysis. We will document the methodological quality of each included trial with relevant information from the text or reviewer notes, or both, for each of the quality domains. We will record all assessments in 'Risk of bias' tables and produce 'Risk of bias' summary graphs. MCF and ES will independently make a summary 'Risk of bias' judgment for each included trial after considering all documented threats to
We will consider using ORs. We will extract the reported data, along with ICCs and design effects to adjust for clustering. We will adjust for clustering using the following equation: unadjusted SE of the log RR = SE(lnRR)*DE \[SE(lnRR)*DE = adjusted SE(lnRR)\]. Where none of the pooled trials adjust for clustering, we will adjust the sample size for clustering whereby DE = 1 + \[
\frac{(average\ cluster\ size -1) \times ICC}{1 + ICC}\]. Where ICCs are unavailable, we will request data from the trial authors. If the trial authors do not provide these data, we will use ICCs from a similar trial or location where possible. Where ICCs have been estimated, we will conduct a sensitivity analysis comparing these trials to ones where we derived the ICCs empirically.

We expect trials that randomize at the individual level to be less likely to require statistical adjustment, assuming that the participant assignment sequence is generated randomly and concealed effectively.

We may include trials with multiple trial arms in more than one comparison.

Dealing with missing data

We will contact the trial authors to request missing data. We will also report whether participants or trial clusters were lost to follow-up during the trial time period. We will analyse data according to a complete case analysis. Also, we will perform a sensitivity analyses to assess the effect of missing data and to ensure that our conclusions are robust.

Assessment of heterogeneity

When we combine trials via meta-analysis, we will assess heterogeneity by inspecting forest plots to detect overlapping 95% CIs. We will additionally use Moran’s I² statistic and Cochran’s Q tests to determine the heterogeneity between trials. We will consider an I² statistic value of greater than 70% as an indicator of significant heterogeneity. If the I² statistic value is between 50 and 70%, we will also check the Q test for a P value of less than 0.1.

We will consider variations between interventions as an important potential source of heterogeneity. For the primary outcome (any STH), we will deem differences in prevalence between STH species as an important potential source of heterogeneity.

Assessment of reporting biases

We will assess publication bias by cross-checking public study protocols and trial registrations against completed publications. For study registrations released in 2012 or earlier (three-year time buffer) that do not have corresponding published results, we will contact trial authors to identify causes of delays. If the trial authors do not provide reasonable reasons, we will assume that publication bias may impact all relevant outcomes that were listed in the trial protocol.

When there are more than 10 included trials available for an intervention and outcome, we will also investigate publication bias with funnel plot assessments. However, due to the difficulty involved in detecting publication bias when strong heterogeneity exists between studies, funnel plots may be of limited usefulness.

Where appropriate, however, we will conduct tests by Harbord 2006 and Peters 2006 for outcomes that use ORs.

Data synthesis

We will compile and analyse data using RevMan. Where possible, we will recalculate effect estimates to ORs based on the available data. We will perform meta-analyses to calculate a weighted effect across trials if three or more included trials are similar regarding interventions and STH outcome (for example, STH type and data type). Due to the diversity in WASH interventions, we expect substantial heterogeneity and will employ a random-effects approach in meta-analyses using the DerSimonian and Laird method. We will consider using a fixed-effect approach if interventions, trial participants, and environmental context are highly similar. Where strong heterogeneity is present, we will not conduct meta-analyses, but will present forest plots and may conduct additional subgroup analyses.

We will qualitatively summarize all included evidence that does not qualify for meta-analysis.

Subgroup analysis and investigation of heterogeneity

If there are 10 or more included trials available for an intervention and outcome, we will systematically investigate heterogeneity through subgroup analysis or meta-regression, or both. We have identified the following factors as important potential sources of heterogeneity.

Interventions to improve water, sanitation, and hygiene for preventing soil-transmitted helminth infection (Protocol)
1. Region/location of study.
2. Participant age distribution.
3. STH burden (prevalence, intensity).
4. Diagnostic assay.
5. Variations between similar interventions.

