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

Freeman MC, Strunz E, Utzinger J, Addiss DG

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[Intervention Protocol]

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 (Stoltzfus 1998; Gulani 2007), poor nutrition and stunting (Stoltzfus 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 (Keiser 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 (Hotez 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 may 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 nor 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 (Fewtrell 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 recontamination, though evidence suggests that access to an improved source does not guarantee microbiological safety (Brown 2013). 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

Specialized Trials Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; PubMed (MEDLINE); EMBASE; ISI Web of Knowledge; and LILACS . We will also search the following ongoing trials registers: the *meta*Register of Controlled trials (www.controlled-trials.com); the U.S. National Institutes of Health Register (www.clinicaltrials.gov);and the World Health Organization (WHO) International Clinical Trials Registry platform (ICTRP) (www.who.int/trialsearch). We will examine the Chinese language databases available in the China National Knowledge Infrastructure and the Wan Fang Portal.

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 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

internal validity. When necessary, a third review author (DGA) will facilitate discussion until consensus is reached.

Measures of treatment effect

We expect that results may draw upon dichotomous data (measuring differences in prevalence), count data (measuring differences in infection intensity), or time-to-event data (using survival analysis). Possible dichotomous outcomes include risk ratios, prevalence ratios, and ORs. We expect count outcomes to be rate ratios, and time-to-event outcomes to be HRs.

For dichotomous outcomes, we will present the risk ratio, odds ratio (OR), or prevalence ratio. We will present all results with 95% confidence intervals (CIs). We will describe measures of effect for count data. We will use rate ratios to combine count data. We will use HRs for time-to-event data. When continuous data are summarized using geometric means, we will present geometric mean ratios with medians and ranges in a table.

Unit of analysis issues

If cluster RCTs report results without adjustment for clustering, 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 $^{0.5}$ = adjusted SE(lnRR). Where none of the pooled trials adjust for clustering, we will adjust the sample size for clustering whereby DE = 1 + [(average cluster size -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 I^2 statistic and Cochran's Q tests to determine the heterogeneity between trials. We will consider an I^2 statistic value of greater than 70% as an indicator of significant heterogeneity. If the I^2 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 (RevMan 2014). 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 (DerSimonian 1986). 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.

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 to different thresholds for risk of bias. We will base our primary review findings in 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) (www.gradepro.org).

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REFERENCES

Additional references

Al-Delaimy 2014
Al-Delaimy AK, Al-Mekhlafi HM, Nasr NA, Sady H, Atroosh WM, Nashiry M, et al. Epidemiology of intestinal polyparasitism among Orang Asli school children in rural Malaysia. *PLoS Neglected Tropical Diseases* 2014;**8**(8):e3074.

Awasthi 2013
Awasthi S, Peto R, Read S, Richards SM, Pande V, Bundy D, DEVTA (Deworming and Enhanced Vitamin A) team. Population deworming every 6 months with albendazole in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *The Lancet* 2013;**381**(9876): 1478–86.

Bartram 2010
Bartram J, Cairncross S. Hygiene, sanitation, and water: forgotten foundations of health. *PLoS Medicine* 2010;**7** (11):e1000367.

Bethony 2006
Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *The Lancet* 2006; **367**(9521):1521–32.

Brown 2013
Brown J, Hien VT, McMahan L, Jenkins MW, Thie L, Liang K, et al. Relative benefits of on-plot water supply over other 'improved' sources in rural Vietnam. *Tropical Medicine & International Health* 2013;**18**(1):65–74.

Cappello 2004
Cappello M. Global health impact of soil-transmitted nematodes. *The Pediatric Infectious Disease Journal* 2004;**23** (7):663–4.

Clasen 2007
Clasen T, Schmidt WP, Rabie T, Roberts I, Cairncross S. Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis. *BMJ* 2007; **334**(7597):782.

Crompton 2000
Crompton DW. The public health importance of hookworm disease. *Parasitology* 2000;**121 Suppl**:S39–50.

Crompton 2002
Crompton DW, Nesheim MC. Nutritional impact of intestinal helminthiasis during the human life cycle. *Annual Review of Nutrition* 2002;**22**:35–59.

Dangour 2013
Dangour AD, Watson L, Cumming O, Boisson S, Che Y, Velleman Y, et al. Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD009382.pub2]

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Emerson 2012
Emerson P, Kollmann M, MacArthur C, Bush S, Haddad D. SAFE strategy for blinding trachoma addresses sanitation, the other half of MDG7. *Lancet* 2012;**380**(9836):27–8.

Esrey 1991
Esrey SA, Potash JB, Roberts L, Shiff C. Effects of improved water supply and sanitation on ascariasis, diarrhoea, dracunculiasis, hookworm infection, schistosomiasis, and trachoma. *Bulletin of the World Health Organization* 1991; **69**(5):609–21.