**Sensitivity analysis**

Provided that a sufficient number of trials meet the inclusion criteria, we will perform sensitivity analysis to investigate the robustness of the results for different thresholds for risk of bias. We will base our primary review findings on evidence at low risk of bias, so we will expand the sensitivity analysis to include trials with an overall unclear or high risk of bias, or both.

We will also investigate the effect of missing data using sensitivity analysis, assuming reasonable best and worst case scenarios for the missing data.

**Quality of the evidence**

We will assess the quality of the evidence using the GRADE approach, which consists of five factors to assess the quality of the evidence: study limitations (risk of bias), inconsistency, indirectness, imprecision, and publication bias (Guyatt 2008). We will summarize the quality of the evidence in 'Summary of findings' tables that we will create using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guideline Development Tool (GDT) (wwwGRADEpro.org).

**Acknowledgements**

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). The views expressed in this protocol do not necessarily reflect UK government policy.

**References**

Al-Delaimy 2014

Awasthi 2013

Bartram 2010

Bethony 2006

Brown 2013

Cappello 2004

Clasen 2007

Crompton 2000

Crompton 2002

Dangour 2013

DerSimonian 1986

Emerson 2012

Esrey 1991
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Fewtrell 2005

Freeman 2013

Grimes 2014

Gulani 2007

Guyatt 2008

Harbord 2006

Holland 2001

Horton 2003

Hotez 2006

Hotez 2007

Howard 2003

IRC 2014

Jia 2012

Kar 2008

Keiser 2008

Lancet 2012

Leslie 2011

Miguel 2004

Murray 2013

Peters 2006

Pruß-Ustün 2014

Pullan 2014
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### Appendix 1. Search strategy

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<td>4</td>
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<tr>
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<td>6</td>
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<td>18</td>
<td>Limit 17 to Humans</td>
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This is the preliminary search strategy for MEDLINE. We will adapt it for other electronic databases. We will report all search strategies in full in the final version of the review.
### Appendix 2. Data to be extracted

<table>
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<td>Allocation of intervention and control group</td>
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<td>Sample size (number of clusters, individuals)</td>
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<td>Intervention components</td>
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<td>Definition and practices of control group</td>
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<td></td>
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<tr>
<td>The selection process (for example, random selection)</td>
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<tr>
<td>WASH factors measured (for example, water access, latrine use)</td>
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<tr>
<td>Diagnostic assay, including information about quality control</td>
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<tr>
<td>Which STH species were measured</td>
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<td>Prescribed criteria of methodological quality</td>
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<td>Publication status</td>
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<tr>
<td>Age groups and stratification</td>
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<tr>
<td>Baseline characteristics</td>
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</table>

**Abbreviations:** STH: soil-transmitted helminth; WASH: water, sanitation, and hygiene

### Contributions of Authors

MCF conceived the review. MCF and ES wrote the first draft of the protocol. MCF, ES, DGA, and JU decided on the search strategy, data analysis plan, and reviewed the final draft of the protocol.
DECLARATIONS OF INTEREST

MCF serves on the Soil-Transmitted Helminthiasis Advisory Committee, which receives funding from Johnson & Johnson and GlaxoSmithKline. MCF has a grant from Johnson & Johnson for work assessing the impact of school-based water, sanitation, and hygiene on STH.

JU is a co-investigator of a grant by the UBS Optimus Foundation that investigates the effect of community-led total sanitation and health education against soil-transmitted helminthiasis and diarrhoea. JU also acts as the chair of the Soil-Transmitted Helminthiasis Advisory Committee, which receives funding from Johnson & Johnson and GlaxoSmithKline.

DGA and ES are affiliated with the Children Without Worms (CWW) programme at the Task Force for Global Health. CWW receives financial support from Johnson & Johnson, GlaxoSmithKline, and the Children’s Investment Fund Foundation, as well as individual donors.

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