Fewtrell 2005
Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM Jr. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2005;**5**(1):42–52.

Freeman 2013
Freeman MC, Ogden S, Jacobson J, Abbott D, Addiss DG, Amnie AG, et al. Integration of water, sanitation, and hygiene for the prevention and control of neglected tropical diseases: a rationale for inter-sectoral collaboration. *PLoS Neglected Tropical Diseases* 2013;**7**(9):e2439.

Grimes 2014
Grimes JE, Croll D, Harrison WE, Utzinger J, Freeman MC, Templeton MR. The relationship between water, sanitation and schistosomiasis: a systematic review and meta-analysis. *PLoS Neglected Tropical Diseases* 2014;**8**(12): e3296.

Gulani 2007
Gulani A, Nagpal J, Osmond C, Sachdev HP. Effect of administration of intestinal anthelmintic drugs on haemoglobin: systematic review of randomised controlled trials. *BMJ* 2007;**334**(7603):1095.

Guyatt 2008
Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, GRADE Working Group. Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**(7651):995–8.

Harbord 2006
Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20): 3443–57.

Holland 2001
Holland CV, Kennedy MW. *The Geohelminths: Ascaris, Trichuris and Hookworm*. Vol. **2**, New York: Springer US, 2001.

Horton 2003
Horton J. Global anthelmintic chemotherapy programs: learning from history. *Trends in Parasitology* 2003;**19**(9): 405–9.

Hotez 2006
Hotez PJ, Bundy DAP, Beegle K, Brooker S, Drake L, de Silva N, et al. Chapter 24: Helminth Infections: Soil-Transmitted Helminth Infections and Schistosomiasis. *Disease Control Priorities in Developing Countries*. New York: Oxford University Press, 2006:467–82.

Hotez 2007
Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, et al. Control of neglected tropical diseases. *New England Journal of Medicine* 2007;**357**(10):1018–27.

Howard 2003
Howard G, Bartram J. *Domestic Water Quantity, Service Level, and Health*. Geneva: World Health Organization, 2003.

IRC 2014
IRC. Life-cycle costing tool. http://www.ircwash.org/projects/life-cycle-costing-tools. The Hague, (accessed 3 February 2016).

Jia 2012
Jia TW, Melville S, Utzinger J, King CH, Zhou XN. Soil-transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis. *PLoS Neglected Tropical Diseases* 2012;**6**(5):e1621.

Kar 2008
Kar K, Chambers R. Handbook on Community-Led Total Sanitation. March 2008. http://www.communityledtotalsanitation.org/sites/communityledtotalsanitation.org/files/cltshandbook.pdf. London, UK: IDS and PLAN International, (accessed 2 February 2016).

Keiser 2008
Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008;**299**(16):1937–48.

Lancet 2012
Lancet Editorial Board. Progress in sanitation needed for neglected tropical diseases. *The Lancet* 2012;**379**(9820): 978.

Leslie 2011
Leslie J, Garba A, Oliva EB, Barkire A, Tinni AA, Djibo A, et al. Schistosomiais and soil-transmitted helminth control in Niger: cost effectiveness of school based and community distributed mass drug administration. *PLoS Neglected Tropical Diseases* 2011;**5**(10):e1326.

Miguel 2004
Miguel E, Kremer M. Worms: Identifying impacts on education and health in the presence of treatment externalities. *Econometrica* 2004;**72**(1):159–217.

Murray 2013
Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2013;**380**(9859):2197–223.

Peters 2006
Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;**295**(6):676-80.

Prüss-Ustün 2014
Prüss-Ustün A, Bartram J, Clasen T, Colford JM Jr, Cumming O, Curtis V, et al. Burden of disease from inadequate water, sanitation and hygiene in low- and middle-income settings: a retrospective analysis of data from 145 countries. *Tropical Medicine & International Health* 2014;**19**(8):894–905.

Pullan 2014
Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasites & Vectors* 2014;**7**:37.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sanchez 2013
Sanchez AL, Gabrie JA, Usuanlele MT, Rueda MM, Canales M, Gyorkos TW. Soil-transmitted helminth infections and nutritional status in school-age children from rural communities in Honduras. *PLoS Neglected Tropical Diseases* 2013;**7**(8):e2378.

Soares Magalhães 2011
Soares Magalhães RJ, Barnett AG, Clements AC. Geographical analysis of the role of water supply and sanitation in the risk of helminth infections of children in West Africa. *Proceedings of the National Academy of Sciences of the United States of America* 2011;**108**(50):20084–9.

Speich 2015
Speich B, Ali SM, Ame SM, Albonico M, Utzinger J, Keiser J. Quality control in the diagnosis of Trichuris trichiura and Ascaris lumbricoides using the Kato-Katz technique: experience from three randomised controlled trials. *Parasites & Vectors* 2015;**8**:82.

Stocks 2014
Stocks ME, Ogden S, Haddad D, Addiss DG, McGuire C, Freeman MC. Effect of water, sanitation, and hygiene on the prevention of trachoma: a systematic review and meta-analysis. *PLoS Medicine* 2014;**11**(2):e1001605.

Stoltzfus 1997
Stoltzfus RJ, Albonico M, Tielsch JM, Chwaya HM, Savioli L. School-based deworming program yields small improvement in growth of Zanzibari school children after one year. *Journal of Nutrition* 1997;**127**(11):2187–93.

Stoltzfus 1998
Stoltzfus RJ, Albonico M, Chwaya HM, Tielsch JM, Schulze KJ, Savioli L. Effects of the Zanzibar school-based deworming program on iron status of children. *American Journal of Clinical Nutrition* 1998;**68**(1):179–86.

Strunz 2014
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 Medicine* 2014;**11**(3):e1001620.

Taylor-Robinson 2015
Taylor-Robinson DC, Maayan N, Soares-Weiser K, Donegan S, Garner P. Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD000371.pub6]

Utzinger 2004
Utzinger J, Keiser J. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. *Expert Opinion on Pharmacotherapy* 2004;**5**(2):263–85.

Utzinger 2009
Utzinger J, Raso G, Brooker S, De Savigny D, Tanner M, Ørnbjerg N, et al. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. *Parasitology* 2009;**136**(13):1859–74.

WaterAid 2012
WaterAid. WASH: The silent weapon against NTDs. Working together to achieve prevention, control and elimination. http://www.wateraid.org/us/~/media/Publications/WASH-the-silent-weapon-against-NTDs.pdf?la=en-US. London, UK, (accessed 3 February 2016).

WHO 2002
World Health Organization. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. Report of a WHO expert committee. WHO Technical Report Series 912. 2002. http://apps.who.int/iris/bitstream/10665/42588/1/WHO_TRS_912.pdf. Geneva: World Health Organization, (accessed 3 February 2016).

WHO 2012a
World Health Organization. Soil-transmitted helminthiasis. Eliminating soil-transmitted helminthiasis as a public health problem in children. Progress report 2001-2010 and strategic plan 2011-2020. http://apps.who.int/iris/bitstream/10665/44804/1/9789241503129_eng.pdf. Geneva: World Health Organization, (accessed 3 February 2016).

WHO 2012b
World Health Organization. Accelarating work to overcome the global impact of neglected tropical diseases. A roadmap for implementation. http://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf (accessed 3 February 2016).

WHO 2013
World Health Organization. Preventive Chemotherapy Databank. http://www.who.int/neglected_diseases/preventive_chemotherapy/databank/en/ (accessed 3 February 2016).

Wright 2004
Wright J, Gundry S, Conroy R. Household drinking water in developing countries: a systematic review of microbiological contamination between source and point-of-use. *Tropical Medicine & International Health* 2004;**9**(1):106–17.

Ziegelbauer 2012
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):e1001162.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

Search set	MEDLINE
1	Soil-transmitted helmint* ti, ab
2	Geohelmin* ti, ab
3	"Ancylostomiasis"[Mesh] OR "Ancylostoma"[Mesh] OR ancylostom* ti, ab
4	"Necator americanus"[Mesh] OR necator ti, ab
5	"Ascariasis"[Mesh] OR "Ascaris"[Mesh] OR ascari* ti, ab
6	"Trichuris"[Mesh] OR trichuris ti, ab
7	"Hookworm Infections"[Mesh] OR hookworm* ti, ab
8	"Strongyloidiasis"[Mesh] OR "Strongyloides"[Mesh] OR strongyloid* ti, ab
9	1-8/OR
10	"Sanitation"[Mesh] OR "Water Supply"[Mesh] OR "Hand Disinfection"[Mesh] OR "Waste Management"[Mesh]
11	"Hand hygiene" [Mesh] OR "Toilet facilities" [Mesh] OR "Health education" [Mesh]
12	Sanitary engineering ti, ab
13	hand washing OR handwashing OR hand-washing ti, ab
14	Latrine OR toilet* OR sanitation ti, ab
15	WASH ti, ab
16	10-15/OR
17	9 AND 16
18	Limit 17 to Humans

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

Fields
Trial description (for example, study design, setting, year)
Allocation of intervention and control group
Sample size (number of clusters, individuals)
Intervention components
Definition and practices of control group
The primary research question
Details on the trial population (for example, age groups)
The selection process (for example, random selection)
WASH factors measured (for example, water access, latrine use)
Diagnostic assay, including information about quality control
Which STH species were measured
Prescribed criteria of methodological quality
Publication status
Age groups and stratification
Baseline characteristics

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 eduction 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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